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REVIEW ARTICLE

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Iodine: Physiological importance and food sources

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Abstract

Iodine is essential for humans who can ingest or inhale different forms of this microelement. Its primary role is to be a constituent of thyroid hormones that control basal metabolism, growth, and development. Iodine deficiency causes major health problems and still persists in the population. During pregnancy, it may endanger neurodevelopment and even the life of the fetus. The objective of this article is to review the physiological importance of iodine, the consequences of iodine deficiency, methods to determine iodine status, recommendations for satisfactory iodine intake and risk limits, data on iodine concentrations in most common foods, as well as procedures that can increase iodine content in food. Iodization of kitchen salt is a method used for almost a century, but newer techniques for the production of iodine-fortified foods have emerged offering additional means to deal with insufficient iodine intake. Biotechnology solutions for food fortification, which include iodine addition during and after plant/animal growth, are reviewed as well. Although the general health situation regarding iodine status has improved over years, iodine deficiency has not been eradicated. Further efforts to create safe and more efficient fortification procedures, focused follow-up programs and healthy nutritional habits are still needed.

KEYWORDS

cycling in the nature, food sources, iodine, metabolism, salt and food fortification

1 | INTRODUCTION

Iodine is an essential microelement for humans. It must be supplied externally through food or supplements. Its concentration in the body primarily depends on the concentration in the ingested food and metabolism, mostly in the thyroid gland where iodine accumulates and becomes a constituent of the protein thyroglobulin (TG). Thyroid hormones are derived from TG: thyroxine (T4) and triiodothyronine (T3). Inadequate iodine intake results in thyroid dysfunction leading to hypo- or hyperthyroidism with potentially severe consequences. Iodine deficiency still remains a global problem (Hatch-McChesney & Lieberman, 2022). Regardless of the worldwide salt fortification program and large improvements in the iodine status in the population, inadequate iodine intake persists in some regions and as a result of specific diets. Dietary education is needed for the effective creation of necessary knowledge and healthy nutritional habits which can ensure individual favorable iodine status. This review article summarizes information on iodine metabolism and requirements in humans, iodine availability in nature and more specifically in food, as well as fortification strategies employed to overcome iodine deficiency.

2 | PHYSIOLOGICAL IMPORTANCE OF IODINE

2.1 | Metabolism of iodine

Several forms of iodine can be taken from the environment—some ingested through food, some inhaled. Iodide (I^-) is almost completely absorbed in the gastrointestinal tract while iodate (IO_3^-) is first reduced to iodide and then absorbed. Absorption of iodide occurs via Na^+/I^- symporter (NIS) (Nicola et al., 2009). Thyroid gland and several extrathyroidal tissues, such as salivary and mammary glands, stomach, and intestine, uptake iodide, also via NIS (Riesco-Eizaguirre et al., 2021). Iodide is oxidized by thyroid peroxidase and incorporated in tyrosine (Tyr) residues of TG. Two iodinated Tyr form T4 and T3 which reside within TG until released upon demand. The expression and distribution of NIS in the thyroid gland are under the control of the thyroid-stimulating hormone (TSH) (Weiss et al., 1984) and iodide itself, as an excess of iodide inhibits its own transport into thyroid cells (Braverman & Ingbar, 1963).

Thyroid hormones in the circulation exist in free, physiologically active form (the so-called free T4 and T3, FT4 and FT3) and are bound to proteins. Less than 1% of total T4 and T3 is found in a free form, while the majority is bound to thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin, which buffer their concentration in blood (Salas-Lucia & Bianco, 2022). The distribution of thyroid hormones between proteins is governed by their affinity for T4/T3 resulting in 75% of hormones bound to TBG, 20% to TTR, and 5% to albumin (Refetoff, 2000). FT4 and FT3 enter cells via specific transporters, they bind to cytoplasmic proteins and further enter the nucleus where they bind to thyroid receptors (TRs). The affinity of TR for T3 is approximately 20 times greater than for T4 (Salas-Lucia & Bianco, 2022). In the nucleus, thyroid hormones affect gene expression but exert some nongenomic effects as well (Davis et al., 2021, 2023). Thyroid hormones control basal metabolism, development, and growth. Apart from being a constituent of thyroid hormones, iodine plays other physiological roles and was recognized as an antioxidant of free radicals, an inducer of the expression of antioxidant enzymes, an activator of apoptotic pathways in neoplastic cells, and a modulator of the immune response (Aceves et al., 2021).

Thyroid malfunctioning affects metabolism and interconnected pathways while iodine deficiency and consequent dysbalance in thyroid hormone synthesis during pregnancy may have adverse neurodevelopmental effects on the fetus including cretinism (Pearce et al., 2016; Woodside & Mullan, 2021; Zimmermann, 2009). Fetal and infant death may result from thyroid malfunctioning. A study by Savin et al. (2001) has shown that the concentration of iodine in the thyroid gland of a fetus increases with gestational age and the survival period postpartum is correlated with the thyroid iodine content of the newborn. Likewise, the concentration of thyroid iodine is correlated with the concentration of T4 and T3 in its thyroid tissue (Savin-Zegarac et al., 2002). Goiter (enlarged thyroid gland) is the most frequent manifestation of iodine deficiency and hypothyroidism in adults.

2.2 | Determination of iodine status

Iodide clearance occurs via kidneys and depends on iodine intake, iodine stores in the thyroid gland, and other factors such as obesity (Moleti et al., 2021). Urinary iodine concentration (UIC) reflects its daily intake and may significantly vary from day to day. The measurement of the concentration of iodine in 24-h urine (UIC) is the most frequently applied method to assess iodine status and is expressed in µg/L. Sometimes it is expressed in relation to the concentration of creatinine in 24-h urine (µg/g). It is suggested to measure urinary iodine in 10 samples from the same individual to reliably estimate his/her iodine status (König et al., 2011). A lower concentration of urinary iodine in a spot sample does not indicate iodine deficiency. Most investigations, however, tend to estimate the iodine status of the population, by assessing a large number of individual specimens (Wainwright & Cook, 2019). Monitoring iodine status is of national importance and there are numerous reports for a certain country or region.

Studies on the association between maternal iodine in urine, dietary intake, and neurodevelopmental consequences on the offspring show no uniform approach in the investigation, as was reviewed by Monaghan et al. (2021). Urin is sampled at different gestational ages (13th–28th week), children are also examined at different ages (4–14 years) and different methodologies are applied to assess their development, behavior, and skills. Some studies showed no correlation between maternal iodine concentration and cognitive outcomes (such as spelling, grammar, reading ability, memory, and motor skills), while others reported better results in children from mothers with higher urinary iodine.

Determination of the thyroid volume by ultrasonography enables the detection of thyroid changes due to hyper- or hypothyroidism. Thyroid size, however, may stay unaltered for a long period of time in spite of deficiency or corrected deficiency, disabling estimation of the current iodine status (Moleti et al., 2021). When using this parameter, the results should be interpreted taking into account age, gender, and body size, as they are influential regardless of the nutritional iodine status (Hegedüs et al., 1983). The measurement of TG and hormones TSH, T4, and T3 offers additional information which takes into consideration iodine metabolism in the thyroid itself (Wainwright & Cook, 2019). Biban and Lichiardopol (2017) reviewed the advantages and limitations of laboratory methods used for the estimation of iodine status.

Another approach to estimate iodine status is to define dietary intake as µg/kg of body mass and it relies mostly on the questionnaire on nutritional habits of the surveyed, the most used being the Food Frequency Questionnaire and Dietary Recall.

Different international authorities have defined daily iodine requirements which vary to some extent. World

Health Organization (WHO) and European Food Safety Authority have summarized them and they are given in Table 1 (EFSA NDA Panel, 2014; WHO, 2007a, 2007b).

Iodine deficiency is diagnosed when UIC is below 100 μg/L in adults, 150 μg/L in pregnant women, and 100 μg/L in lactating women. Increased requirements during pregnancy are associated with an increased maternal need for thyroid hormones and their transfer to the fetus to ensure correct development. Lactating women have the same requirements for iodine as pregnant but excrete iodine via milk besides urine. WHO epidemiological criteria for assessing iodine nutritional status and more close definition of mild, moderate, and severe iodine deficiency are given in Table 2 (WHO, 2013).

According to the European Commission/Scientific Committee on Food, tolerable upper intake levels for iodine are given in Table 3 (WHO, 2007a). Iodine excess is also recognized as an unfavorable condition causing complex and incompletely understood effects, possibly leading to either hyper- and hypothyroidism (Wainwright & Cook, 2019).

2.3 | Adverse situations related to iodine status

Besides iodine deficiency or excess due to nutritional habits, there is a possibility of iodine overload due to nonnutritional reasons: (i) iodine supplements, (ii) thyroid drugs such as amiodarone, which contains approximately 37% iodine by weight (Narayana et al., 2011), (iii) iodinated preparations used in radiological investigations and (iv) iodine-containing anti-septic products.

Some iodine preparations, such as iodinated contrast agents used for radiological examinations (e.g., computed tomography scanning), contain iodine in several thousand times higher concentrations than the recommended maximum daily intake. It was found that these preparations can cause thyroid dysfunction in susceptible persons even after a single exposure (Duborská et al., 2020; Lee et al., 2015).

Sufficient iodine intake is also very important in rare cases when the population or an individual is exposed to radioactive iodine isotopes. ^{127}I is the most abundant

TABLE 1 Daily iodine requirements.

Population group (years)	Recommended daily iodine (μg/day)
Up to 1	90
2–6	90
7–19	150
20–51	150
Above 51	180
Pregnant and lactating women	250

TABLE 3 Tolerable upper intake concentrations of iodine.

Population group (years)	Tolerable daily iodine (μg/day)
1–3	200
4–6	250
7–10	300
11–14	450
15–17	500
Above 17	600
Pregnant and lactating women	600

TABLE 2 Criteria for assessing iodine nutritional status.

Population group	Median iodine concentration in urine (μg/L)	Iodine status
Children above 6 and adults	Less than 20	Severe deficiency
Children above 6 and adults	20–49	Moderate deficiency
Children above 6 and adults	50–99	Mild deficiency
Children above 6 and adults	100–199	Adequate
Children above 6 and adults	Above 300	Excessive intake
Pregnant women	Less than 150	Deficiency
Pregnant women	150–250	Adequate
Pregnant women	Above 500	Excessive intake
Lactating women and children with less than 2	Less than 100	Deficiency
Lactating women and children with less than 2	Above 100	Adequate

naturally occurring iodine isotope and it establishes equilibrium with other isotopes. Due to ion exchange, other isotopes are diluted in a particular environment, including the human body. ^{131}I was the most radiologically important radionuclide released during Chernobyl accident in 1986, exposing thyroid glands to varying doses of radioactivity, even up to 42 Gy. The exposition dose depended on the age of the person, proximity to the nuclear plant, weather conditions, and individual cow's milk consumption (Drozdovitch, 2021). As a consequence, an increase in the rate of thyroid cancer and other thyroid diseases in the population was detected. Sufficient nutritional iodine intake may alleviate the contaminating effect via the isotopic exchange process.

Manufacturers of diagnostic clinical tests may use radioiodine as a molecular marker. ^{125}I is applied for radiolabeling of proteins. Antigens or antibodies labeled with ^{125}I are constituents of radioimmunoassays for the quantitation of hormones, tumor markers, and autoantibodies. Laboratory personnel involved in the production of such assays, as well as in the performance of testing, is exposed to some extent to this radioisotope regardless of the taken safety measures. Sufficient nutritional iodine intake in these persons, most often confirmed as UIC, is a specific preventive measure in such cases (Nedic et al., 2002).

3 | IODINE IN THE ENVIRONMENT

The content of iodine in food depends on the amount of iodine in soil, the proximity of seawater, farming practice, and different programs for sodium chloride (kitchen) salt and food fortification with iodine. In general, iodine cycles in nature establish a dynamic balance between different forms and locations (Figure 1).

The concentration of iodine in the soil varies between soil types, locations, and seasons, due to the application of fertilizers and other preparations (such as iodine-containing compounds used for disinfection), as well as due to the presence of animals. Subclinical iodine deficiencies are often endemic and related to the geochemical environment (Duborská et al., 2021).

Iodine concentration in topsoil is on average 2.5 mg/kg and approximately 10% is soluble in water (Johnson, 2003). Other forms of iodine are recognized as: (i) exchangeable, (ii) bound to carbonates, (iii) bound to metal oxides, and (iv) bound to organic matter (Duborská et al., 2021). The equilibrium between different forms depends on the constituents and pH of the soil. Iodine in the ground originates mostly from sea aerosol and dust, in some cases also from volcanic ash (Šeda et al., 2012).

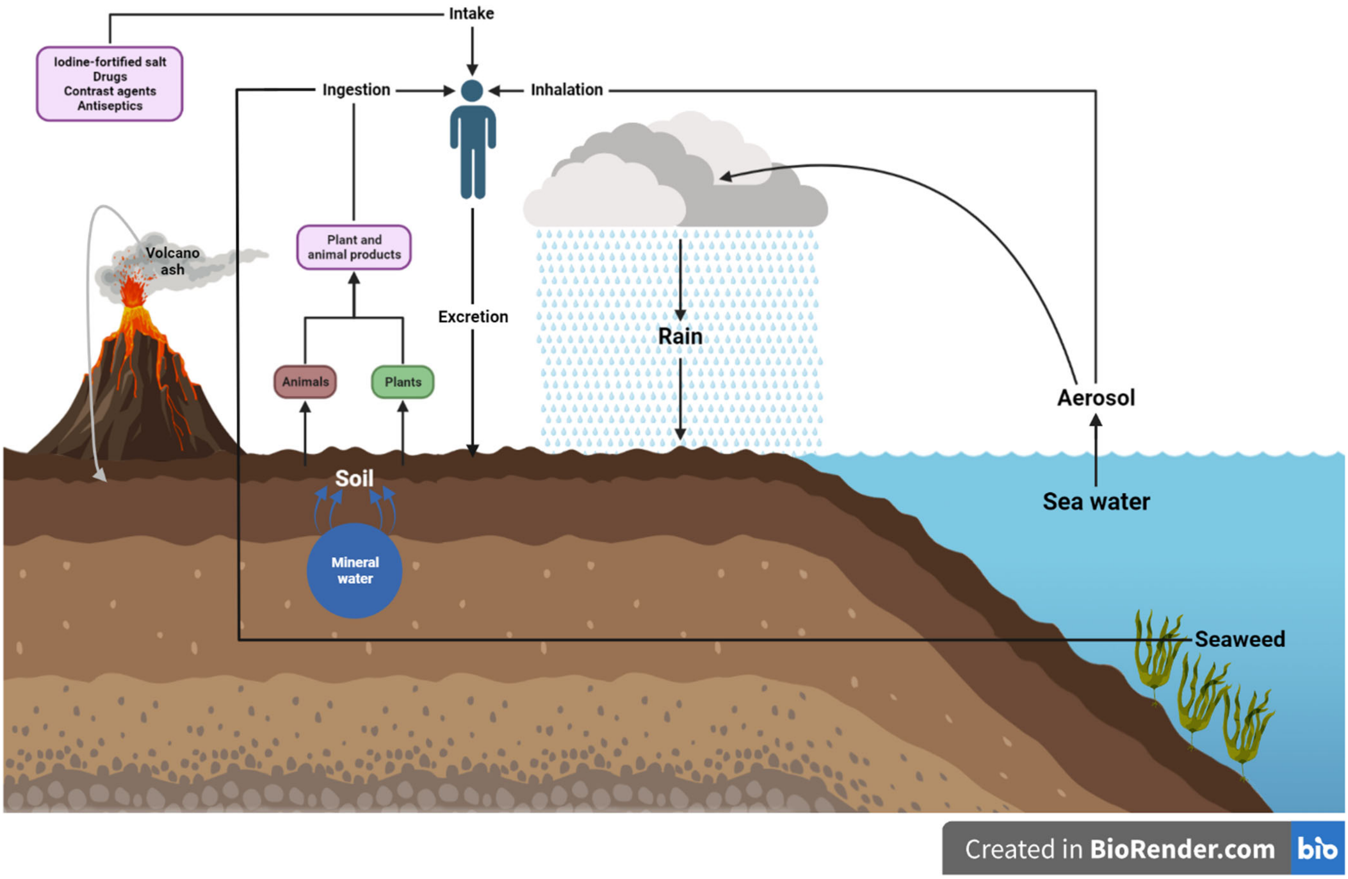

FIGURE 1 Relation between iodine cycling in nature and human intake/excretion.

Iodide and iodate are the most abundant forms present in water while iodine incorporated into biomolecules can be found in sediments. Iodomethane (CH_3I), hypoiodous acid (HIO), and molecular iodine (I_2) are in gaseous form and present in the atmosphere (Duborská et al., 2021). Seawater is the largest reservoir of iodine, which evaporates and, after cycling, returns to water. The concentration of iodine in groundwater can be very high exposing the local population to excessive iodine (Farebrother et al., 2018).

4 | IODINE IN FOOD

4.1 | Iodine in naturally occurring food

Iodine is present in a range of foods, the richest sources are fish, seaweed, milk, and dairy products. Whitefish have more iodine than oily and different species have different content. Most people take iodine by consuming milk and dairy products (BDA, 2016). Average iodine concentrations in some foods are given in Table 4 (BDA, 2016). Meat products may have much more iodine than native meat, up to 400 µg/kg (Duborská et al., 2020). Seaweeds contain high concentrations of iodine, in the range of mg/kg (Yeh et al., 2014) and their excessive consumption (more than once a week) can induce iodine overload.

Most adults having a balanced diet should be able to avoid iodine deficiency. Specific dietary regimes, however, may subject individuals to the risk of insufficient supply. Veganism, for example, is associated with a low intake of various vitamins and essential elements, iodine being among them. An increased prevalence of vegans in developed countries (1%–10% in the European Community) may increase the portion of the population with iodine deficiency and there is a debate if vegans should use supplements (Allès et al., 2017). A systematic review of the adequacy of a vegan diet has shown that iodine intake is low and often below the recommended value (Bakaloudi et al., 2021; Schüpbach et al., 2017).

TABLE 4 Iodine concentration in selected common food.

Food	Average iodine concentration (µg/kg or µg/L)
Haddock	3250
Cod	1920
Salmon fillet	140
Canned tuna	120
Prawns	100
Scampi	940
Cow's milk	250–500 (higher in winter)
Yogurt	330–670 (higher in winter milk)
Cheese	375
Eggs	500 (20 eggs)
Meat/poultry	100
Nuts	200
Bread	140
Fruits and vegetables	37

Iodine deficiency and consequent serious health problems may be relatively easily overcome, or at least improved, by the addition of iodine salts to kitchen salt. This approach is applied worldwide and health effects are monitored by national and international authorities. More recently, food fortification with iodine has emerged.

4.2 | Iodine fortified salt

The salt fortification program was initiated in the 1930s, first through cattle feeds and disinfectants (Phillips, 1997), which significantly increased the iodine content in milk (McKernan et al., 2020). Later on, salt fortification via iodization was introduced as the principle strategy adopted by the WHO to regulate iodine status in the population (WHO, 2007c). As a result, 124 countries worldwide have mandatory legislation for salt iodization and 21 have voluntarily regulations (Zimmermann & Andersson, 2021). Thus, 89% of the population is supplied with fortified salt (UNICEF, 2022). According to the global survey, adequate iodine intake was reported for 118 countries, insufficient for 21, and overdosed for 13 countries in 2020 (Zimmermann & Andersson, 2021). Proper salt iodization is achieved with 15–40 mg/kg iodine (WHO, 2014). WHO recommends iodization of salt taking into consideration approximately 30% loss during storage and transport. Although marine salt has considerable quantities of iodine (on average 14 mg/kg), the amount is insufficient to avoid iodine deficiency. Fortification of marine salt is recommended as well, reaching iodine content between 35 and 90 mg/kg (Lobato et al., 2019).

As iodine is not the only micronutrient commonly found to be deficient in people, a search for biotechnology solutions that enable supplementation of more than one micronutrient in kitchen salt was initiated. Decades have passed since double-fortified salt with iodine and iron was made, and more recently multiple-fortified salts were prepared. The most recently reported is a cost-effective extrusion technology for the simultaneous addition of zinc, iron, and iodine to kitchen salt (Vatandoust et al., 2023). At the moment, a randomized, controlled, community-based trial to examine the effects of quintuply-fortified salt with iodine, iron, zinc, vitamin B12, and folic acid is going on in women of reproductive age and preschool children in India (McDonald et al., 2022).

4.3 | Iodine fortified food

Iodine food fortification is a term that assumes iodine addition to naturally occurring food—during and after plant/animal growth, as well as supplementation to artificially created nutritional items to increase their nutritional value. Examples given here illustrate the most common fortification approaches.

The intake of cow's milk has declined in the last 50 years. At the same time, organic milk and milk-alternative drinks became increasingly popular. However, iodine content is lower in organic than in conventional milk by approximately 25%–40% (Bath et al., 2012) and alternative drinks, such as soya, rice, coconut, and oat milk, have a very low concentration of iodine, approximately 7 μg/L (Bath et al., 2017). Fortified milk-alternative drinks in the United Kingdom have iodine between 250 and 300 μg/L, approaching the concentration of conventional cow's milk (Woodside & Mullan, 2021).

Zaremba et al. (2022) investigated the effect of vegetable impregnation using potassium salts, KI and KIO_3, to obtain iodine carriers. They examined pumpkin, cauliflower, broccoli, and carrot and found that they can all serve such a purpose. Dietary wheat fibers and soy protein were also documented as potential iodine carriers (Szymandera-Buszka et al., 2021). Saha and Roy (2020) demonstrated that iodine can be incorporated into whole rice grains. Exogenous iodine in fish feed during fish production was shown to successfully supplement fish meat (Ramalho Ribeiro et al., 2019).

Iodine is not an essential element for many plants and its concentration is usually low. Biofortification of growing agricultural plants with iodine became attractive (Golubkina et al., 2021). Certain problems, however, are connected with a form of iodine to be added, applied concentration, and a method. Different plant species respond differently to such supplementation (Duborská et al., 2020). For example, KIO_3 application in strawberries under stress conditions increases the activity of ascorbate peroxidase and catalase, and the concentration of glutathione without biomass loss (Medrano Macías et al., 2021). KI and iodo-salicylic acids cause a decrease in ascorbic acid and an increase in dehydroascorbic with no significant effect on catalase and peroxidase activity in tomato leaves (Halka et al., 2020). Thus, iodine supplementation is not just iodine supplementation—it may affect other characteristics of food.

Inorganic iodine forms are transported in plants via sodium-potassium/chloride transporters, while organic iodine compounds utilize amino-acid transporters (Golubkina et al., 2021). A number of plants subjected to fortification with iodine are reviewed in the study of Duborská et al. (2020). The fortification procedure enables an increase of iodine in plant fresh weight several times. For example, the concentration of iodine in celery, after the addition of KI in soil, was up to 160 μg/kg (Hong et al., 2008). It was also shown that fungi, algae, and some plants, such as carrots and sweetcorn, characterized by high vanadium accumulation, may assimilate high quantities of supplemented iodine (Golubkina et al., 2021; Grzanka et al., 2020; Smoleń et al., 2019).

It is estimated that the production of fortified food in the future will mostly depend on the price of the manufacturing process, the willingness of consumers to use that type of food, and their readiness to pay its price. However, although the food fortification program is generally welcome, there is still an insufficient number of trials that follow up with consumers. Producers of fortified food are well aware of the upper concentration limits of various micronutrients, but particular combinations still need additional testing for safety as well as their metabolic behavior.

5 | CONCLUSIONS

Iodine, being an essential exogenous microelement, must be taken regularly. Daily requirements, according to age and physiological status, have been established as well as methods to monitor individual and population iodine status. The composition of different foods with respect to iodine content has been determined and nutritional recommendations are given. Kitchen salt and food fortification programs have been developed to ensure proper iodine supplementation and new fortification practices are under examination. National and international authorities are engaged to follow up on the iodine status in the population. However, in spite of all measures taken, iodine deficiency is still a health problem and further efforts are needed to overcome it.

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CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

ETHICS STATEMENT

None declared.

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