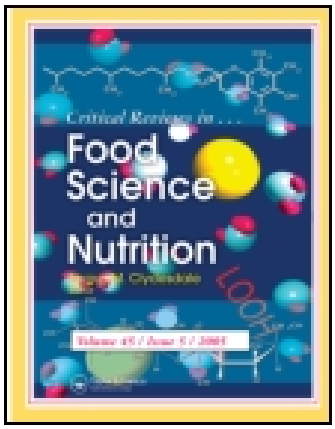

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EURRECA—Estimating Iodine Requirements for Deriving Dietary Reference Values

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EURRECA—Estimating Iodine Requirements for Deriving Dietary Reference Values

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Iodine is an essential component of thyroid hormones, and current recommendations for intake are based on urinary iodine excretion, assessment of thyroid size, thyroidal iodine accumulation and turnover, radioactive iodine uptake, balance studies, and epidemiological studies. Dietary iodine is rapidly and almost completely absorbed. The prevalence of inadequate iodine intake is high: 29% of the world's population lives in iodine-deficient areas and 44% of Europe remains mildly iodine deficient. To assess current data and update evidence for setting dietary recommendations for iodine, the EURRECA Network of Excellence has undertaken systematic review and evaluation of (i) the usefulness of iodine status biomarkers (ii) the relationship between iodine status biomarkers and dietary iodine intake, and (iii) the relationship between iodine intake and health outcomes (endemic goiter, hypothyroidism, and cognitive function). This review summarizes the main research outputs: the key findings of the literature review, results of the meta-analyses, and discussion of the main conclusions. Currently, data for relevant intake–status–health relationships for iodine are limited, particularly for population groups such as children under two years, pregnant women, and the elderly. The EURRECA Network developed best practice guidelines for the identification of pertinent iodine studies based on a systematic review approach. This approach aimed to identify comparable data, suitable for meta-analysis, for different countries and across all age ranges. When new data are available, the EURRECA Network best practice guidelines will provide a better understanding of iodine requirements for different health outcomes which could be used to set evidence-based dietary iodine recommendations for optimal health.

Keywords Iodine, dietary recommendation, iodine intake, systematic review, iodine status, iodine bioavailability, iodine requirements, EURRECA

FUNCTION, ESSENTIALITY, PHYSIOLOGY AND METABOLISM

Inadequate intake of iodine is associated with impaired thyroid function and may result in several other iodine deficiency disorders (IDD). The human body contains approximately 10–20 mg of iodine, of which 70–80% is concentrated in the thyroid gland. Iodine is essential for the synthesis of the thyroid hormones, thyroxine (T_4) and the biologically active form 3,5,3′-triiodthyronine (T_3), which maintain the body's basal metabolic rate by controlling energy production and oxygen consumption in cells. These hormones are essential for normal growth and maturation along with the development of the central nervous system (Perez-Lopez, 2007). Iodine is primarily obtained through the diet but it is also a component of some medications.

Iodine is ingested in a range of forms that are readily reduced to iodide in the gut prior to absorption. The amount of iodine absorbed is largely dependent on the level of dietary iodine intake, rather than on its chemical form or the composition of the diet (Fairweather-Tait and Hurrell, 1996). Absorption is extremely efficient and takes place mainly in the stomach and upper small intestine. In healthy adults, the absorption of iodide is greater than 90% (Alexander et al., 1967). Fifteen percent of ingested iodine is taken up by the thyroid gland within 24 hours of ingestion (Larsen et al., 1981). The synthesis and release of the thyroid hormones, T_3 and T_4, are regulated by thyroid-stimulating hormone (TSH or "thyrotropin") secreted by the pituitary gland into the circulation. In addition to actively extracting circulating iodide, thyroid follicular epithelial cells translocate iodide into

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a central intrafollicular compartment, where thyroglobulin (Tg) is iodinated to form the key protein precursor to T_4 and T_3. This regulation is subject to feedback inhibition deficiency. Circulating T_4 and T_3 are bound to various iodine-binding transport proteins including albumin, T_4-binding globulin, and transthyretin (Fisher and Oddie, 1969). Once delivered to the relevant target tissues T_4 is deiodinated to the metabolically active form, T_3. The released iodine is returned to the serum iodine pool where it can be taken up by the thyroid or excreted in the urine (iodine clearance approximately 40 mL/min). Fecal losses vary but are generally low (10–20 μg/day; Vought and London, 1964), and small amounts are also lost via the skin (Mao et al., 1990).

Twenty-nine percent of the world's population living in approximately 130 countries is estimated to live in areas of ID. Despite remarkable progress in the control of iodine deficiency disorders (IDD), ID remains a significant global public health problem. Forty-four percent of Europe remains mildly iodine deficient (urinary iodine excretion [UIE] cutoff < 50 and > 20 μg/L) and iodine intakes in other industrialized countries including the United States and Australia, have fallen in recent years (World Health Organization [WHO], 2007; Zimmermann and Andersson, 2011). Optimal dietary iodine intake is between 100 and 200 μg/day and primarily comes from iodized salt, saltwater fish, seaweed, and grains (although in trace amounts for the latter; Haldimann et al., 2005). The iodine in drinking water varies considerably between regions. Iodine can be added to salt as potassium iodide, potassium iodate, or, less frequently, sodium iodide. In many countries, the use of iodized salt in households for cooking and at the table provides additional iodine. Supplements vary in iodine content and form and may be available as potassium iodide tablets, prenatal multivitamin preparations, or iodized oil. Both ID and excess iodine intake are associated with well-known health problems (this issue will be discussed later in the review).

CURRENT DIETARY RECOMMENDATIONS

Several indicators are used to assess iodine requirements, including UIE, assessment of thyroid size, thyroidal iodine accumulation and turnover, radioactive iodine uptake, balance studies, and epidemiological, population studies. The WHO, International Council for the Control of Iodine Deficiency Disorders (ICCIDD) and United Nations Children's Fund (UNICEF) recommend daily iodine intakes of 90 μg/day for preschool children and 150 μg/day for adults, reaching 250 μg/day for pregnant/lactating women (Food and Agriculture Organization of the United Nations [FAO]/WHO, 2002; WHO and FAO, 2004; WHO/UNICEF/ICCIDD, 2007). A brief summary of key recommended intakes for iodine at various life stages, as established by several European countries or expert organizations, is shown in Table 1 (European Commission [EC], 2002; German Nutrition Society, 2000; Nordic Council of Ministers, 2004; WHO, 2004; Australian Government Department of Health and Aging New Zealand Ministry of Health and National Health and Medical Research Council, 2005). The "Nutri-RecQuest" database developed by the EURRECA Network (www.serbianfood.info/eurreca/index.php) provides a full summary of dietary iodine recommendations (Doets et al., 2008; Cavelaars et al., 2010). With respect to adequate iodine intake, the cutoff values are set at the levels that should be optimal for "general health" and "prevention of deficiency" (in Hungary, Italy, Latvia, Lithuania, Romania and the United Kingdom; Doets et al., 2008). Altenatively, other endpoints used to assess adequacy are "adequate iodine concentration in the thyroid gland" and "iodine turnover" (the Nordic countries, the DACH [D-Germany; A-Austria; CH-Switzerland] countries, WHO/FAO, 2002), or more generally, "a proper thyroid function" (Belgium, the United Kingdom, WHO/FAO, and EC) and "iodine balance" (EC).

CURRENT INTAKES/ADEQUACY (SEE ALSO ACTIVITY 7 IN DHONUKSHE-RUTTEN ET AL., 2013)

The intake of iodine in Europe based on upper levels of intake was reported in the International Life Sciences Institute (ILSI) Europe Addition of Nutrients to Food Task Force (Flynn et al., 2009). Most countries and organizations use data from epidemiological studies as a base for defining iodine recommendations in addition to expert opinion (Cavelaars et al., 2010). The DACH countries, France, EC, and WHO/FAO used physiological or mechanistic (balance and turnover) iodine studies (DACH, EC). In the context of the EURRECA Network of Excellence, the intake of several micronutrients including iodine was analyzed and the prevalence of inadequacy in intake was estimated as based on data from the European Nutrition and Health Report II (Elmadfa et al., 2005). The studies from Denmark (adults and elderly males) and Finland (only elderly) showed that 10% or less of the population had inadequate iodine intakes (Roman Vinas et al., 2011). More than 20% of the adult population in Finland and the adult and elderly population in Germany, as well as the elderly population in Ireland (females only) had iodine intakes below the average requirement (AR; Roman Vinas et al., 2011). Data for adults, on the other hand, are scarce and no regional comparisons (Central and Eastern Europe, Scandinavia, Western, and Mediterranean countries) could be made. A recent review of open-access and gray literature, by Novakovic et al. (2012b) reports that unlike other EURRECA prioritized micronutrients, data for iodine are abundant, but for children only. Results indicate mild ID among children in some Central and Eastern European (CEE) countries and in Italy and Belgium. With respect to adults, median urinary iodine (UI) concentrations were below the cutoff (<100 μg/L) for males and females in Italy, France, and Germany and for females in Romania.

Following the EURRECA Best Practice Methods (see also activities 1, 3, and 7 in Dhonukshe-Rutten et al., 2013) for dietary assessment methods and biomarkers of status, a systematic literature review was undertaken to determine associations between socioeconomic status (SES) indicators and micronutrient

Table 1 Selected† recommended daily intake levels for IODINE (μg)

		Population groups (age, iodine intake in μg)							
Data source/year	Gender	Infants	Children	Adolescents	Adults	Elderly	Lactation	Pregnancy	Upper level of safe intake
WHO/FAO, 2004	Male	0–6 m, 90 7–12 m, 90	1–3 y, 90 4–6 y, 90 6–12 y, 120	13–18 y, 150	19–65 y, 150	>65 y, 150	—	—	—
WHO, 2007	Female	0–6 m, 90 7–12 m, 90	1–3 y, 90 4–6 y, 90 6–12 y, 120	13–18 y, 150	19–65 y, 150	>65 y, 150	250	250	—
Nordic/2004	Male	<6 m, NULL 6–11 m, NULL	2–5 y, 90 6–9 y, 120 10–13 y, 150	14–17 y, 150	18–74 y, 150	≥75 y, 150	—	—	—
Australia/NZ/2005	Male	0–6 m, 90 7–12 m, 110	1–3 y, 90 4–8 y, 90 9–13 y, 120	14–18 y, 150	19–30 y, 150 31–50 y, 150 51–70 y, 150	>70 y, 150	—	—	1–3 y, 200 4–8 y, 300 9–13 y, 600 14–18 y, 900 19 y, >1100
	Female	0–6 m, 90 7–12 m, 110	1–3 y, 90 4–8 y, 90 9–13 y, 120	14–18 y, 150	19–30 y, 150 31–50 y, 150 51–70 y, 150	>70 y, 150	270	220	1–3 y, 200 4–8 y, 300 9–13 y, 600 14–18 y, 900 19 yr, >1100 Pregnancy, >1000 Lactation, >1100
DACH (Germany, Austria)/2004	Male	0 to under 4 m, 40 4 to under 12 m, 80	1 to under 4 y, 100 4 to under 7 y, 120 7 to under 10 y, 140 10 to under 13 y, 180 13 to under 15 y, 200	15 to under 19 y, 200	19 to under 25 y, 200 25 to under 51 y, 200 51 to under 65 y, 180	>65 y, 180			Adult, 500

(Continued on next page)

Table 1 Selected† recommended daily intake levels for IODINE (μg) *(Continued)*

Data source/year	Gender	Population groups (age, iodine intake in μg)							
		Infants	Children	Adolescents	Adults	Elderly	Lactation	Pregnancy	Upper level of safe intake
	Female	0 to under 4 m, 40 4 to under 12 m, 80	1 to under 4 y, 100 4 to under 7 y, 120 7 to under 10 y, 140 10 to under 13 y, 180 13 to under 15 y, 200	15 to under 19 y, 200	19 to under 25 y, 200 25 to under 51 y, 200 51 to under 65 y, 180	>65 y, 180	260	230	Adult, 500
EC/1993/2002	Male	6–11 m, 50	1–3 y, 70 4–6 y, 90 7–10 y, 100	11–14 y, 120 15–17 y, 130	≥18 y, 100	—	—	—	1–3 y, 200 4–6 y 250 7–10 y, 300 11–14 y, 600 15–17 y, 500 Adult, >600*
	Female	6–11 m, 50	1–3 y, 70 4–6 y, 90 7–10 y, 100	11–14 y, 120 15–17 y, 130	≥18 y, 100	—	160	130	1–3 y, 200 4–6 y, 250 7–10 y, 300 11–14 y, 600 15–17 y, 500 Adult, 600* Pregnancy, 600
IOM (US/Canada)/2001	Male	0–6 m, 110 7–12 m, 130	1–3 y, 90 4–8 y, 90 9–13 y, 120	14–18 y, 150	19–30 y, 150 31–50 y, 150 51–70 y, 150	>70 y, 150	—	—	0–12 m/ not possible to establish 1–3 y, 200 4–8 y, 300 9–13 y, 600 14–18 y, 900 19 y, >1100
	Female	0–6 m, 110 7–12 m, 130	1–3 y, 90 4–8 y, 90 9–13 y, 120	14–18 y, 150	19–30 y, 150 31–50 y, 150 51–70 y, 150	>70 y, 150	290	220	0–12 m not possible to establish 1–3 y, 200 4–8 y, 300 9–13 y, 600 14–18 y, 900 19 y, 1100 pregnancy, lactation > 1100

Note: Data presented in Table 1 was obtained from online EURRECA web resource NutriRecQuest: http://www.serbianfood.info/eurreca/ (Cavelaars et al. 2010) from original source documents (Commission of the European Communities, 1993; German Nutrition Society, 2000; Institute of Medicine Academy of Sciences, 2001; Thomson, 2002; Nordic Council of Ministers, 2004; WHO/UNICEF/ICCIDD, 2007; WHO and FAO, 2004).

†PRI, population reference intake (EFSA); RNI, recommended nutrient intake (WHO/FAO); RDI, recommended dietary intake (AU/NZ); RI, recommended intake (Nordic).

*Upper level of safe intake for European Community is taken from EC2006 and other EC data from 1993.

intake and status in Europe. Educational level, occupational status, and income were the SES indicators considered. Data on intake of iodine and SES were scarce, with only one relevant study identified in adults (Novakovic et al., 2012b). This study (in French adults) found no difference in mean iodine intake between the lowest and the highest SES groups in males and found a slightly lower intake in the lowest SES group compared with the highest SES group in females. For children, data were identified from Spain with the observed intake being lower in the lowest SES groups than in the highest SES groups. Data on iodine status were identified for Spanish adults only: the median UI level in the lower SES group was lower than in the high SES group; the relative difference between two SES groups was above 10%. Both studies for Spanish populations reported intake and status levels below the reference values, indicating inadequate iodine nutrition status.

A recent overview by Mensink et al. (2013) in the Addition of Nutrients to Foods Task Force—ILSI Europe Expert Group on "Mapping Low Intakes of Micronutrients Across Europe" comparing recent nationally representative dietary survey data from Belgium, Denmark, France, Germany, the Netherlands, Poland, Spain, Serbia (Gurinović et al., 2011), and the United Kingdom reported the prevalence of inadequate micronutrient intake in different population groups. A recently published paper by Zimmermann and Anderson (2011) estimates the prevalence of ID in Europe in 2010, based on a systematic review to update the WHO Vitamin and Mineral Nutrition Information System (VMNIS) database. Based on the national median UI concentration, between 2003 and 2010, the number of European countries in which ID was still a public health concern decreased from 23 to 14 countries. Insufficient iodine intakes in school age children are reported to be at 43.6% in Europe; 15.6% in the countries of Central Asia and the former Union of Soviet Socialist Republics (USSR); 11.9% in Eastern Europe, the Baltic States, and Turkey; and 16.1% in Western Europe (Zimmermann and Andersson, 2011). In areas of iodine sufficiency (UI >150 μg/L), the iodine content of breast milk should be in the range of 100–150 μg/L. Studies from France, Germany, Belgium, Sweden, Spain, Italy, and Denmark have shown that mean iodine content in breast milk is <100 μg/L (Azizi and Smyth, 2009).

ESTABLISHING THE MOST ROBUST METHODOLOGY

Intake Assessment

The EURRECA Network systematic literature reviews of micronutrients including iodine were carried out to identify the best methods for assessing intake in the general population as well as in targeted groups with the potential for higher nutritional risk (see also activity 3 in Dhonukshe-Rutten et al., 2013). No studies of relevance to dietary assessment methods for iodine in infants, children, and adolescents were identified (Ortiz-Andrellucchi et al., 2009b). A systematic search for studies addressing iodine intake validation identified seven studies in the adult population (Serra-Majem et al., 2009), one study in the elderly (Ortiz-Andrellucchi et al., 2009c), and three studies in pregnant women (Ortiz-Andrellucchi et al., 2009a). The mean correlation coefficients (CC) for iodine intake comparing food frequency questionnaires (FFQ) to the dietary records (DRs) reference method were 0.60 and 0.44 in the adult population and pregnant women, respectively. For iodine, the mean CC of estimated DR was calculated since there were no studies applying a weighed DR in adults. The mean CC for iodine intake assessment when compared with UI (five studies) as the reference method was 0.47, and the EURRECA Network quality scoring system indicated that food records, dietary recall, and biomarker validation showed acceptable correlation (>0.4) in adults and pregnant women. UIE was used as the biomarker for iodine status in all included studies. Iodine intake is difficult to determine by dietary assessment, since the iodine content of foods is variable and reliable values are not always available in food composition tables. However, 24-hour recall appeared to be the most appropriate method to assess iodine intake.

Status Assessment

A recent evidence-based systematic review conducted for the EURRECA Network assessed the available evidence to determine the usefulness of iodine status biomarkers (Ristic-Medic et al., 2009). The review highlighted four biomarkers, namely, UI, Tg, T_4, and serum TSH that are useful biomarkers of iodine status. The systematic review found that UI (in children and adolescents, and in the general population with low and moderate baseline iodine status), serum Tg (in children and adolescents, but not in pregnant and lactating women), serum T_4 (in children and adolescents, adults, women, and those with moderate baseline T_4 status, but not in pregnant and lactating women), and TSH (in pregnant and lactating women, adult females, but not in children and adolescents or those at moderate baseline TSH status) all appear to be useful biomarkers of iodine status (Ristic-Medic et al., 2009). The EURRECA Network has collaborated with a working party of invited experts to produce a table including a list of potential iodine biomarkers with star rating, indicating usefulness and quality of the biomarkers (http://www.eurreca.org/folders/3772/) along with an eminence-based review paper (Zimmermann, 2008). The group selected several indicators of which UI, serum Tg, and serum TSH are considered by EURRECA experts to be the most valuable for assessing ID and the development of IDD.

Health Outcomes

Important health problems related to iodine intake or status were identified by literature search. The health outcomes chosen were those most relevant to the population group (based on public health reports and the scientific literature, i.e., current evidence of a relationship and the number of preliminary search

hits from online databases, i.e., Medline) and not recently and thoroughly covered by a similar review. Severe ID within populations leads to endemic goiter, hypothyroidism, retardation of growth and development of the central nervous system in children (cretinism), decreased fertility rates, increased neonatal and infant mortality, mental retardation, and an increase of fluid in the tissues (myxoedema; Clar et al., 2002; Wu et al., 2002; Zimmermann, 2009; Laurberg et al., 2010). ID is the main cause of preventable mental retardation in childhood and it is still prevalent in large parts of the world. Healthy women maintain iodine stores of 15–20 mg in the thyroid (Vanderpas, 2006). During pregnancy, to help meet the approximate 50% increase in maternal iodine requirement, women may draw on the significant iodine stores. However, in iodine-deficient regions, women enter pregnancy with already depleted iodine stores and pathological changes including goiter and hypothyroidism may occur that can adversely affect maternal and fetal health (Laurberg et al., 2010). Dietary iodine supplementation can prevent endemic goiter and cretinism in iodine-deficient regions (Delange, 1994; Buyukgebiz, 2006; Zimmermann, 2007, 2009). Early diagnosis and treatment of congenital hypothyroidism prevents severe mental retardation and other neurologic complications (Rovet, 1999). Diagnosis of primary hypothyroidism is confirmed by demonstrating decreased levels of serum thyroid hormone (total or free T_4) and elevated levels of TSH. Neonatal hypothyroidism screening, using TSH levels, has made diagnosis of infants with congenital hypothyroidism possible within the first three weeks of life, which has proven helpful in countries with mild to absent ID (Buyukgebiz, 2006). Children with congenital hypothyroidism should be monitored clinically and biochemically. Clinical parameters should include linear growth, weight gain, developmental progression, and overall well being (Delange, 1994; Zimmermann, 2009). The postnatal effects of ID on cognitive function are much less clear. In adults, ID causes hypothyroidism and increased levels of TSH, causing hyperplasia of thyroid tissue resulting in goiter at iodine intakes below 50 μg/day (Harrison, 1968). As part of the EURRECA systematic review of iodine intake–status–health relationships, generic health outcomes, such as endemic goiter and hypothyroidism for all population groups, and cognitive function and cretinism for infants and children were selected. However, within the published studies, these generic health outcomes are measured in different ways. For example, endemic goiter may be measured using thyroid size (grade or stage, palpitation method), thyroid volume (mL, mean $\pm$ SD, thyroid ultrasonography method), the epidemiological prevalence of abnormal thyroid volume (WHO goal prevalence), or total goiter rate (TGR; WHO/UNICEF/ICCIDD, 2007). In the assessment of goiter size, simplified WHO classifications of the goiter by palpitation was used: grade 0 is defined as a thyroid that is not palpable or visible, grade 1 is a goiter that is palpable but not visible when the neck is in the normal position, and grade 2 goiter is a thyroid that is clearly visible when the neck is in a normal position. Age- and body-surface-area-specific 97th percentiles of thyroid volume (TV; mL) measured by ultrasound were calculated for boys and girls (WHO/UNICEF/ICCIDD, 2007). In an adult population, thyroid enlargement was defined as a TV $>$ 18 mL for women and $>$ 25 mL for men, which corresponds to the mean + 3 SDs in iodine-sufficient populations (Gutekunst et al., 1986).

The WHO recommends that the TGR (number with goiters of grades 1 and 2 divided by total examined) of 5% or more in schoolchildren 6–12 years of age should be used to define severe ID in populations by using the following criteria: if the TGR is less than 5%, it corresponds to iodine sufficiency within the study population: 5.0–19.9% refers to mild deficiency; 20.0–29.9% refers to moderate deficiency; whereas a goiter rate above 30% indicates severe ID (WHO/UNICEF/ICCIDD, 2007). Other health outcomes presented included maternal subclinical hypothyroidism (an increased concentration of TSH in the second trimester), maternal hypothyroxinemia (a free T_4 concentration $<$ tenth percentile at 12-week gestation), adult hypothyroidism defined by elevated TSH (TSH $>$ 4.2 mIU/L), low fT_4 (fT_4 $<$ 10.3 pmol/L), and subclinical hypothyroidism defined as elevated TSH (TSH $>$ 4.2 mIU/L) and fT_4 $>$10.3 pmol/L. The most important manifestations of cognitive function, and impaired physical and intellectual growth as well as hearing deficit were assessed using various methodological tests. In summary, the ways in which the health outcomes were presented in the published papers were so diverse that it was not possible to combine palpitation or ultrasonography methods or different psychomotor tests in a single meta-analysis (EURRECA Network, 2009).

POPULATION-SPECIFIC ISSUES

Iodine intake is required to prevent the onset of subclinical hypothyroidism of the mother and fetus during pregnancy and to prevent the possible risk of brain damage to the fetus (Azizi and Smyth, 2009). The technical consultation (Andersson et al., 2007) proposed to increase the current FAO/WHO reference nutrient intake (RNI) for iodine during pregnancy from 200 to 250 μg/day. A daily intake greater than 500 μg/day would not provide any additional benefit for health and theoretically may be associated with impaired thyroid function. Lactating women were advised to continue to consume 250 μg of iodine/day. The consultation made several specific recommendations concerning requirements, indicators, and strategies to control IDD in vulnerable groups, in pregnant and lactating women, and in children less than two years old. The recommended daily iodine intakes of 220 to 250 μg for pregnancy (Institute of Medicine Academy of Sciences, 2001; WHO, 2007) would correspond to a UI concentration of approximately 135–150 μg/L. In developing countries, in child-bearing age pregnancy, in a 15-year-old girl weighing approximately 50 kg, a daily iodine intake of 220 and 250 μg would correspond to a UI concentration of 185–215 μg/L (WHO, 2007). A study in lactating women in the United States with a median UI concentration of 114 μg/L reported a median breast milk iodine concentration (BMIC) of

155 μg/L (Pearce et al., 2004). The full-term infant's requirement for iodine, based on a balance study by Delange et al. (1984), is approximately 7 μg/kg. It is proposed that if the optimal volume for breast milk excretion is 0.78 L, then a BMIC of 80 μg/L could cover the infant's iodine requirement. The intake required to achieve a positive iodine balance is at least 15 μg/kg/day in full-term and 30 μg/kg/day in preterm infants (Delange et al., 1984). The average nutrient requirement (ANR) for iodine in adult populations, for men and nonpregnant, nonlactating women over 14 years of age, is set at 95 μg/day. There is no evidence to suggest that the average iodine requirement in adults varies with age (Institute of Medicine Academy of Sciences, 2001; WHO, 2007).

COLLATING, SUMMARIZING, AND INTERPRETING SOURCES OF EVIDENCE

Factorial/Bioavailability Approach

For iodine and iodate from salt and supplements, absorption from the gut is high and not modified by food components (Fairweather-Tait and Hurrell, 1996). Under normal conditions, the absorption of dietary iodine is greater than 90% (Vought and London, 1967; Nath et al., 1992). However, absorption can be reduced by the presence of goitrogens in some foods (including thiocyanates from cassava, glucosinolates from cruciferous vegetables such as cabbage, broccoli, cassava, lima beans, etc.) and by the deficiency of other micronutrients, such as selenium (Yang et al., 1997; Kohrle, 1999) or iron (Zimmermann et al., 2000). A EURRECA search for iodine absorption from whole diets indicated that there were limited data for iodine bioavailability and there was a consensus that bioavailability for iodine is generally high (EURRECA deliverable RA3.3-3). UIE is generally used to assess iodine absorption, and previous EURRECA work on status markers had already reviewed the relationship between UI and supplement intake (Ristic-Medic et al., 2009). Iodine bioavailability may be influenced when encapsulation methods are used for iodine supplements, for example, tablets versus gelatin capsules, different coating substances, or the amount of pressure used to form the tablets (Park et al., 1991), however only limited data are available. Iodized oil, intramuscular (i.m.) or oral administration, provides significant and prolonged iodine supplementation without inducing any clinical or laboratory adverse effects. Supplements with iodized oil give effective prophylaxis in iodine-deficient subjects (follow-up—i.m.: 2–3 years/oral: 1 year; Leverge et al., 2003).

For setting recommendations, there are two parts of the factorial approach: the calculation of basic requirements (needs for growth, maintenance, losses, etc.) and the application of a bioavailability factor (see also activity 6 in (Dhonukshe-Rutten et al., 2013). For iodine, bioavailability can be defined as the combination of absorption of dietary iodine and of thyroid uptake, and utilization of iodine (Alexander et al., 1967; Larsen et al., 1981). It is based on the definition that bioavailability should be sufficiently broad to cover changes in absorption or/and excretion attributable to physiologic regulatory mechanisms that maintain and restore optimal homoeostasis. In Europe, it is well established that iodine absorption is approximately 90% and therefore systematic data collection was not undertaken in this area (EURRECA deliverable RA3.3-3). To identify relevant data for a factorial calculation of losses/maintenance/growth, a systematic review of relevant literature was carried out, by searching Medline electronic databases (EURRECA Network, 2010a) and scientific reports on iodine reference values (WHO/UNICEF/ICCIDD, 2007). The EURRECA systematic search enabled identification of relevant studies and data that reported on iodine losses, the maintenance of iodine body pools, and the requirements for the formation of new tissue. Examples of maintaining body pools for iodine identified by the search were thyroidal iodine accumulation, thyroidal iodine turnover, retention of iodine, UI, and fecal iodine loss. Data on micronutrient losses and maintenance of iodine for all population groups included 2 studies in infants ($n = 251$), 4 in children and adolescents ($n = 506$), 11 in adults and the elderly ($n = 4149$), and 2 in pregnant and lactating women ($n = 436$; EURRECA Network, 2010c). Most of the studies were in older adults over 40 years and were usually conducted in adult male population groups with a small number of participants. In adults, thyroid iodine accumulation is associated with a physiological requirement of 91–96 μg/day (Fisher and Oddie, 1969), fecal iodine losses of 27 μg/day (Vought and London, 1964), UIE of 57 μg/day (Vought and London, 1967), and an average sweat iodine concentration of 3.7 μg/dL (Mao et al., 1990). Results from cohort population subgroups show that age- and gender-dependency are important when comparing UI data with the standard reference cutoff for UIE (Als et al., 2000). A balance study in women showed that 11% of dietary iodine was excreted in feces and 89% by UIE (Jahreis et al., 2001).

In children, 24-hour radioiodine uptake was 30% of the total iodine intake of 60 μg/day (Tovar et al., 1968), fecal iodine excretion was 16 μg/day (Vought and London, 1964), and UIE was 50 μg/day (Malvaux et al., 1969). To achieve thyroid iodine accumulation and physiological requirements, uptake by the fetus was 75 μg/day (Delange, 2007). Data from Bakker et al. (1999) showed a lower mean of UIE in thyroid agenesis infants (28 μg/24 hour) compared to euthyroid (46 μg/24 hour) and thyroid dysgenesis infants (38 μg/24 hour). This study is the first to report that the extra amount of iodine excreted in the urine of these euthyroid newborns, compared with thyroid agenesis infants, originates from the major storage place of iodine: the thyroid gland.

There was evidence that reference intervals for UIE specific to each trimester of pregnancy need to be established in order to enable accurate assessment of the dietary adequacy of pregnant populations residing in regions of marginal iodine sufficiency (Stilwell et al., 2008). The EURRECA Network also used a systematic search approach to identify published data for additional iodine requirements in pregnancy. There were 24 studies included which used some of the following indicators: fetal

iodine thyroid content, iodine content in placenta, amniotic iodine fluid content, and fetal thyroid hormone concentrations (EURRECA Network, 2010b, 2010d). Data were also collected for the secretion of iodine in breast milk to inform on the requirements for lactating mothers and their infants. The use of breast milk data to calculate requirements for these population groups is generally considered valid in the absence of other information. Three independent studies (from 2000 onwards) were included from the EURRECA systematic search (EURRECA Network, 2010e) that reported on the iodine content in breast milk (assuming 800 mL/day of milk produced) that comply with findings of the Scientific Committee of Food of the EC and the WHO (EC, 2002; WHO and FAO, 2004).

Intake–Status–Health Relationships

The EURRECA objective was to assess the tripartite relationship between dietary iodine intakes, iodine status, and health outcomes in all population subgroups: infants, children and adolescents, adults and the elderly, and pregnant and lactating women. Systematic searches were conducted, and the resulting references were assessed according to strict inclusion criteria standardized across the priority micronutrients and then tailored to the individual micronutrients. For iodine, intake measures were only considered if suitable for the study design and population groups, in accordance with the best practice for intake assessment established during EURRECA activities (see section 4a). Where status was assessed, only the biomarkers identified as relevant for the different population groups and previously identified as the most robust biomarkers available were accepted (see section 4b). The principal inclusion criteria for iodine were as follows: (1) apparently healthy participants from any population group, including studies of children with goiter or populations from iodine-deficient regions; (2) randomized controlled trials (RCTs) or quasi-RCTs (where placebo-controlled groups are ethically unfeasible), prospective cohort, and nested case–control study designs; (3) assessment of a relationship between iodine intake and status, intake and a defined health outcome (goiter, hypothyroidism, and cognitive function), or status and one of the defined health outcomes; (4) dietary intake assessment meeting the criteria set out in the EURRECA best practice (see activity 3 in Dhonukshe-Rutten et al., 2013), or the WHO criteria for assessing iodine intake (see below); (5) measurement of iodine status using the most robust and sensitive status biomarkers, i.e., UI, Tg, and TSH; and (6) a study duration of at least two weeks (duration for iodine intake to be accurately reflected by status (Zimmermann, 2008).

In addition to the assessment of iodine intake by a robust method, as set out in the EURRECA best practice, the assessment of iodine intake using the WHO specific criteria for calculating iodine intake in epidemiological settings was also accepted (Institute of Medicine Academy of Sciences, 2001; WHO, 2007). This method of population intake assessment is based upon the measurement of mean UI concentration and uses the formula UI (μg/L) $\times$ 0.0235 $\times$ body weight (kg) to calculate daily iodine intake. A median UI of 100 μg/L corresponds to an average intake of 150 μg/day in an adult population.

The systematic searches for iodine, conducted on three databases, resulted in 4070 hits for all population groups. Screening of reference titles and abstracts, followed by full-text assessment of the pertinent studies, resulted in 12 studies that met the EURRECA inclusion criteria for infants, 22 studies for children and adolescents, 16 studies for adults and the elderly, and 16 studies for pregnant and lactating women. For each of these studies, data were extracted and entered into an access database (EURRECA Network, 2010b). Information about study characteristics and study quality was also extracted, and validity of the studies was assessed using a standardized EURRECA system based on study design (Ristic-Medic et al., 2010).

Intake–Status Relationships

A systematic review was undertaken investigating the impact of dietary iodine intake on iodine status biomarkers: UI concentration, serum TSH, and serum Tg. Eight RCT studies met the inclusion criteria for adults and the elderly, 15 for children and adolescents, 8 for pregnant women, and 1 for infants. The meta-analyses showed that iodine supplementation exerts a significant effect on UI levels in children and adolescents (pooled effect size: 0.19, $p < 0.00001$), pregnant women (pooled effect size: 0.62, $p < 0.00001$), and adults (pooled effect size: 0.65, $p < 0.00001$). The effect of iodine supplementation (as iodized oil) on serum TSH levels was significant in children and adolescents (pooled effect size: 0.02, $p < 0.001$) and adults (pooled effect size: -0.08, $p < 0.003$). The meta-analyses showed that iodine supplementation in the form of potassium iodide exerts a significant effect on TSH levels in pregnant women (pooled effect size: -0.18, $p < 0.05$) and adults (pooled effect size: 0.11, $p < 0.001$). For Tg levels, iodine supplementation was significant only in pregnant women (pooled effect size: -0.54, $p <$ 0.00001). Most studies were at a high risk of bias, and there was a large heterogeneity between the studies (EURRECA Network, 2010b; Ristic-Medic et al., 2013).

Intake–Health Relationships

An additional systematic review conducted by the EURRECA Network on iodine health outcomes indicated that thyroid volume, as an indicator of goiter, is associated with iodine intake but the data showed a high degree of heterogeneity. Based on RCT data, the effect of iodine supplementation on endemic goiter was significant in children (7 RCTs, ultrasonography, pooled effect size: -0.10, $p < 0.0001$, $I^2 = 93\%$) and pregnant women (5 RCTs, ultrasonography, pooled effect size: -0.12, $p < 0.002$, $I^2 = 68\%$). There was a high degree of heterogeneity in the data (EURRECA Network, 2010b; Ristic-Medic et al., 2013). In adults, the meta-analyses indicated that iodine supplementation exerts a significant effect on endemic goiter (4 RCTs, palpitation method, pooled effect size: -0.05, $p < 0.02$,

$I^2 = 53\%$) and the incidence of hypothyroidism (6 estimates, but only 2 RCT studies, pooled effect size: -0.25, $p < 0.04$, $I^2 = 0\%$; EURRECA Network, 2010b; Ristic-Medic et al., 2013).

The data available on the relationship between iodine intake and cognitive function often provided test *z*-scores or included surplus data on variance and noncomparable cognitive test data (Ristic-Medic et al., 2010). This was not in line with the EURRECA study search criteria which initially aimed to analyze the data by meta-analysis. Thirteen studies (5 RCTs, 4 cross-sectional studies, and 4 nested case–control studies) were included in the systematic review. In the intervention studies, subjects were given a single dose of iodized oil each year (400–540 mg of iodine), with a follow-up period of 4–22 months. Only one study used daily doses of iodine, supplementing at 150 μg I/day, as tablets of potassium iodide versus placebo tablets, and this intervention was 28 weeks in duration. However, methods to evaluate cognitive function varied between studies, different IQ tests were used in 11 studies and Raven's Colored Progressive Matrices test (RCPM) was used in 5 studies. Only two studies at a low risk of bias were identified. The results from the included RCTs were inconsistent, probably due to high or moderate risk of bias in most of the included studies. The number of included studies for moderate ID was generally small and methodologically weak. Observation studies in severely ID groups indicated a relationship between iodine intake/status and mental impairment (Ristic-Medic et al., 2010). Literature on cognition in relation to iodine intake/status is limited and assessment tests were highly variable between studies. The implementation of a standardized methodology would be recommended to enable comparison between different studies. Data in infant populations were limited, most likely due to the difficulties in measuring health outcomes such as cognition in this population.

Multiple Micronutrients (Interactions)

There are recognized interactions between iodine and selenium arising from their roles in thyroid hormone metabolism (Triggiani et al., 2009). Deficiencies of both micronutrients often coexist, with selenium status influencing the outcome of ID (Zimmermann and Kohrle, 2002; Hess and Zimmermann, 2004). In anemic pregnant women, endemic goiter may exacerbate anemia (Zimmermann, 2006). There was some evidence that chronic ID favors subclinical hypothyroidism and that anemia in goiter patients increased the risk of hypothyroidism (Zimmermann, 2006). The addition of encapsulated iron to iodized salt improves the effectiveness of iodine in goitrous children where the prevalence of anemia is high (Zimmermann, 2006). There is some evidence that intervention trials in iodine and iron-deficient populations have shown that providing iron in conjunction with iodine supplements results in greater improvements in thyroid function and volume (Zimmermann et al., 2000; Eftekhari et al., 2006). Other common deficiencies of micronutrients such as vitamin A, and possibly zinc, may interact with iodine nutrition and status and thyroid function (Hess, 2010). Vitamin A supplementation given alone or in combination with iodized salt can have a beneficial impact on thyroid function and thyroid size (Hess, 2010).

The EURRECA Network did not conduct any specific research into the impact of interactions between iodine and other micronutrients in relation to deriving dietary requirements and recommendations. Limited data indicated that micronutrient interactions in metabolism may influence iodine requirements. For example, iron and selenium deficiencies, which are relevant for Europe, may impair iodine/thyroid metabolism (Hess and Zimmermann, 2004; Triggiani et al., 2009; Hess, 2010). Vitamin A deficiency can act as a goitrogen if concomitant with ID, but is not relevant in the European context (Asia and Africa; Zimmermann, 2007).

Polymorphisms

Iodine is reported to be involved in gene expression and the synthesis of xenobiotic-metabolizing enzymes in the liver. Excess dietary iodine differentially affects thyroid gene expression in diabetes and thyroiditis and may be implicated in autoimmune thyroiditis and insulitis pathogenesis (Swist et al., 2011). Relatively few iodine status-related polymorphisms have been identified to date, therefore iodine was not covered in the EURRECA micronutrient status-genotype database task. Genotype differences that predict differences in requirements have not yet been identified as important at the population level, although genotype may influence the risk of thyroid autoimmune disease in iodine repletion studies.

INTEGRATING THE EVIDENCE

The work presented above illustrated that available evidence on long-term health outcomes in relation to iodine intake is very limited and not suitable for setting recommendations. During the EURRECA workshop in Leiden (the Netherlands, 2011) experts and partners were invited to contribute to the identification and evaluation of all available sources of information that might provide useful data on the relationship between dietary iodine intake and status on a range of selected health outcomes for different population groups. It was agreed that methods for measuring iodine status are adequate and cover most population groups. Factorial estimates for requirements which are used for pregnant and lactating women are generally considered valid. The same estimates are also used for infants because of the lack of alternatives but should not be considered as robust. In conclusion, the group agreed that further work is needed to harmonize iodine fortification legislation across Europe and facilitate the coordination of public health work. In the future, sources of iodine intake should be identified for each country, as within some countries, iodized salt is used by the food industry while others have a tendency to reduce salt intake. In addition, future

research on iodine intake–status–health relationships in infants and the elderly is particularly important, as requirements and health effects in these population groups are lacking.

Scaling and Population Groups

During the EURRECA workshop in Leiden, partners and experts discussed if future research should be done to improve scaling down to estimate the adequate intake for infants. In addition, extrapolation of reference values for middle-aged adults to elderly populations may not be appropriate, although it is done universally. The group agreed that elderly populations may have specific requirements/reference values for iodine because of changes in TSH and thyroid function associated with aging, which could impact on cognition, obesity, and iodine absorption. Vegans were identified as a population at higher risk of low intakes of iodine. Interindividual differences in the thyroid axis may result in differences in iodine metabolism, utilization, and excretion. These factors have not been well studied. However, the main predictor of variable response to different intakes of iodine is the individual's or population's baseline iodine status: deficient individuals or populations will react differently to a high iodine intake than a replete individual or population would. Thus, other recognized determinants of response should be taken into account when evaluating interventions. For example, baseline iodine status and iron and selenium deficiencies are important variables to consider.

RESEARCH GAPS AND PRIORITIES

The EURRECA Network workshop in Leiden along with experts and partners identified six key areas where future iodine research should be focused. These were as follows: (1) iodine intake assessment is needed for all population groups; (2) FFQ for iodine intake in multiple settings should be validated; (3) status assessment methods at the individual level should be addressed; (4) the lack of knowledge on iodine dietary requirements and intake assessment in infant populations should be addressed because their neurodevelopmental outcomes can be impaired irreversibly by ID; (5) the elderly should be considered as a discrete population group due to alterations in iodine metabolism by the aging process; and (6) further research is needed to assess the interactions between iron or selenium deficiency and ID.

Research gaps and priorities were discussed by partners throughout the duration of the network and the need for more RCTs to determine the influence of iodine on cognitive outcomes was recognized. The AR for infants and the elderly remains uncertain. Also, the RNI for pregnant and lactating women was set at 250 μg, which seems to be a management decision based solely on convenience. Hence these requirements could be refined as they are used by many European countries. Identified population groups with no data on intake for iodine were infants (except Norway, France, Finland, and the United Kingdom), lactating women, pregnant women, and low-income groups (except Poland and the United Kingdom).

During the EURRECA/WHO workshop in Brussels (Belgium, 2012), representatives from European (both European Union [EU] and non-EU) Nutrient Recommendation Setting Bodies were invited to test the EURRECA micronutrient requirement process flowchart. Conclusions and comments during the EURRECA/WHO workshop for iodine were as follows: (1) intake assessment methods are too strict for iodine and there is a need to be less strict in the study inclusion criteria used by the EURRECA Network of Excellence. The reason for this is the lack of suitable data in general, iodine studies do not include dietary assessment methods; a useful guide was the epidemiological WHO/IOM (Institute of Medicine) criteria that a UI concentration of 100 μg/L indicated 150 μg/day of iodine intake; (2) specific criteria for determining dietary iodine intake in different countries should be developed due to different dietary habits in some European regions; (3) recommended values for iodine should be specific for different countries due to differences in the prevalence of ID; (4) the EURRECA Network of Excellence should undertake a critical analysis and propose biomarkers which are suitable to determine iodine status; and (5) best practice methodology as proposed by the EURRECA consortium is important for future research.

SUMMARY AND CONCLUSIONS

To date, expert bodies have used physiological or mechanistic (balance and turnover) iodine studies to derive dietary reference values (DRVs) for iodine. The EURRECA Network of Excellence has established that the dose–response relationship can be used as complementary data to that derived from currently used balance studies and repletion/depletion studies when setting iodine recommendations. Clearly, the shape of the intake–status relationship has an important bearing on the predicted ANR estimates using iodine status biomarkers. In populations, median UI concentrations of 100–200 mg/L indicate adequate iodine intake and optimal iodine nutrition. As an indicator of iodine intake, median UI concentration does not provide direct information about thyroid function. However, a low median UI concentration indicates that a population is at risk of developing thyroid disorders. It is important to note that the relationship between iodine intake of the population and the occurrence of thyroid disorders in the population is U-shaped. Reference ranges for thyroid hormone tests (TSH, fT_4) are wide, making it difficult to use them to assess iodine status in relationship to impaired thyroid function. Further RCTs are recommended.

In conclusion by using a series of systematic reviews, we have established that biomarkers are responsive to iodine intake and that ID is associated with impaired cognitive function in children. We have provided some evidence that more adequate iodine intakes have a beneficial effect on thyroid volume and function, but data on the benefits of iodine supplementation are less convincing. The EURRECA Network iodine databases

have the potential to be further used as a valuable resource for a range of expert bodies and groups. Considering the lack of high-quality studies, further research, particularly in the domain of RCTs, is needed to establish a convincing relationship between iodine intake or status, i.e. dose–response relationships, and cognitive function and thyroid disease. High quality prospective control studies across all population groups and life stages which measure relevant long-term developmental outcomes across all levels of baseline iodine intake and status biomarkers are also needed to confirm these results and to generate robust data for setting DRVs for iodine. It is important to note that recommendations to reduce dietary salt intake, to lower blood pressure and improve health benefits, could adversely impact implemented programs of iodized salt for the prevention of IDD.

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ABBREVIATIONS:

AR = Average requirement
ANR = Average nutrient requirement
CC = Correlation coefficients
CEE = Central and Eastern Europe
DACH = countries D-Germany; A-Austria; CH-Switzerland
DRs = Dietary records
DRV = Dietary reference value
EC = European Commission
EFSA = European Food Safety Authority
EU = European Union
EURRECA = EURopean micronutrient RECommendations Aligned
FAO = Food and Agriculture Organization of the United Nations
FFQ = Food frequency questionnaire
ICCIDD = International Council for the Control of Iodine Deficiency Disorders
IDD = Iodine deficiency disorders
ILSI = International Life Sciences Institute
IOM = Institute of Medicine
PRI = Population reference intake
RCT = Randomized controlled trial
RNI = Reference nutrient intake
RDI = Recommended dietary intake
SES = Socioeconomic status
TV = Thyroid volume
TGR = Total goiter rate
TSH = Thyroid-stimulating hormone
Tg = Thyroglobulin
VMNIS = Vitamin and Mineral Nutrition Information System
WHO = World Health Organization
UIE = Urinary iodine excretion
UI = Urinary iodine
UNICEF = United Nations Children's Fund
USSR = Union of Soviet Socialist Republics

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