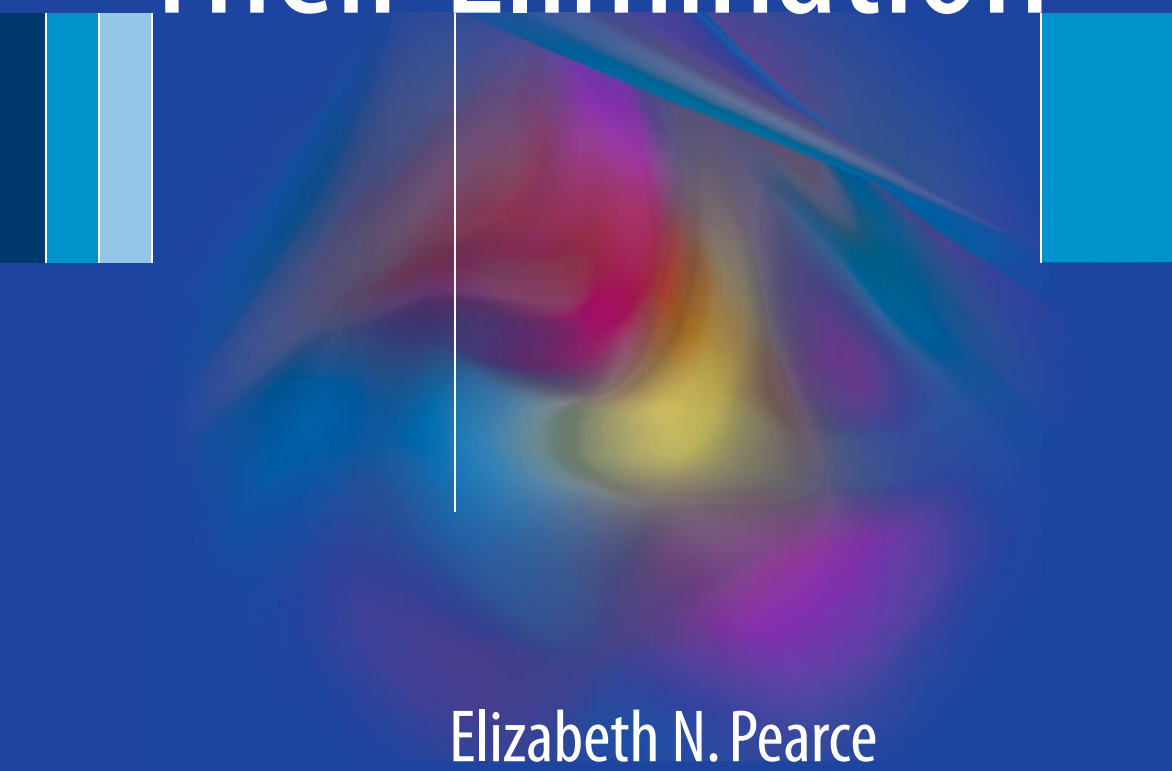
Iodine Deficiency Disorders and Their Elimination



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Preface

Iodine is an essential micronutrient and an integral component of the thyroid hormones, which are required for normal growth and development. The term “iodine deficiency disorders” (IDD), first coined by Basil Hetzel, encompasses a spectrum of adverse health effects including goiter, cretinism, hypothyroidism, growth retardation, and increased pregnancy loss and infant mortality. Thyroid hormone is particularly crucial for neurodevelopment in early life. Insufficient maternal iodine intake during pregnancy may result in neurological and cognitive deficits in children. Despite substantial public health efforts, IDD is currently considered the leading preventable cause of intellectual impairment worldwide.

In ancient geologic times, iodine was distributed evenly over the earth's crust, but in many regions processes such as glaciation and repeated flooding have stripped iodine from the soil. The iodine content of foods depends on the iodine content of the soil in which they are grown, and, therefore, may vary considerably from region to region. The ocean is a rich source of iodine, and seafood, particularly saltwater seafood, is a good iodine source of iodine nutrition. However, there is very substantial variation in the iodine content of fish and seafood across species and locations. Seaweed concentrates iodine from seawater and is, therefore, a good natural source of iodine nutrition although, as for fish, there is considerable variation in seaweed iodine content. The iodine content of meat and milk is increased when livestock feed is fortified with iodine. Iodine may be added to foods as a public health measure, as is the case for iodized salt. It may also be added to the food supply simply to facilitate food processing as in, for example, the use of iodate dough conditioners by some commercial bread bakers in the United States, or the use of iodophor cleansers by the dairy industry. This inadvertent food fortification has been referred to as “silent prophylaxis.”

IDD can never be eradicated, in the way that infectious diseases such as smallpox have been completely and permanently wiped out. However, global IDD elimination – ongoing public health efforts to abolish IDD combined with continuous monitoring to sustain IDD prevention – is an important international public health goal.

This volume is intended to summarize the current understanding of the effects of iodine deficiency as well as iodine excess, and state-of the art methods for IDD

elimination. The history of the discovery of iodine and its effects on human health is fascinating, and is described by Drs. J. Woody Sistrunk and Frits van der Haar in Chap. 1. The accurate assessment of population iodine status is essential for designing IDD prevention efforts. Biomarkers for iodine nutrition and the use of other metrics such iodine intake assessments are discussed by Drs. Zheng Feei Ma and Sheila Skeaff in Chap. 2. Chapter 3 is an up-to-date discussion of the current global status of iodine nutrition, compiled by Gosia Gizak and Dr. Maria Andersson.

Salt iodization and other preventive strategies have substantially improved iodine nutrition worldwide. Consequently, severely iodine-deficient regions are, happily, uncommon at present. The manifestations of severe iodine deficiency are described by Drs. Eduardo Pretell and Chandra Pandav in Chap. 4. In Chap. 5, Drs. Creswell Eastman and Mu Li discuss the milder end of the IDD spectrum, and current data gaps related to how we define and identify mild-to-moderate iodine deficiency. Excessive iodine intake can cause alterations in thyroid function in susceptible individuals; defining safe upper levels for chronic iodine intake has been challenging, as described by Dr. Angela Leung in Chap. 6. The evolution of modern methods for salt iodization, the mainstay of global IDD prevention efforts, is discussed by Dr. Frits van Der Haar in Chap. 7. Optimal methods for the intentional iodine fortification of foods other than table salt, such as the mandated use of iodized salt in bread sold in Denmark, is explored by Drs. Lone Banke Rasmussen and Peter Laurberg in Chap. 8.

Iodine supplementation has been advocated in regions where adequate iodine intakes cannot be assured by dietary intake alone. Both risks and benefits of iodine supplementation, particularly for vulnerable populations such as pregnant and lactating women, are outlined by Drs. Peter Taylor and Onyebuchi Okosieme in Chap. 9. Finally, low-level environmental exposure to chemicals such as perchlorate and thiocyanate, which competitively block thyroidal iodine uptake, appears to be ubiquitous worldwide. There has been recent concern that such environmental exposures might pose a health hazard by inducing or aggravating underlying thyroid dysfunction. This is discussed by myself and Dr. Lewis Braverman in Chap. 10.

The authors of this volume include international experts on iodine nutrition and metabolism and leaders in IDD eradication efforts. I am grateful to my colleagues for their outstanding contributions to this book. It is with both thanks and deep sadness that I would like to particularly acknowledge the contribution of Dr. Peter Laurberg, who died during the preparation of this volume.

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Chapter 1
A History of Iodine Deficiency Disorder Eradication Efforts

J. Woody Sistrunk and Frits van der Haar

Abstract Perhaps one of the most important developments in modern medicine, second only to the development of antibiotics and vaccines, is the development of efforts to eradicate the iodine deficiency disorders. Endemic goiter, the most visible aspect of iodine deficiency, has been apparent in many regions for millennia. Over the course of history, multiple different etiologies and remedies for endemic goiter have been proposed. It was not until the nineteenth century that iodine was identified and proposed as a treatment for goiter. In the early twentieth century Dr. David Marine stated that "simple goiter is the easiest of all known diseases to prevent … It may be excluded from the list of human diseases as soon as society determines to make the effort" [1]. The story of the development of interventions to prevent iodine deficiency can be viewed as a dramatic saga.

Iodine Deficiency in the Ancient World

An understanding of the use of iodine for goiter prevention can be dated back as far as the Chinese emperor Shennong (2838–2698 BC). His book of herbal treatments, *Pen-tsao Ching,* contains a description of seaweed as an effective treatment for goiter [2]. This was written almost five millennia before iodine was isolated by Bernard Courtois [3]. In *Shan Khai Tsing* (A Treatise on Waters and Dry Lands), which dates from approximately 770–220 BC, goiter was attributed to poor water quality, a belief which held firm well into the early twentieth century [2, 4].

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Additional postulated causes of goiter including "deep mental emotions" and "certain conditions of life in mountainous regions" were introduced during the Han dynasty (206 BC–220 AD) and the Wei Dynasty (200–464 AD) [2].

With the advent of a greater, although limited, understanding of the etiology of goiter, new treatments were devised. The Chinese writer Ge-Khun (317–419 AD) clearly described a treatment regimen for goiter that included both Sargassum and Laminaria Japonica Aresch seaweeds [2]. Approximately 1500 years prior to the current use of desiccated thyroid, animal thyroid was used in China for the treatment of goiter, as referenced in the book *Shen Shi-Fan* (420–501 AD). Medicinal use of pig and deer thyroid was also described in *Pen-Ts'ao Kang-Mu*, written by the physician Li Shi-Chen (1552–1578) [2].

Endemic goiter was not limited to China, and therapeutic interventions must have been considered throughout the rest of the ancient world. We know that incantations against goiter are recorded in the Hindu *Atharva-Veda* from around 2000 BC [2]. Egyptian accounts from approximately 1500 BC describe the use of applications of salt in the treatment of neck tumors [2]. Goiter is frequent in pregnant women in iodine-deficient regions, and it is said that in ancient Egypt it was the custom to tie a thread around the neck of young brides; breaking of the thread due to thyroid enlargement was an early sign of pregnancy [4].

The Historical Understanding of Iodine Deficiency in Europe

In Hippocrates' *On Airs, Waters and Places*, from 400 BC, drinking water was considered to be a possible cause of goiter [2]. In the first century AD the Greek physician Dioscorides discussed the use of seashells, plants, animals, and lizard and dog excrement to treat goiter in his work *De Materia Medica* [5]. Around the same time, the Roman poet Juvenal (first century AD) wrote: "Quistumidum guttur miratur in Alpibus?" which can be translated as "Who wonders at a swelling of the neck in the Alps?" [6]. This is remarkably similar to Mark Twain's famous statement in 1880 that "I am satisfied. I have seen the principal features of Swiss scenery – Mont Blanc and the goiter – and now for home" [7]. The first century BC Roman architect Vitruvius wrote, "Aequiculis in Italia et in Alpibus nationi Medullorum est genus aquae, quam qui bibunt afficiuntur turgidis, gutturibus," which is translates as "the Acquiculi in Italy and the nation of the Medulli in the Alps have a kind of water which causes those who drink it to have swollen throats" [6].

In medieval Europe goiter was variously thought to be due to exertion, frequent coughing, consumption of gall-nuts, or the phases of the moon [2]. It was also postulated that goiter could result from difficult labor, prompting the tradition of tying a lace around the neck of women during childbirth [2]. In the twelfth century AD, burnt sea sponge was one of 13 ingredients used in an electuary proposed by Rogerius Salernitanus for the treatment of goiter [2]. During the Renaissance, Paracelsus described goiter, and linked the disorder to deficient minerals in drinking

water [2]. Felix Platter, a Swiss physician, provided the first detailed description of cretinism in 1602: "it is usual that many infants suffer from innate folly. Besides, the head is sometimes misshapen: the tongue is huge and swollen; they are dumb; the throat is often goitrous. Thus they present an ugly sight; and sitting in the streets and looking into the sun, and putting little sticks in between their fingers, twisting their bodies in various ways, with their mouths agape they provoke passersby to laughter and astonishment" [6].

Proposed Etiologies for Endemic Goiter

Opinions about the etiology of goiter varied so widely that in 1867 Saint-Lager compiled a list of 43 different causes of goiter as described by 378 different authors [8]. Nineteen accounts attributed goiter to properties of water including both an excess and deficiency of minerals. Eleven accounts postulated that goiter was due to atmospheric properties such as humidity, temperature, chemical composition, or lack of sunshine. Additional hypothesized etiologies included poverty, faulty nutrition, insanity, poor living conditions, alcoholism, and consanguineous marriage.

It was also suspected that endemic goiter might be due to infection, a concept which proved surprisingly persistent. This theory of an infectious agent was mentioned in Charles H. Mayo and Henry W. Plummer's 1925 book *The Thyroid Gland* [9]. Even as late as the 1960s, Greenwald argued that goiter is caused by an infectious agent: "Is it not possible that the variations in the rate of onset, in the proportion of accompanying cretinism, deaf-mutism and hyperthyroidism, and in the occurrence in infants and in animals (affecting different species in different regions) are due to differences in the strains of the infectious agent? May not the geographic localization be due to the participation, perhaps necessary, of a vector of limited range?" [10].

Discovery and Early Uses of Iodine

In 1811, with France at war with many of its neighbors, the French organic chemist Bernard Courtois was extracting soda from wood ash to manufacture saltpeter to concoct gunpowder for Napoleon's army. Because wood ash was in short supply, Courtois used soda ash from burnt seaweed (kelp) instead, which left a crust of corrosion on the bottom of his copper extraction vessels. When he attempted to remove the deposit with sulfuric acid, an intense violet-colored vapor arose and condensed on the cooler upper part of the vessel in the form of metal-like crystals. Courtois proceeded to investigate the lustrous substance but he ran out of funds and sent some specimens to the prominent French scientist Joseph Louis Gay-Lussac, who identified it as a new chemical element, naming it "iode" from the Greek word for violet. After Napoleon's war, the Institut de France honored Courtois in 1831 for his

discovery with a prize of 6,000 francs. Despite an increase in demand for iodine when more became known about its medicinal properties, Courtois did not succeed in his venture of setting up a business of marketing iodine and iodine compounds and he left no assets for his widow and son at his death in 1838 [11].

Quite soon after Courtois isolated iodine, iodine was first used for the treatment of goiter in 1819 by J. Elliotson at the St. Thomas' Hospital in London. This use was initially suggested in 1816 by Dr. William Prout, a British physician-chemist; however Prout did not publish this recommendation until 1834 [12]. In 1820 the Swiss physician Jean Francois Coindet started using an oral solution of iodine in alcohol on his goitrous patients in Geneva [13, 14] and observed that the large, long-standing goiters in many patients began to soften and shrink within a week and completely disappeared after 6–10 weeks of daily therapy. Coindet's work quickly became well known based on a series of publications in which he proposed use of iodine not just as a cure for goiter but also as an aphrodisiac, and Coindet himself estimated that by 1821, a thousand people had been treated with iodine [15]. Because the iodine dose used was 2,500–5,000 times optimal, side effects occurred and Coindet attributed the tremor, palpitations and weight loss in some of his patients to excess iodine. Coindet, the editor of the Bibliothèque Universelle, published a stern warning to his readers: "We have been sent various observations concerning the danger of the use of iodine, even when prescribed by careful physicians and with the appropriate precautions. From these observations it appears that some constitutions are severely affected at the same dose that others take without any untoward effect." The iodine treatment of goiter with high iodine doses, pioneered by Coindet, was doomed to failure given the state of knowledge at his time and, even though Coindet insisted that his prescription was safe if cautiously applied and closely monitored, it was fiercely opposed by many who deemed iodine poisonous. Hence, the new therapy fell into disrepute and generated an acrimonious, long-lasting debate on the safety of iodine. It was said that "Coindet would not leave his house for fear of being stoned in the street by his poisoned patients" [7].

In 1825, based on Coindet's work, Commissioner David Scott, the British ruler of Assam, India, described his use of iodine to treat goiter: "My patients are all alive and well, and have not suffered any inconvenience from the use of the iodine, besides occasional squeamishness after taking their dose. The first case was that of Gujra … his neck was so much enlarged as to impede respiration, and induce a sense of suffocation, on his running or taking any violent exercise. This inconvenience has now entirely ceased, and the enlargement of the throat is reduced to about one fourth of its original size. He has taken, not very regularly, for almost two months, twenty drops twice a day of a solution of ten grains of iodine in two oz. of spirits of wine." [16].

The idea of using iodized salt for goiter prophylaxis was devised in 1831 by a French agricultural chemist Jean-Baptiste Boussingault during his work in New Grenada, present day Colombia. Boussingault collected naturally iodine-containing salt from the goiter-free villages in Antioquia Department and introduced it in the goitrous localities around Bogota [17, 18]. While he did not suggest that low dietary

iodine was the cause of goiter, Boussingault was the first to recommend the introduction of iodized salt into the common food supply. The authorities of Columbia did not act on this advice, however. In 1846, building on the work of Coindet, Jean Louis Prevost conducted dose titration studies, noting efficacy from even very small doses of iodine [19]. In 1849 Jules Grange misidentified the cause of endemic goiter as excess magnesium in drinking water, but suggested to the French Academy of Sciences that kitchen salt should be iodized at the ratio of 1:10,000 to prevent the effects of magnesium excess [20, 21].

That endemic goiter is associated with low environmental iodine was discovered by the chemist Caspar-Adolphe Chatin [22], director of the School of Pharmacy in Paris, who in 1851 published the findings from a series of comparative surveys in different areas of Europe and demonstrated an ecological co-occurrence across areas between endemic goiter and the iodine content in air, drinking water, soil, vegetables and dairy products. Chatin then proposed supplying iodized salt in the highly goiter-affected areas of the French Alps, but this failed to be endorsed by the French Academy of Science who considered his goiter association theory inconclusive. Despite the skepticism of the French Academy of Science, Boussingault and Chatin's work generated several initiatives during the next decades to reduce goiter in school children and adults by the introduction of iodized salt. For example, distribution of iodine tablets and iodized salt in iodine deficient regions of France was described in *The Lancet* in 1869 as part of a public health intervention designed to reduce goiter rates (which also, due to a lack of understanding of endemic goiter etiology, included such items as tree felling and draining of wet streets) [23]. However, because the iodine levels in the salt supplies were 5–10 times higher than at present, consequences of iodine excess such as those noted earlier by Coindet were not uncommon and so the strategy of goiter prophylaxis by supplies of iodized salt fell into discredit and, ultimately, petered out.

With ongoing time, the interest in using iodine to treat and prevent goiter was revived by additional scientific discoveries. Near the end of the nineteenth century, German and British physicians showed that the thyroid gland contains iodine and then successfully used the gland's extract in the treatment of adult goiter and myxedema. In 1895 Eugen Baumann was the first to demonstrate the iodine content of the thyroid after isolation of a compound he called "iodothyrin" which contained 10% iodine [24]. With the studies of the chemical composition and structure of the substances isolated from the thyroid by Oswald in 1899 [25], the isolation of crystallized thyroxine by Dr. Edward Kendall in 1919 [26], and the synthetic preparation of thyroxine by C.R. Harington [27], it became clear that iodine was a critical component of thyroid hormone. Next, during the early twentieth century, nutrition scientists in America and Germany demonstrated that even a tiny shortage of certain dietary substances, subsequently named vitamins and minerals, can cause disease. The combination of these new insights led to an increased appreciation by health scientists and experts for Chatin's finding of the association of endemic goiter with low environmental iodine exposure [28].

From Knowledge to Practice

In his speech at the annual meeting of the Medical Society in 1914, the Swiss physician Heinrich Hunziker-Shild from Aldiswil suggested that goiter was an adaptation of the thyroid gland to low iodine intake from the diet [29] and ventured further by saying that "We should endeavor to provide a population with sufficient iodine that prevents the natural enlargement of the thyroid gland. The recommended best and simplest way to achieve this is by mixing the smallest required amount of iodine into common salt." Hunzicker's lecture was followed by a report in 1918 of the Swiss physician Otto Bayard from Zermatt of a dose-response study of the effect of iodized salt supply on endemic goiter of the inhabitants of Grachen, an Alpine village near the Matterhorn. Meanwhile, during 1917–1919, the American physicians David Marine and O.P. Kimball conducted the first case-control study of iodine supplements among adolescent schoolgirls in Akron, Ohio [30]. Bayard in Switzerland demonstrated that the addition of ±30 μg dietary iodine per day with iodized salt for 1 year led to a significant reduction of goiter size among the villagers of Grachen [31]. These original experiments on ways to address endemic goiter established the prophylactic efficacy of iodine, the nutrient discovered by Courtois a century earlier.

United States

In 1905, after his medical studies at Johns Hopkins University, David Marine started working as resident pathologist at Lakeside Hospital in Cleveland, Ohio. At Johns Hopkins, where the previous theory of iodine deficiency from Coindet had been discarded as erroneous, Marine had been taught that goiter was caused by an unknown parasite. On the day he was to meet his new mentor, a bacteriologist, he was walking to work and noticed that the streets of Cleveland were full of both women and dogs with visible goiter [32]. Simple, or common, goiter and its associated disorders had long been recognized as a serious problem among people in the Great Lakes basin, especially in the Upper Peninsula of Michigan and the adjacent Wisconsin area. Marine's initial studies suggested that goiter represented a compensatory reaction to iodine deficiency. By comparative studies of the cellular makeup and tissue composition of thyroid glands from dogs with and without goiter, Marine surmised a critical need to understand whether the low iodine levels in enlarged thyroid glands were caused by a deficient dietary intake or by an inefficient uptake by the gland [33]. Invited in 1909 as an expert adviser to investigate suspected thyroid carcinomas in farm-raised trout (a carnivorous fish), Marine dismissed the suspicion of cancer and then documented in detailed reports [34, 35] that adding Lugol's solution[1] to the hatchery water or changing the trouts' regular feed from

[1] Lugol's solution consists of a mixture of potassium iodine and elemental iodine.

chopped-up hog's hearts and livers to fresh sea fish successfully prevented the development of goiter and restored the normal growth of the trout. Marine's final publication on fish in 1914 [36] formulated a link with diet by stating that "incomplete diet was the most important factor in bringing about a fault of nutrition, which stimulated the thyroid to compensatory overgrowth," a statement remarkably similar to the proposition by Hunzicker of the same year that goiter was an adaptation to low dietary iodine intake.

As part of his clinical duties, Marine used iodide syrup to relieve children who were suffering from simple goiter. After failing in a first appeal to the school authorities in his home city of Cleveland, Marine started collaborating with Oliver Perry Kimball, at the time a second-year medical student. Together with Kimball, who had worked as a teacher in Akron prior to starting medical school, Marine was able to obtain consent from the school board in Akron for the conduct of a community trial with iodine supplements for goiter prophylaxis. Akron school superintendent H.V. Hotchkiss had received his Ph.D. from Johns Hopkins. Marine later reminisced "He asked what school I was graduated from, and I told him Johns Hopkins … He sort of put his arm around me and said "Same school for my Ph.D., and I know you're not a damn crook" [32].

Schoolgirls were selected because goiter was more common in girls than boys. Pupils from the 5th to 12th grade (i.e., 10–18 years old) were separated into an experimental group of girls whose parents had given permission and a control group of those girls whose parents did not give consent for treatment. Every 6 months during the period April 1917 to October 1919, girls in the experimental group were given a 200 mg solution of sodium iodide (170 mg iodine), divided into 10 daily doses over 2 weeks. Although this study had a major impact on world health, it was not particularly well designed by modern standards. It had no ethics committee approval of any kind, no randomization, no blinding, no progress reports, there was overt selection bias, and the whole study was carried out by a 4th year medical student while David Marine was serving in World War I. Similar to the trout studies, Marine and Kimball published their findings of changes in goiter size in the girls of Akron in a series of meticulously detailed papers. A comparative data table in their final report [37] summarized the striking benefits of treatment: Among the 2,190 goitrous girls in the treatment group, the goiter size decreased in 60.3% (773), while a decrease in goiter size was documented in only 10.4% (145) of the 1,395 untreated girls with goiter at baseline. Conversely during the 2.5 year period, the thyroid gland enlarged in 27.6% (347) of 1,257 control girls who were initially goiter-free, while in the 908 treated girls without goiter at the start, only 0.2% (2) had developed an enlarged thyroid at conclusion of the trial. In their writings, Marine and Kimball emphasized the value of iodine to prevent goiter and remarked that this should ideally take place already before the youngest age of the girls in their study. They also repeatedly stated that "the disease is as easily prevented in man as in fish or in domestic animals."

Even while questions remained regarding the exact etiology of endemic goiter, the findings of Marine and Kimball represented a clear call for prevention. Because a massive scale-up of individual treatment would be exceedingly burdensome, prevention of the wide-spread goiter burden suggested the need for an approach that

provides iodine throughout society in an amount that the thyroid gland of the recipients can store without excessive stimulation. The idea of using common salt for this purpose was well-known from history and similar efforts concurrently ongoing in Switzerland. While Marine and Kimball continued working on improved supplementation methods, the critical impetus toward the adoption of salt iodization for the delivery of additional dietary iodine came from David Murray Cowie, professor of Pediatrics at the Medical School of the University of Michigan in Ann Arbor [38]. In the course of 1921, Cowie initiated a number of informal discussions on the feasibility of a law on salt iodization with Michigan state attorneys and senators and then in 1922, he persuaded the Michigan State Medical Society to set up an Advisory Committee, with an aim to focus on the prevention of simple goiter. The resourcefulness of Cowie was apparent by his inclusion of an advisor, named William Hale, from the Dow Chemical Company of Midland, Michigan. A chemist by profession, Hale produced the first iodized salt in America in 1923 with the use of Diamond Crystal and Morton shaker salt. He reported to the Committee that sodium iodide levels in salt up to 1 per cent were barely noticeable from the taste and did not change the color of the product. Hale further ascertained that such small percentages of sodium iodide in iodized salt had no effect on the taste or utility of butter, meat and starch products, and no deleterious effects in the tanning of animal hides.

After studying and reviewing a set of scientific questions on the effects of iodine on hyperthyroidism, data on the incidence of goiter and associated deaths in Michigan, and measurements of the iodine contents of drinking water, soils and vegetables in Michigan, it appeared at the 2nd "Iodized Salt Committee" meeting in September 1923 that all members were in favor of a bill to mandate the iodization of common salt to protect all citizens from goiter. At Cowie's invitation, an attorney of the Consumer Power Company named Clyde J Holmes attended in this meeting to give advice on important legal and strategic matters. Holmes disagreed with the Committee's position and argued that many people would oppose a dictate from the state on the type of salt which could be served at the dining table and others, due to suspicion that iodine was harmful or deadly, would be afraid to consume iodized salt. Referring to the high interest in the country in good health through proper nutrition and suggesting that manufacturers would have an incentive to supply healthier foods, Holmes stated his confidence that the salt manufacturers could be convinced to provide uniformly well-iodized salt on voluntary appeal if the state mounted an education campaign with support from the medical profession. Cowie, who had initially planned for the mandatory option, appreciated the clarity of Holmes' reasoning and, due to the political nature of a decision related to the common American inclination toward individualism, fundamental rights and distrust of authorities, Cowie adjusted his views and started steering the Committee in the direction counseled by Holmes.

With support of the staff at the University's extension division, later joined by a large number of state health department extension workers, a massive number of presentations on the benefit of iodized salt were organized state-wide with Cowie's leadership and technical input, starting in 1923 and running into 1930. Salt companies' advertising (e.g. "Children are becoming more healthy and vigorous – Morton's

Iodized Salt Prevents Goiter") also helped to spread the public health message about the benefits of iodized salt. With encouragement and, finally, formal endorsement from the State Medical Society, Cowie also started collaborating with a range of companies who had their salt markets in Michigan, patiently proceeding step-by-step through the misperceptions, financial objections, and hesitant changes in the habits of the salt manufacturing and supply sector, in the end converting all the companies to put iodized salt on the shelves of the groceries in Michigan from May, 1924 on. Only 6 years later, in 1930, the ratio of sales of iodized salt to plain salt in Michigan had reached 8:1. Of particular note was the role of the Morton Salt Company, a major American manufacturer with sales networks throughout the United States. Initially resistant due to a misunderstanding that it had to separate its salt destined for Michigan from their nation-wide supply, Morton's attitude turned around when the Secretary of the Michigan Salt Producers' Association started suggesting that all of their members should supply iodized salt a much larger market than Michigan alone "as a means of public service and delivery of a product that consumers see as improved and desirable." After the American Medical Association's Committee on Food endorsed the nation-wide extension of iodized salt in 1934, Morton developed its brand imprint "When it Rains it Pours" and expanded the deliveries of round-can shakers with free-flow iodized salt throughout the markets in America. Simple mantras like the one that appeared on a button from the Michigan Child Health Campaign of 1937–1938: "Save your child from goiter" likely added to the success and acceptance of the widespread use of iodine prophylaxis. The share of iodized table salt in the US households increased and remained quite steady at ±65% for decades, although most recent sales data [39] suggest a downward trend towards 50%.

Other Early Twentieth Century Iodine-Containing Goiter Remedies in the U.S.

Parallel to the development of iodized salt, the use of iodine in the prevention of goiter in the United States became a tool for many physicians and companies marketing what we would now consider medical quackery. In 1916, predating the Marine/Kimball study by 1 year, Frederick C. Werner of Watertown, Wisconsin, applied for and was granted US Patent # 1,190,831 for a goiter necklace which purported to generate a galvanic current on contact with the skin. The patent stated that "… the wearer can apply the treatment with a minimum discomfort and inconvenience." The necklace did contain "mercurous iodid" that may have been the major active ingredient, with or without additional benefit from the galvanic current [40].

By 1924, pharmaceutical companies such as Abbott Laboratories sought to be a part of the goiter prevention hoopla, promoting "Cocoa Calcidin," chocolate-flavored tablets containing sufficient iodine to prevent goiter. At least two varieties of goiter-preventing chewing gum were sold. Goiter Gum, described as an "anti-goiter gum" was copyrighted in 1931 with the slogan, "A stick a day keeps goiter away." Iodigum

carried the simpler slogan, “A preventive for simple goiter.” Some pamphleteer physicians likely utilized iodine in their products before acceptance by the rest of the medical community. Physicians like A.A. Rock of Milwaukee, Wisconsin promised “goiter cure without a knife.” William Thompson Bobo, MD, of Battle Creek, Michigan, demonstrated that goiter treatment was big business, claiming to have treated 200,000 cases with a mail-order product which promised “Goitre removal at home without Operation or Danger.” Among other causes of goiter, Dr. Bobo described “fright, sudden great grief, continual worry, or severe or prolonged mental strain and shock.” He also stated that “school teachers and expert criminologists likewise became interested when it was learned that much backwardness in children and numerous instances of lawbreaking could be traced to thyroid trouble.” Despite the 40 pages of incredible testimonials in Dr. Bobo’s manifesto, iodine was not mentioned. One wonders whether iodine may have been the secret ingredient in Dr. Bobo’s goiter ointment [41]. One can only imagine what Will and Charlie Mayo, George Crile, and Frank Lahey must have thought, reading the Saturday Evening Post by the light of a fire on a cold winter night, wondering if these ads for the “goiter cure” would impact their surgical volumes.

Switzerland

The grave devastation from iodine deficiency in Switzerland has long been remarked upon in historical accounts of many early travelers. Population-based surveys in many Swiss cantons around 1850 yielded astonishing numbers of inhabitants affected by goiter and associated symptoms, in particular deaf-mutism and intellectual disabilities, i.e., cretinism. A monograph in 1883 by Heinrich Bircher, a surgeon at the University of Bern [42], summed up all the data and described a close existing association between the prevalence of goiter in males at recruitment age and the concurrent rates of deaf-mutism and cretinism across the towns and villages of Switzerland. Bircher calculated that 24.5 per 10,000 of all Swiss citizens had deaf-mutism, i.e., three times the rate in any other European country. Clearly, the burden of goiter and its related neurological disabilities on the Swiss population was far beyond trivial. However, the state of scientific knowledge about the cause continued to vacillate at that time across a range of theories of environmental and infectious factors. In 1907, inspired by the surgeon and later Nobel prize-winner Theodor Kocher, a Committee for the Study of Goiter was formed with the purpose of stimulating a coordinated effort to ascertain the underlying cause and devise a remedy. In addition to a series of animal studies, the Committee succeeded in convening an ever-growing number of scientists across all of Switzerland in the generation of a large number of canton-wide surveys, which allowed the testing of the various competing theories and eventually led to the common acceptance of Hunziker’s postulate that a shortfall of iodine in the common diet was to blame. The time had come to test Hunzicker’s proposed solution in actual practice.

Each of the 25 cantons in Switzerland had its own salt monopoly, in which the canton health authorities decided on the origin and type of salt permitted within its boundaries. In 1921, a chief surgeon named Eggenberger started campaigning for goiter prophylaxis with iodized salt by giving evening lectures in the communities of his canton Appenzell-Ausserrhoden. He collected a total of 3,480 signatures for a petition to the canton government, who permitted the supply of iodized salt at 10mg potassium iodine per kg (7.5 mg iodine per kg salt). Together with members of his family, Eggenberger produced iodized salt by the method of hand-mixing of Bayard and, 1 year later, compared families who used this salt on regular basis with the families who did not. The contrast was spectacular: newborn goiter disappeared entirely, no more cretins were born, and the existing goiters in children reduced in size or disappeared altogether [7, 43]. The Committee for the Study of Goiter had meanwhile been succeeded by a Swiss Goiter Commission, with most Swiss scientists engaged in goiter research as members. This Commission, after reviewing the work of Bayard, Hunziger and Eggenberger, advised the Federal Office of Health in June 1922 that all the cantons in Switzerland should permit voluntary supplies of salt, iodized with 2.5–5 mg KI per kg. While some Commission members stayed opposed and a few cantons remained reluctant for a long time, the supply of iodized salt as principal strategy to improve the iodine intake of the population has been at the core of the Swiss national iodine deficiency disorders program since 1922 [44], the time when the United Swiss Rhine Salt Works, exclusive supplier in 24 of the 25 cantons in Switzerland, took up the wet-spraying method of iodized salt production.

Conclusions

Over the course of history, multiple different etiologies and remedies for endemic goiter have been proposed. A period of rapid scientific discovery, starting early in the nineteenth century, culminated in our modern understanding of endemic goiter as a manifestation of iodine deficiency, and in the development of salt iodization as a preventive measure.

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Chapter 2
Assessment of Population Iodine Status

Zheng Feei Ma and Sheila A. Skeaff

Abstract Iodine deficiency is one of the most common micronutrient deficiencies, affecting 30 % of the world's population. Iodine status in a population is usually assessed by urinary iodine concentration (UIC) in spot urine samples; UIC is associated with large inter- and intra-individual variation. Other biomarkers including thyroid-stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4) can be used to assess iodine status, however, the normal reference ranges are wide, making it difficult to use these to detect mild iodine deficiency. Another thyroid-specific protein, thyroglobulin (Tg), is considered to be more sensitive to improvements of iodine status in mildly iodine deficient populations but validated cut-offs for adults are lacking. Dietary assessment methods often underestimate iodine intake because of the difficulty in accurately quantifying the contribution of iodized salt to total iodine intake. Future research should focus on the development and validation of more accurate and reliable biomarkers, particularly for individuals.

List of Abbreviations

CV	Coefficient of variation
FFQ	Food frequency questionnaires
FSANZ	Food Standards Australia New Zealand
ICCIDD	International Council for the Control of Iodine Deficiency Disorders (now known as Iodine Global Network)
I/Cr	Iodine-to-creatinine ratio
NZ	New Zealand
Tg	Thyroglobulin
TgAb	Thyroglobulin antibody
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone

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T3	Triiodothyronine
T4	Thyroxine
UCr	Urinary creatinine
UIC	Urinary iodine concentration
UIE	Urinary iodine excretion
UNICEF	United Nations Children's Emergency Fund
WHO	World Health Organisation

Assessment of Iodine Status

Iodine deficiency is one of the most prevalent micronutrient deficiencies, affecting 30 % of the world's populations. Iodine deficiency causes adverse health consequences that are collectively known as iodine deficiency disorders (IDD). In order to reduce the risk of IDD, it is important to assess the iodine status of a population using a number of biochemical, clinical and dietary indices.

Biochemical Assessment

The most commonly used measures of iodine status in a population are biochemical. Urinary iodine concentration (UIC) can be determined in urine samples and thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4) and thyroglobulin (Tg) can be measured in blood samples.

Urinary Iodine

The measurement of UIC is recommended by WHO/UNICEF/ICCIDD [1] to assess the iodine status in a population. UIC is a good biomarker of short-term iodine status (i.e. days) [2] because ~90 % of dietary iodine is excreted into the urine [3], therefore, a higher excretion of urinary iodine is indicative of a high recent dietary iodine intake and vice versa [4].

UIC can be determined in either 24-h or spot urine samples [1]. A 24-h urine sample is suggested by some to be the "reference" standard because the urinary iodine excretion (UIE) calculated from a 24-h urine sample represents daily iodine intake and takes diurnal variation into account [5]. However, UIE varies considerably from day to day due to changes in iodine intake [6] and can also be influenced by other factors such as renal clearance and urine volume [7]. Johner et al. [7] reported a positive association between UIE and urine volume. Therefore, a single 24-h urine sample is insufficient to reliably assess individual iodine status [6, 8], however, the collection of multiple 24-h urine samples is associated with a large respondent burden. Another issue with 24-h urine samples is the completeness of the sample (i.e. missing voids) [9]. Compliance can be checked by the recovery of *para*-aminobenzoic acid, although the use of *para*-aminobenzoic acid is associated

Table 2.1 Cut-offs of median UIC to determine iodine status in a population

Median UIC (μg/L)	Corresponding iodine intake (μg/day)	Assessment of iodine status
<20	<30	Severe deficiency
20–49	30–74	Moderate deficiency
50–99	75–149	Mild deficiency
100–199	150–299	Adequate/optimal
200–299	300–499	>Adequate
>299	>499	Possible excess

Adapted from Ref. [1]

Table 2.2 Cut-offs of median UIC to determine iodine intake in pregnant women

Median UIC (μg/L)	Assessment of iodine intake
<150	Insufficient
150–249	Adequate
250–499	More than adequate
500≥	Excessive

Adapted from Ref. [1]

with its own errors [10]. For example, of 156 Danish adults who were asked to collect one 24-h urine sample, 18 % of the participants did not complete the urine collection when the completeness of the sample was assessed using the *para*-aminobenzoic acid method; incomplete 24-h urine collections are typically excluded from the dataset [11].

The collection of casual or spot urine samples is most commonly used in population studies because they are relatively easy to obtain from most age groups [1]. Even in young infants, a validated method has been developed for spot urine sample collection using pads [12]. According to WHO/UNICEF/ICCIDD, spot urine samples have been shown to give a satisfactory evaluation of iodine status in populations [1]. The median UIC of spot samples is used to categorize the iodine status of a population. Iodine status in a population is considered sufficient when the median UIC is ≥100 μg/L and <20 % of population has a UIC <50 μg/L (Table 2.1) [1]. For pregnant women, a median UIC of ≥150 μg/L is considered iodine sufficient (Table 2.2) [1]. It is important to note that the cut-offs of median UIC are population-based and derived from the UIC data of school-aged children whose urine volume is approximately 1 L per day [13]. Zimmermann and Andersson [13] advocated that the median UIC cut-off to determine iodine sufficiency in groups of adults should be lowered to 60–70 μg/L because adults have a higher mean urine volume of >1.5 L per day [14]. Moreover, the use of median UIC does not quantify the proportion of individuals who have either inadequate or excessive iodine intakes [15].

Similar to the UIE from a 24-h urine sample, UIC has high daily variation in individuals [16]. Thus, the UIC of a spot urine sample from an individual is not suitable to assess individual iodine status [5]. Busnardo et al. [17] reported that the coefficient of variation (CV) of UIC for an individual ranged between 19 % and 53 %. In studies conducted in middle-aged and older adults, Konig et al. estimated

that ten 24-h urine samples [6] or 13–15 spot urine samples [6, 18, 19] are needed from an individual to assess their iodine status with a precision of 20 %.

Similar to UIE, UIC determined from spot urine samples can be confounded by hydration status because UIC varies according to fluid intake [5, 13]. In a study comparing the median urine osmolality of spot urine samples in German adults, males categorized as iodine deficient (i.e. median UIC 54 μg/L) had a lower median urine osmolality value than those with adequate iodine status (median UIC 139 μg/L) (median urine osmolality value: 472 vs. 909 mosm/L; $P < 0.0001$) [20], despite the fact that both groups had a similar estimated iodine intake (126 vs 130 μg iodine/day; $P = 0.200$). The results of this study challenge the current perception that adjustment of hydration status for UIC is not needed. It is possible that groups with a better hydration status might have a lower UIC, despite having consumed an adequate intake of iodine, because a higher fluid intake dilutes the urine sample. Zimmermann and Andersson have suggested that a median UIC of 60–70 μg/L might be more appropriate to determine iodine sufficiency in these groups [13], although this has not, to date, been adopted as an official recommendation.

In an effort to reduce variability in UIC, studies have reported the iodine-to-creatinine ratio (I/Cr), with some authors suggesting this provides a better measure of iodine status [6, 21, 22]. However, the use of this ratio introduces another source of variability related to the excretion of urinary creatinine (UCr) [5]. UCr excretion is not constant from day to day in individuals [8], and similar to UIC, UCr has high intra- and inter-individual variation [23]. The I/Cr ratio will overestimate the measurement of UIC in populations with low UCr excretion [21] and it will underestimate the measurement in populations with high UCr excretion [24]. A poor correlation between I/Cr ratio and UIE in mildly iodine deficient populations has been reported by Thomson et al. [25]. The I/Cr ratio can also be confounded by age because creatinine excretion declines with age [4], possibly due to the loss of the lean muscle [26]. Therefore, WHO/UNICEF/ICCIDD [1] does not recommend I/Cr ratio to assess iodine status.

Thyroid-Stimulating Hormone

TSH is a 2-chain glycoprotein (~28 kDa) with two non-covalently linked subunits, α and β [27]. Serum TSH is used as a primary screening test to diagnose thyroid dysfunction [28]. When the synthesis of T4 is low, thyrotropin-releasing hormone (TRH) from the hypothalamus will trigger the thyrotropic cells of the anterior pituitary gland to secrete TSH [29]. Subsequently, an increased concentration of TSH stimulates thyroid hormone production which maintains normal thyroid hormone concentration [30].

In a meta-analysis of 16 studies investigating the effect of iodine intake on TSH concentration, the usefulness of TSH to assess iodine status in populations of infants, children and adults was reported to be unclear [31]. This conclusion was based on the fact that the TSH concentration of mildly iodine deficient populations usually falls within the normal reference range [32]. In neonates, WHO/UNICEF/ICCIDD state that a prevalence of <3 % of neonatal aged 3–4 days with a blood spot

TSH >5 mIU/L indicates iodine sufficiency in populations [1]. However, a prevalence of <3 % of neonatal TSH >5 mIU/L has been reported in several mildly iodine deficient populations [33–35]. For pregnant women, although trimester-specific TSH ranges are available for some assays [36], these ranges cannot be used to differentiate between iodine deficiency and iodine sufficiency [37].

The TSH concentration of mildly iodine deficient populations often overlaps with iodine sufficient populations because the normal reference range for TSH is wide [38]. Only in severe iodine deficiency does TSH increase sufficiently to fall above the reference range [38]. Thus, TSH is an insensitive biomarker of iodine status because TSH concentration cannot be reliably used to differentiate between mildly iodine deficient and iodine sufficient populations.

Thyroid Hormones

Thyroid hormones are formed from the coupling reaction of iodotyrosines in the thyroid gland. The synthesis of thyroid hormones is stimulated by TSH, which is regulated by TRH. T4 is considered to be the pro-hormone and is converted into the active form, T3, at the target tissues [39]. The thyroid gland releases all circulating T4 [40] but only ~20 % of T3 in the bloodstream originates from the thyroid [41, 42]. The remainder of T3 is derived from the conversion from T4 by the type 1 5'-deiodinase enzyme [43]. Although the concentration of circulating T4 is ~100 times higher than circulating T3, T3 has 4–15 times higher biological activity than T4 [44]. The vast majority of thyroid hormone (>99 %) circulates in plasma bound to thyroxine binding globulin and other proteins, and it is only the small unbound fraction that has biological activity.

Similar to TSH, neither total or free serum T3 and T4 concentrations can be used to differentiate mild iodine deficiency and iodine sufficiency in a population [45]. Although a small increase or no change in T3 concentration and a decrease in T4 concentration are reported in iodine deficient populations, the changes in T3 and T4 concentrations typically remain within the normal reference range [2]. As with TSH, T3 and T4 concentrations of both mildly iodine deficient and iodine sufficient populations of children and adults fall within the normal reference range [32]. Thyroid hormone concentrations are unreliable for assessing iodine status in pregnant women, as for other groups, with the additional difficulty that there is a lack of established trimester-specific free T4 ranges [46]. In an extensive review, an expert panel of the Biomarkers of Nutrition for Development (BOND) on Iodine [46] stated that total and free T3 and T4 are poor biomarkers of iodine status in populations.

Thyroglobulin

Tg is a glycoprotein that comprises two 330 kDa protein chains synthesized only in the thyrocyte [47]. In iodine deficiency, an increased amount of Tg is released into the blood, which is positively correlated with thyroid volume [1]. Therefore, a higher concentration of Tg may be indicative of iodine deficiency. However, an

elevated Tg concentration can also be found in populations exposed to excessively high iodine intake, suggesting that Tg is sensitive to iodine intake [48]. In contrast to UIC, Tg is a longer term biomarker of iodine status (i.e. weeks to months) [2]. Tg has been suggested as a better index than UIC for monitoring iodine status in groups of children and adults [49, 50]. In a multicentre study, a median Tg concentration of <13 μg/L and/or <3 % of Tg values >40 μg/L was recommended to indicate iodine sufficiency in school-aged children [48]. Ma and Skeaff [51] reviewed the usefulness of a median Tg concentration of <13 μg/L to assess iodine sufficiency in different population groups. Their review included six observational studies and four interventional studies that were conducted in school-aged children. The majority of observational and interventional studies in iodine sufficient children had a median Tg <13 μg/L, supporting the 13 μg/L cut-off proposed by Zimmermann et al. [48]. In adults, twelve observational studies and two interventional studies were included in their review. Iodine deficient adults were reported to have median Tg values of either <13 or ≥13 μg/L. However, a recent randomized controlled trial of mildly iodine deficient adults supplemented with iodine for 6 months reported that Tg decreased to 13 μg/L when UIC was ≥100 μg/L [50]. Therefore, it is not possible to make conclusions regarding the efficacy of the 13 μg/L cut-off in adults.

The usefulness of Tg to assess iodine status in pregnant women is unknown because of a lack of evidence [51]. Ma and Skeaff [51] reviewed eight observational studies and three interventional studies that were conducted in pregnant women; iodine deficient pregnant women typically had a median Tg ≥13 μg/L. However, there is limited evidence to show that iodine sufficient pregnant women have a median Tg <13 μg/L. Moreover, it is also unclear whether the Tg cut-off needs to be trimester-specific.

A dried blood spot (DBS) method, which requires only a drop of blood from a finger prick, has been developed for the determination of Tg. In contrast to the collection of urine, the DBS method is advantageous because the cards can be easily stored and shipped [38]. However, Tg concentration can be confounded in individuals positive for thyroglobulin antibody (TgAb), in whom Tg measurements may be spuriously low or, less frequently, elevated [52]. The prevalence of TgAb in the general population is approximately 10 % [53], but a low prevalence (<1 %) is reported in populations of children [48]. Another issue with Tg measurement is that there is a large inter-assay variation between methods, even after the standardisation with the Certified Reference Material Community Bureau of Reference-457 (CRM BCR®-457) for Tg [51].

Clinical Assessment

Thyroid Volume

Goiter is an adaptation of the thyroid gland to iodine deficiency [1]. The secretion of TSH by the pituitary gland in response to low circulating levels of T4 increases the division of follicular cells and the subsequent enlargement of the thyroid gland

Table 2.3 The epidemiological criteria for assessing the severity of iodine deficiency disorders (IDD) based on the prevalence of goiter in school-aged children

	Degree of IDD			
	None	Mild	Moderate	Severe
Total goiter rate	0.0–4.9 %	5.0–19.9 %	20.0–29.9 %	≥30 %

Adapted from Ref. [1]

(i.e. goiter) [54]. Thyroid volume can be measured by palpation or ultrasonography. Ultrasonography is more accurate and sensitive than palpation and is better able to detect the subtle increase in thyroid volume seen in mildly iodine deficient children [2]. The thyroid gland is assessed by measuring its volume; goiter is defined as a thyroid volume >97th percentile of the reference population [1]. There are no cut-offs to categorise iodine status in adults using thyroid volume [55]; cut-offs are only available for school-aged children [56]. When a total goiter rate ≥5 % is reported in school-aged children, the population is considered as iodine deficient (Table 2.3).

The total goiter rate takes a relatively long time (i.e. months to years) to normalize after an improvement in iodine status due to the introduction of fortification or supplementation programs [2]. During this lag period, the iodine status in population is difficult to interpret using thyroid volume because this reflects both previous and current iodine status [57]. In addition, the thyroid volume of mildly iodine deficient and iodine sufficient populations can overlap and fall within a similar range [2, 58].

Dietary Assessment

Iodine intake can be measured using diet records, 24-h recalls and food frequency questionnaires (FFQ). In countries such as New Zealand (NZ), iodized salt is permitted to contain between 25 and 65 mg iodine/kg, but on average contains 45 mg iodine/kg [59]. Thus, one teaspoon of iodized salt (i.e. ~5 g) contains ~240 μg iodine [14, 59]. In many countries, the consumption of iodized salt makes a significant contribution to the iodine intake of the population [13]. A systematic review reported that there is a significant increase in UIC in populations that use iodized salt compared to non-iodized salt (mean difference of 59.22 μg/L, 95 % CI = 50.40 to 68.04) [60].

A major limitation associated with all dietary assessment methods is the difficulty in accurately measuring the quantity of iodine that is derived from iodized salt, used both at the table and in cooking [37]. Discretionary iodized salt used in cooking and seasoning can be added in many different ways and quantities [37]. For example, iodized salt can be added using a person's hand (i.e. a pinch), a salt sachet, or a salt shaker [37]. The amount of iodine from iodized salt that will be incorporated into foods also depends upon the cooking techniques and types of foods [37]. During cooking, the loss of iodine ranges from 6 to 63 % [61–63]. The highest loss of iodine is found during boiling because the iodine in the salt is leached out and lost in the boiling water, while roasting leads to the lowest loss of iodine [64].

Weighed diet records are the gold standard to measure nutrient intake because they provide a detailed description of all the food and drink consumed over a specific period of time [65]. However, diet records are associated with large respondent burden, which can change usual food consumption. In a prospective cohort study of Danish adults, the iodine intake determined from 4-day weighed diet records was significantly correlated with the estimated 24-h iodine excretion calculated from UIC [11]. However, of the 417 adults who were asked to carry out the 4-day weighed diet records in the study, only 65 % of them completed useful records, demonstrating that multiple-day diet records require highly motivated participants [11].

Compared to the diet record, the 24-h recall relies on the participants' memory and ability to accurately recall both the kind and amount of food consumed. The 24-h recall involves a structured interview whereby participants are asked to remember all the food and drink they consumed, usually over the previous day [66]. It is suitable for use with large numbers of participants such as in national nutrition surveys [67]. In the United States, a 24-h recall was used in the National Health and Nutrition Examination Survey (NHANES) to assess dietary iodine intake in the American population [68]. However, the large intra-individual variation in dietary intake means that a single 24-h recall is unlikely to accurately determine nutrient intake in smaller groups of people [69].

Another type of dietary assessment method is the food frequency questionnaire (FFQ). FFQs can be used to determine usual intake. Participants are asked to report on the frequency (i.e. how many times per day/week/month) of consumption of a list of foods over a specified period of time [70]. A FFQ is relatively inexpensive and typically self-administered, with less respondent burden than other types of dietary assessment methods [71, 72]. However, the FFQ needs to be validated against a reference or "gold standard" [37], either with a diet record or UIC, which is problematic. Development of FFQs also requires validated tables for the iodine content of different foods, which are unavailable in many regions.

Only five studies have used a validated iodine-specific FFQ to assess iodine intake in populations including pregnant women [73–77]. The iodine-containing food items ranged from 17 to 53 and the period of time covered by the FFQ ranged from 1 to 24 weeks [73–77]. A 53-item iodine-specific FFQ (iodine intake from diet and supplements) was significantly correlated with 24-h urinary iodine excretion in a Danish adult population ($r = 0.66$, $P < 0.001$) [73], providing evidence that an iodine-specific FFQ can be a useful method to assess the iodine intake.

Since an iodine-specific FFQ focuses on the usual intake of iodine-containing foods, it is better at identifying iodine-rich foods that are consumed frequently such as fish and sushi [14], which could be missed with a diet record or a 24-h recall. In addition, an iodine-specific FFQ can also be used as a screening tool in iodine supplementation trials as a means to eliminate subjects who are frequent consumers of iodine-rich foods, as this may skew results [78]. Another advantage of using an iodine-specific FFQ is that questions about the type of salt used, the frequency and serving size of iodized salt added to the cooking or at the table can be ascertained [14]. For these reasons, the FFQ is often the preferred method in studies that assess iodine intake [14, 79].

Table 2.4 Biomarker of iodine status in populations

Biomarkers	Advantages	Disadvantages
Diet records, 24-h recall, and Food Frequency Questionnaire	Useful to identify the most important sources of iodine in the diet	Some food composition databases do not contain information on the iodine content of foods Difficult to quantify iodine intake from iodized salt used in cooking or at the table
Goiter rate	Non-invasive method Reference ranges for thyroid volume are available for school-aged children	Palpation of goiter has poor sensitivity and specificity in mild iodine deficient populations Difference in techniques of thyroid ultrasound measurement can produce large inter-observer error in thyroid volume measurement Takes a relatively long time (i.e. months to years) to normalize after an improvement in iodine status
UIC	>90 % of ingested iodine is excreted in the urine Spot urine samples are relatively easy to be collected compared to 24-h urine samples	UIC requires about n = 300–500 people per age group because of high intra- and inter-individual variation in UIC UIC can be affected by hydration status Does not provide any information on thyroid function
TSH	A useful screening test to check for thyroid dysfunction Can be measured using dried blood spot methods	Slightly increased in iodine deficient populations TSH values of mildly iodine deficient populations often remain within the normal range and overlap with iodine sufficient populations
Thyroid hormones	Direct reflection of thyroid function	T3 and T4 concentrations of mildly iodine deficient populations often remain within the normal range in mildly iodine deficient adults and overlap with iodine sufficient populations
Tg	An increased amount of Tg is positively correlated with thyroid volume in iodine deficient populations Can be measured using dried blood spot methods	Can be confounded by the presence of TgAb and the prevalence of TgAb in many populations is unknown Reference material Tg CRM-457 is available for assay standardization but large inter-assay variability still exists No cut-offs for adults or pregnant women No cut-offs to determine the severity of iodine deficiency

Adapted from Ref. [46]

Conclusion and Future Research

A summary of the advantages and disadvantages of each biomarker is given in Table 2.4. WHO/UNICEF/ICCIDD recommends UIC to assess the iodine status in populations, however, UIC does not provide any information on the thyroid function [1]. Furthermore, UIC determined from a single spot urine sample cannot be used to assess individual iodine status because it is associated with high intra- and

inter-individual variation [6]. The normal reference ranges of TSH, T3 and T4 are wide [2], thus these are insensitive indices to detect mild or moderate iodine deficiency in populations. Although Tg is regarded as a promising biomarker of iodine status, particularly in populations with mild iodine deficiency, there is a lack of evidence to support the median Tg cut-off of 13 μg/L in populations groups other than children. The biggest limitation in the assessment of iodine status is the lack of an index to assess individual iodine status.

Future research should focus on the determination of iodine status in individuals, particularly those at risk of iodine deficiency. There is a need for the development and validation of biomarkers of individual iodine status [80], needed to link functional indices, such as cognition, to status. For example, additional work is required to investigate whether inorganic iodine in blood can be used to assess iodine status. The standardization of T3 and T4 methods is required, especially for the establishment of trimester-specific thyroid hormone ranges. Finally, further validation studies are needed to confirm if a median Tg <13 μg/L can be used in other groups than children.

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Chapter 3
Epidemiology of Iodine Deficiency

Małgorzata Gizak, Jonathan Gorstein, and Maria Andersson

Abstract Global efforts to control iodine deficiency through the highly successful strategy of salt iodization have been in effect for over two decades. In 2016, urinary iodine concentration (UIC) data in school-age children are available for 127 countries: 15 countries are classified as iodine deficient, 102 have optimal iodine nutrition, and 10 have excess iodine intakes. This reflects tremendous global progress against iodine deficiency. Increasingly, countries are recognizing the importance of monitoring the iodine status in populations that are particularly vulnerable to the negative consequences of iodine deficiency, such as pregnant women. For the first time, global UIC data in pregnant women have been compiled and presented, based on surveys from 65 countries. The iodine intake in pregnant women is insufficient in 37 countries, and the main challenge is to further strengthen the delivery of salt iodization programs to ensure that iodized salt meets the iodine requirements of pregnant women.

Abbreviations

EAR	Estimated average requirement
IDD	Iodine deficiency disorders
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
IGN	Iodine Global Network
PW	Pregnant women
SAC	School-age children
TGR	Total goiter rate
UIC	Urinary iodine concentration
WHO	World Health Organization
WRA	Women of reproductive age

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Introduction

Iodine deficiency is the result of insufficient dietary iodine intake, which can lead to inadequate production of thyroid hormones and many adverse effects at all life stages, collectively known as iodine deficiency disorders (IDD) [1–3]. Thyroid hormones are particularly critical for fetal neurodevelopment, and severe iodine deficiency during pregnancy may result in maternal and fetal hypothyroidism and cognitive impairment in children, but the effects of mild-to-moderate iodine deficiency are less clear [4, 5]. Iodine deficiency during pregnancy remains a common cause of preventable cognitive impairment worldwide [6, 7]. The universality of iodine deficiency and its devastating impact on health and development have been at the root of global control efforts through salt iodization since the 1920s [8]. Yet, in spite of tremendous progress realized and achievement of high levels of program coverage in many countries, iodine deficiency remains a threat to global public health, with its greatest impact on infants and pregnant women [9].

Global Distribution of Iodine Deficiency

Iodine deficiency is an ecological phenomenon in many parts of the world [2]. Iodine distribution in the environment is wide but uneven, with the highest concentrations found in the oceans (45–60 μg/L) [10]. From the ocean surface, iodine volatilizes into the atmosphere and is returned to land with rain and snowfall [11]. In areas affected by past glaciation and denudation this cycle is slow, and iodine is only partially replenished [12]. In many regions, the loss of iodine from the topsoil is exacerbated by high rainfall, flooding, deforestation, and overgrazing by livestock. Crops grown in iodine-depleted soils typically do not contain enough iodine to cover the dietary needs of people and livestock. As a result, populations consuming them will become iodine deficient unless iodine is reintroduced into the food chain through deliberate efforts or public health programs, e.g., salt iodization [13].

A recognized clinical indicator of thyroid dysfunction, goiter was traditionally relied on to identify regions of low iodine intake [14]. High goiter rates were reported among populations living in mountain ranges and on alluvial plains, which led to the misperception that iodine deficiency was geographically confined to these areas [2]. With the increasing use of urinary iodine concentration (UIC), which reflects a broad range of iodine intakes, the global distribution of iodine deficiency has been better understood. It is now recognized that iodine deficiency may be present (albeit in milder forms) in regions without endemic goiter, in coastal areas, large cities, and industrialized countries, where it previously had been considered to be non-existent [2, 15]. Many of the worst affected regions are also the most heavily populated (Table 3.1) [16].

Table 3.1 Regions with naturally low soil iodine levels

Asia, including parts of China, India, Bangladesh, the Himalayan hillsides, and Indonesia
Africa, including the mountains of Morocco and Algeria (e.g., Atlas Mountains); much of west and central Africa (e.g., Nigeria, Cameroon, the Central African Republic, Democratic Republic of Congo), and some areas of East Africa (e.g., Uganda, Ethiopia)
Europe, including the European Alps and the Pyrenees, inland areas of England and Wales, Greece, and The Netherlands
South America, including the Andes and inland Brazil
Midwestern United States
Southern Australia
Highlands of New Guinea

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Global Monitoring of Iodine Nutrition

Collecting and reporting of national, regional, and global data on iodine status has been essential for estimating the current magnitude of iodine deficiency, tracking national progress and effectiveness of prevention strategies, and identifying population groups or pocket areas that may be at risk of insufficient or excessive iodine intakes [2]. Since 2005, the World Health Organization (WHO) has reported on the global iodine status to the World Health Assembly every 3 years, most recently in 2016 [17, 18]. All countries are advised to assess their population iodine status every 5 years, even if they have already achieved optimal iodine nutrition, to reinforce the importance of program sustainability, as well as to safeguard against program backsliding and re-emergence of iodine deficiency as a public health problem [2, 17, 19].

Biomarkers of Iodine Status

Since 2001, UIC in school-age children (SAC, aged 6–12 years) has been the main indicator of iodine status and has been considered a proxy for the general population. Criteria have been established based on the median UIC level to determine the iodine status of populations (Table 3.2) [2]. The shift from reliance on goiter to an objective biomarker of exposure has improved the availability and quality of nationally representative data. Unlike goiter, UIC reacts immediately to changes in iodine intake and is, thus, ideal for monitoring the impact of salt iodization programs [2, 20].

Table 3.2 Epidemiological criteria for assessing population iodine nutrition based on median urinary iodine concentrations (mUIC) of school-age children (≥6 years)[a] [2]

Median UIC (μg/L)	Iodine intake	Iodine nutrition status
<20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Adequate iodine nutrition
200–299	Above requirements	Likely to provide adequate intake for pregnant/lactating women, but may pose a slight risk of more than adequate intake in the overall population
≥300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid diseases)

Permission to reproduce obtained from [2]
[a]Applies to adults, but not to pregnant and lactating women

Global Databases on Iodine Nutrition

The WHO online Global Database on Iodine Deficiency is a repository of national and sub-national data from population-based surveys of iodine status conducted between 1960 and 2007 [21]. Although the mandate to track and report the global progress against iodine deficiency lies with WHO, since 2011 the collection of population data has been supported by the Iodine Global Network (IGN, previously known as the International Council for the Control of Iodine Deficiency Disorders, ICCIDD), a technical advisory group to the WHO on iodine nutrition [22]. The available studies and estimates can be accessed on the IGN's website, where they are regularly updated [23].

Methods to Estimate the Global Burden of Iodine Deficiency

To estimate the global status of iodine nutrition, national or sub-national UIC surveys with a population-based sampling frame and using accredited UIC analysis techniques are considered for inclusion. Nationally-representative UIC surveys are given priority over sub-national studies. Between 2003 and 2012, global estimates reported UIC data collected over the preceding 10 year period, while the 2016 estimates extend this time-frame to 15 years. In an effort to harmonize data reporting, the 2016 global estimate is the first to rely exclusively on data in school-age children (6–12 years) to estimate the iodine status in the general population (see Sect. 5 and Table 3.3). Previous global estimates included national UIC data from pre-school children, women of reproductive age, and adults when data in SAC were not available. But because the epidemiological criteria for assessing population iodine nutrition (in Table 3.2) were developed based on urine volumes and

Table 3.3 Trends in national iodine status and IDD monitoring over the period 1993–2016

Iodine status	1993[a, b]	2003[c]	2007[d]	2011[e]	2015[f]	2016[g]
Iodine deficiency	113	54	47	32	25	15
Optimal iodine status[h]	8	67	76	105	116	102
Excessive iodine intake	0	5	7	11	13	10
Countries with data	121	126	130	148	154	127
National surveys Sub-national surveys	51 70	75 51	93 37	115 33	126 28	107 20
Surveyed population group[i] SAC only Other Unknown	113 8 –	112 12 2	118 11 1	132 16 –	136 18 –	127 – –
Total countries[j]	**183**	**192**	**193**	**193**	**194**	**194**

[a]Iodine status based on total goiter rate (TGR) in school-age children, classified as deficient if TGR >5%
[b][14]
[c][27]
[d][28]
[e][22]
[f][33]
[g][34]
[h]The optimal iodine status category includes countries with adequate and more than adequate iodine intakes (see Table 3.2) [2, 26]
[i]Iodine status based on the median UIC in school-age children or, where SAC data were not available, in another population group, for example pre-school children, adolescents, reproductive-age women, the general population, or a combination (see Table 3.2) [2]
[j]WHO member states

iodine concentration data in school-age children, their application in other population groups has been challenged [19, 24, 25]. Population UIC is typically not normally distributed, and the median of the UIC distribution is used instead of the mean to classify the countries' iodine status into different degrees of public health significance (Table 3.2). For the current analysis, the acceptable range of median UICs in school-age children (100–299 μg/L) has been presented as a single category of optimal iodine intake [26].

Between 2003 and 2011, efforts were made to estimate the number of iodine deficient individuals using the UIC distribution and the reported proportion of the population with UICs below 100 μg/L [27, 28]. The national prevalence of iodine deficiency was estimated by multiplying this proportion by the country's total population (of SAC and the general population), and the data were pooled for regional and global estimates [19, 22]. In recent years this approach has come under much criticism [19] because it assumes, incorrectly, that the UIC values reported in national surveys reflect habitual iodine intake and are, therefore, good markers of individual iodine status. In practice, this is not the case as UIC levels are highly variable from day to day, and iodine concentration in a single spot urine sample reflects only recent intake [29]. This method is likely to overestimate the real

prevalence of iodine deficiency and has contributed to the erroneous perception that the global progress against iodine deficiency is slowing. In 2011, this approach led to an apparent paradox, where 74% of the children globally who were classified as iodine deficient were living in countries with an adequate median UIC, and only 26% were in countries classified as iodine deficient [19, 22]. Given this limitation, the WHO UIC median of 100 μg/L is the only meaningful metric of population iodine status, as even in countries with effective USI programs and adequate iodine intakes (i.e., median UIC ≥100 μg/L), there will be a proportion of individuals with a UIC below the 100 μg/L cut-off [19]. An alternative approach to estimating the prevalence of inadequate iodine intakes based on the estimated average requirement (EAR), and using repeat spot UIC samples to better characterize variations in iodine consumption, is currently being developed [19, 30]. In the meantime, global iodine status should continue to be reported as the number of countries with overall insufficient, adequate, and excessive iodine intake based on the recommended median UIC cut-off points.

Global Trends in Iodine Nutrition

The first comprehensive review of endemic goiter, undertaken in 1960 by WHO, estimated that iodine deficiency affected approximately 20–60% of the world's population, mostly in low- and middle-income countries [31, 32]. Before the 1990s, only a few countries in the world with previously documented goiter prevalence were considered iodine sufficient, mainly due to iodized salt programs and iodine in dairy products, including Switzerland, some Scandinavian countries, the USA, Canada, and Australia [1]. The first global estimate of the number of individuals at risk of iodine deficiency followed in 1993 [14]. Based on the total prevalence of goiter in more than 120 countries, around 1.57 billion people were estimated to be living in areas at risk of iodine deficiency, 12% of the population had palpable goiter, and 2% suffered from endemic cretinism [14, 31]. Based on a total goiter prevalence (TGR) >5%, 113 out of 121 countries with data were classified as iodine deficient. In subsequent years, many countries introduced and scaled up salt iodization programs, and estimates on the coverage of iodized salt at the household level and on population iodine status became more readily available [15]. Global estimates of iodine deficiency based on UIC were published in 2003, 2007, 2011, 2015, and 2016 [22, 27, 28, 33, 34]. The number of countries classified as iodine deficient has declined consistently over the past two decades, roughly halving every 10 years, and countries classified with severe deficiency (mUIC <20 μg/L) have not been recorded for more than a decade (Fig. 3.1 and Table 3.3). Salt iodization programs, strong political commitment, and engagement with the salt industry at the global, regional, and national level have all played a pivotal role in this achievement.

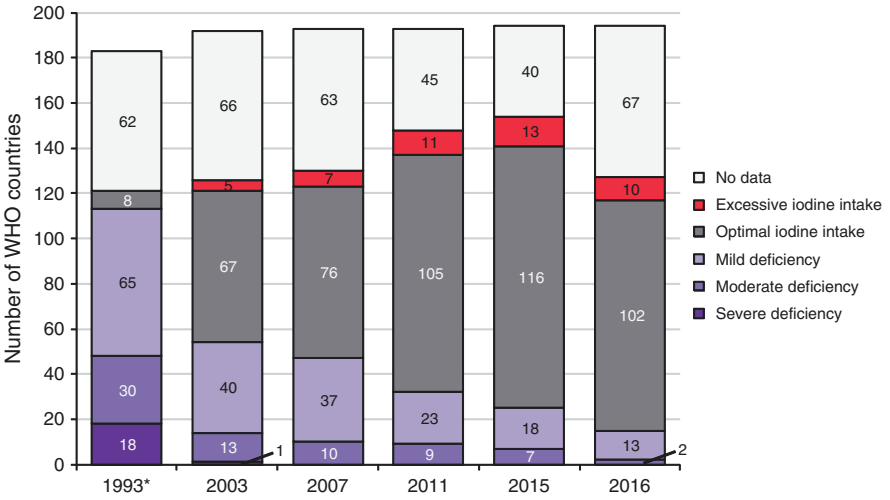

Fig. 3.1 The number of iodine deficient WHO countries has consistently declined between 1993 and 2016 [14, 27, 28, 22, 33, 34]
*In 1993, iodine deficiency is defined using total goiter rate >5%; in 2003–2016 it is defined based on median UIC in school-age children (Table 3.2)

Current Global Iodine Status

School-Age Children

The 2016 global estimate of iodine nutrition, based on surveys of school-age children conducted between 2002 and 2016, shows that the iodine intake is insufficient in 15 countries, sufficient in 102, and excessive in 10 countries (Table 3.3 and Fig. 3.2) [34]. Among the 15 countries with insufficient intake, only two are classified as moderately deficient and 13 as mildly deficient. The dwindling number of countries with insufficient iodine intake, from 32 in 2011 and 25 countries in 2015 to 15 countries in 2016 [22, 33, 34] is mainly a reflection of continuing progress to improve the coverage of iodized salt at the national level. However, the stricter data inclusion criteria applied in 2016 (see Sects. 3.3 and 3.4) have meant that eligible UIC surveys are available for fewer countries: 126 countries in 2016 compared with 154 countries in 2015, and 148 countries in 2011. This represents a drop in global population data coverage from 98.2% of 6–12 year-olds in 2015 to 93.3% in 2016, and it may confound trend analysis (Fig. 3.1). At the same time, many countries continue to sustain or strengthen their iodine monitoring efforts. Since 2015, 18 new nationally-representative surveys in SAC have been reported[1]. In 2016, there is considerable regional variation in population data coverage, ranging from more than

[1] These include Bangladesh, Burkina Faso, China, Ecuador, Egypt, Ethiopia, Indonesia, Japan, Panama, Paraguay, Peru, Spain, Sri Lanka, Switzerland, Uruguay, Venezuela, Vietnam, and Yemen.

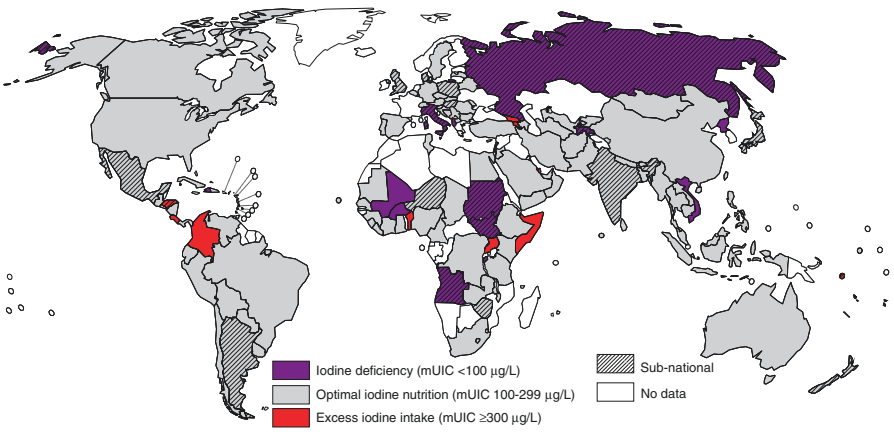

Fig. 3.2 Iodine nutrition based on the median urinary iodine concentration (mUIC) in school-age children, by country in 2016 [34]

99% in the Americas, where salt iodization and national iodine nutrition monitoring programs have been very well-implemented and effective, to approximately 80% in Europe, where iodine nutrition surveillance and prophylaxis are heterogeneous, with many countries lacking regulatory support.

Although the proportion of sub-national surveys is steadily decreasing, in 2016 they cover around 27% of the world's SAC population in 20 countries (Table 3.3). Sub-national UIC surveys are commonly carried out to provide a rapid assessment of iodine status in the population in pre-selected areas, but due to a lack of sampling rigor and adherence to basic principles of randomization, they may over- or underestimate the burden of iodine deficiency at the national level and should be interpreted with caution [1, 22].

Re-emergence of Iodine Deficiency

When iodine deficiency control programs lapse in areas that were previously considered iodine sufficient, the risk of IDD reappears, and such countries require remedial action to revitalize and strengthen the sustainability of their USI programs [35]. Like many countries which pledged to eliminate iodine deficiency at the 1990 World Summit for Children, Vietnam mandated salt iodization in the 1990s. By 2005, adequately iodized salt was reaching more than 90% of households in Vietnam, and the country was declared as iodine sufficient (with a median UIC in SAC of 139 µg/L in 2003) [22]. However, Vietnam downgraded the USI program to voluntary in 2005. The household coverage of iodized salt and the iodine status in SAC declined as a result, but the ongoing monitoring detected these declines and led to renewed efforts to reinstate the program in 2016 [36].

Vietnam's experience highlights the fact that prevention of iodine deficiency is an ongoing process, which necessitates long-term political commitment and sustainable implementation.

Australia and New Zealand are frequently cited as examples of industrialized countries where a change in dairy farming practices led to a re-appearance of iodine deficiency, when iodine-containing sterilizers were replaced with other chemicals, and the consumption of milk, the primary source of iodine in the diet, declined at the same time [37, 38]. To address these decreases in iodine intake, both countries mandated the use of iodized salt in commercially baked bread in 2009, and more recent surveys in SAC have confirmed that the iodine status has improved.

Excess Iodine Intake

Iodine excess occurs when the iodine intake is too high, generally as a result of over-iodization of salt (addition of too much iodine to salt at the point of production due to poor quality control or high iodization standards) or high intake of iodine from other sources, including iodine in local water supplies [39]. A high population intake of iodine, manifesting as a median UIC ≥300 μg/L, was reported in five countries in 2003, seven countries in 2007, and 10 countries in 2016 [27, 28, 34]. This gradual upward trend demonstrates the importance of regular monitoring of iodine status to detect not only inadequate but also excessive iodine intakes, and to better understand the sources of iodine in the diet [22]. It is important to note, however, that the benefits of correcting iodine deficiency far outweigh the health risks associated with excess.

Iodine Status and Trends in Pregnant Women

During pregnancy, the daily requirement for iodine increases from 150 μg in non-pregnant women to 250 μg to account for increased renal clearance of iodine and to cover the needs of the developing fetus [40]. In a population of pregnant women, a median UIC <150 μg/L indicates that iodine intake is insufficient, and a median UIC of 500 μg/L or higher indicates that iodine intakes are excessive (Table 3.4) [2, 41]. The increased requirement puts pregnant women and their offspring at higher risk of iodine deficiency than the general population, particularly if the availability of iodine in the diet is poor [42]. Recent studies indicate that pregnant women may be at risk of iodine deficiency even when school-age children in the same area are maintaining adequate iodine intakes [43–48]. As such, there is growing awareness of the need to monitor the iodine status of pregnant women through national surveys and to make programmatic adjustments to ensure that their needs are met.

Table 3.4 Epidemiological criteria for assessing iodine nutrition based on median and/or range of urinary iodine concentrations (UIC) in pregnant women [2]

Median UIC (μg/L)	Iodine intake	Iodine nutrition status
<150	Insufficient	Iodine deficiency
150–249	Adequate	Optimal
250–499	Above requirements	–
≥500	Excessive[a]	–

Permission to reproduce obtained from [2]
[a]In excess of the amount required to prevent and control iodine deficiency

In 2016, recent surveys (conducted between 2002 and 2016) in pregnant women cover a third of the world's countries (65 out of 194 WHO member states) [34]. By comparison, only 42 countries had data on the iodine status of pregnant women in 2006 according to the WHO Global Database on Iodine Deficiency [20, 21]. Figure 3.3 shows the global status of iodine nutrition in 2016 based on surveys in pregnant women. Although the 65 surveys are distributed across all six WHO regions, 28 (43%) cover more than a half of the European region (Table 3.5). Data coverage is also reasonably high (6 out of 11 of countries) in South-East Asia. The lowest coverage is in Sub-Saharan Africa, where only 17%, or 7 out of 39 countries have data. It should be noted that fewer than a half of the country estimates are based on nationally representative surveys, which adds uncertainty to the data and highlights the need to systematically expand national iodine monitoring to include pregnant women.

The iodine status of pregnant women is sufficient in 23 countries, which in a majority of cases can be attributed to long-standing salt iodization programs. In these countries, the median UIC is generally lower in pregnant women compared to SAC, as seen in China (198 μg/L in SAC vs. 155 μg/L in PW in 2014), Thailand (237 μg/L in SAC vs. 156 μg/L in PW in 2014), Mongolia (171 μg/L in SAC vs. 152 μg/L in PW in 2010), and Indonesia (223 μg/L in SAC vs. 172 μg/L in PW in 2013). However, this is expected given physiological adaptations associated with pregnancy, including increased renal clearance of iodine and greater urine volume.

At the same time, the iodine intake is classified as low in 37 out of the 65 countries with available data. Globally, a number of countries are reporting adequate iodine intakes among SAC coupled with inadequate intakes in pregnant women, such as in the Philippines (mUIC of 168 μg/L in SAC vs. 105 μg/L in PW in 2013), Sri Lanka (164 μg/L in SAC vs. 113 μg/L in PW in 2010), and Belgium (113 μg/L in SAC vs. 124 μg/L in PW) [34]. A previous US NHANES reported a median UIC among 6–11 year-old children to be above 200 μg/L, but only 125 μg/L in pregnant women [49]. In Europe, three-quarters of countries report inadequate iodine intakes among pregnant women, and only 11% of countries among school-age children [34]. This emerging trend clearly highlights the need to make adjustments in the USI strategy to ensure that the dietary needs of pregnant women are met, but also to better understand how to interpret UIC data in this population group.

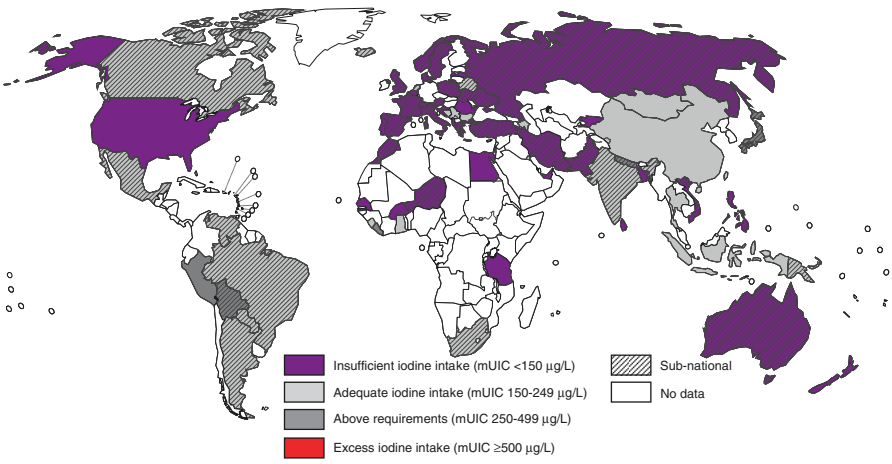

Fig. 3.3 Iodine nutrition based on the median urinary iodine concentration (mUIC) in pregnant women, by country in 2016 [34]

Table 3.5 Classification of iodine status in pregnant women (PW) based on the median urinary iodine concentration (UIC) [2] in 2016, by country [34]

		Iodine status in PW			Survey administrative level		
WHO Region	Total countries[a]	Iodine deficiency	Optimal	Above requirements	National	Sub-national	Countries with no data
Sub-Saharan Africa	47	4	3	1	6	2	39
Americas	35	1	6	2	2	7	26
Eastern Mediterranean	21	5	1	0	3	3	15
Europe	53	21	7	0	11	17	25
South East Asia	11	2	3	1	4	2	5
Western Pacific	27	4	3	1	4	4	19
Total	**194**	**37**	**23**	**5**	**30**	**35**	**129**

[a]194 WHO Member States

WHO/UNICEF recommend iodine supplementation of all pregnant women in countries where salt iodization is not feasible or incomplete [40]. Iodine supplementation of pregnant and lactating women has been recommended by scientific societies and regulatory bodies in Australia [15], USA and Canada [50], and Europe [51, 52], but it has not been widely adopted. Randomized controlled trials investigating the effects of iodine supplementation on pregnant women exposed to

mild-to-moderate iodine deficiency are lacking, and its long-term benefits and safety in this group are unclear [5].

Remaining Challenges

Although USI programs have been implemented in more than 140 countries, and around 75% of households globally have access to adequately iodized salt [53, 54], some countries and sub-groups within countries continue to be at risk of sub-optimal iodine intakes. Despite ongoing efforts to improve access to iodized salt for all populations, disparities in household coverage have been reported at the sub-national level, where coverage could vary between rural and urban areas, or between the poorest and the richest socio-economic strata. In an analysis of iodized salt coverage amongst 11 low- and lower-middle-income countries in 2010, the coverage of iodized salt in urban areas was 8.7% higher than in rural areas, and 19.3% higher in the richest than in the poorest quintile in low-income countries [9]. A recent national survey in the Philippines suggests that such inequity may translate into a significantly lower iodine status among the rural poor [55]. Advocating the importance of iodine to national governments, encouraging the salt industry to iodize all salt for human consumption, and the food industry to use iodized salt in the manufacture of processed foods and condiments are all critical actions needed to ensure progress towards the global elimination of iodine deficiency. While overall program performance may be satisfactory, it is imperative to focus on reaching disadvantaged groups, particularly pregnant women and those of lower SES, in order to ensure that the entire population is protected from IDD.

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Chapter 4
Severe Iodine Deficiency

Eduardo A. Pretell and Chandrakant Pandav

Abstract Severe iodine deficiency is defined as a goiter prevalence greater than 30 % and/or a median urinary iodine concentration (UIC) of less than 20 μg/L in a given population or defined geographical area. The adaptive processes of the thyroid gland may be unable to compensate for this degree of iodine deficiency, leading to manifestations which include endemic goiter, hypothyroidism, obstetric complications, intellectual impairment, and cretinism. However, the manifestations of severe iodine deficiency have decreased globally primarily due to widespread coverage with adequately iodized salt.

Abbreviations

IDA	Iron deficiency anemia
IDD	Iodine deficiency disorders
IGN	Iodine Global Network
PAHO	Pan American Health Organization
SF	Serum ferritin
T3	Triiodothyronine
TGR	Total goiter rate
T4	Thyroxine
TSH	Thyroid stimulation hormone
UIC	Urinary iodine concentration
WHO	World Health Organization

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Introduction

Iodine deficiency is a natural and permanent phenomenon widely distributed around the world. Iodine deficiency affects thyroid hormone production and causes damage throughout the life span through a wide spectrum of diseases grouped as iodine deficiency disorders (IDD). These include hypothyroidism, goiter, and reproductive failure. Traditionally goiter has been viewed as the primary manifestation of iodine deficiency. However, it has recently been recognized that maternal iodine deficiency during pregnancy is a major cause of brain damage and intellectual impairment.

When iodine intake is low, adequate secretion of thyroid hormones may still be achieved by marked modifications of thyroid activity which are triggered and maintained by increased secretion of thyroid stimulating hormone (TSH). These adaptive processes include stimulation of the thyroidal iodine trapping mechanism as well as of the subsequent steps of the intrathyroidal metabolism of iodine, leading to preferential synthesis and secretion of the active hormone triiodothyronine (T3). However, these adaptive mechanisms may be unable to compensate in severe iodine deficiency, leading to decreased production of thyroid hormone [1–6]. Chronic, severe iodine deficiency is usually associated with development of thyroid failure and may cause cretinism.

Population iodine nutrition status is classified by the World Health Organization in three categories, based on the prevalence of goiter and the median UIC in school-aged children (Table 4.1). Severe iodine deficiency is characterized by a goiter prevalence >30 % and median UIC <20 μg/L [7].

Endemic Goiter

Endemic goiter is characterized by enlargement of the thyroid gland in a significantly large fraction of a population group, as a consequence of insufficient iodine in the diet. Most mountainous regions in the world are endemic goiter regions. These regions include the Andes, the whole sweep of the Himalayas, the European Alps, Greece, and the Middle Eastern countries, many foci in the People's Republic of China, and the highlands of New Guinea. Some non-mountainous regions are also endemic zones for goiter. Various reports on endemic goiter from the first half of the twentieth century were extensively reviewed by Kelly and Snedden in 1960 [8].

Table 4.1 Epidemiological criteria for assessing degrees of iodine deficiency

Based on urinary iodine concentration (UIC) and goiter prevalence (TGR) in school age children			
	Mild	Moderate	Severe
TGR, %	5.0–19.9	20.0–29.9	>30
UIC, μg/L	50–99	20–49	<20

Adapted from Assessment of iodine deficiency disorders and monitoring their elimination, Third edition [7]

Epidemiology

According to WHO, UNICEF and IGN, endemic goiter exists in a population when it occurs in more than 5 % of 6–12 year-old children [9]. Goiter prevalence is influenced by both age and sex. In severe endemics goiter affects nearly the whole population, it appears very early in life, and its prevalence increases sharply and attains a peak value during puberty and childbearing age (Fig. 4.1). During adulthood goiter prevalence declines in men [10]. The prevalence of goiter in areas of severe iodine deficiency can be as high as 80 %. In such environments the development and prevalence of thyroid nodules is also very high [11], and most adults, especially women, harbor thyroid nodules.

For public health studies conducted in the field, according to the Pan American Health Organization/World Health Organization (PAHO/WHO) meeting in Lima in 1983 [12], a thyroid gland whose lateral lobes have a volume greater than the terminal phalanges of the thumbs of the person examined is considered goitrous. In order for this to occur, the thyroid size must be enlarged by a factor of at least four to five. For the classification of goiter according to the size of the thyroid gland the following grading has been proposed: Grade 0: no palpable or visible goiter; Grade 1: an enlarged thyroid that is palpable but not visible when the neck is in the neutral position; Grade 2: a swelling in the neck that is visible when the neck is in a normal position. The total goiter rate is the prevalence of grade 1 and 2 in a given area. The TGR can be used to define the severity of iodine deficiency in populations as follows: <5 %, iodine sufficiency; 5–19 %, mild deficiency; 20–29 %, moderate deficiency; and >30 %, severe deficiency.

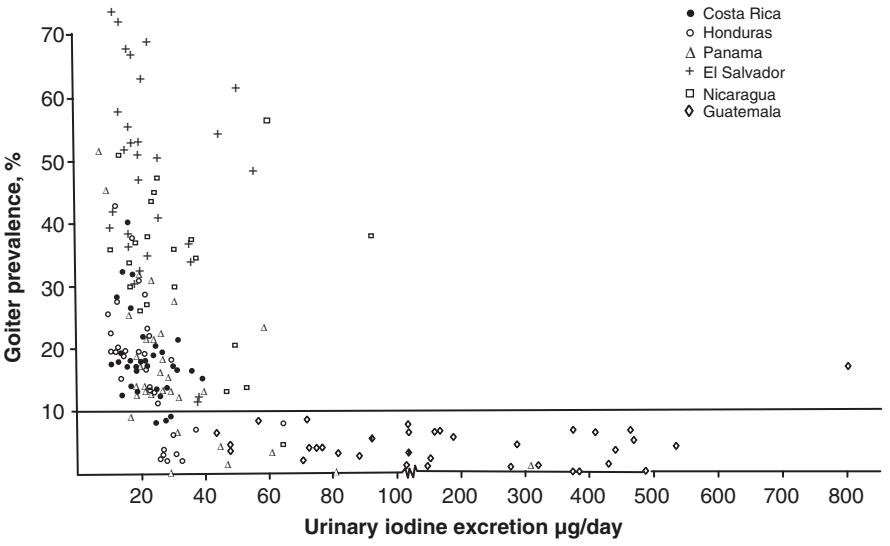

Fig. 4.1 Negative correlation between goiter rate and urinary iodine concentration in 21,611 people from 186 localities in six iodine deficient Central American countries (Reproduced from Arch Latinoamer Nutr (18) with permission from General Editor)

Etiology

A low dietary supply of iodine is the main factor responsible for the development of endemic goiter [13–17]. The association between goiter and UIC in populations with severe iodine deficiency has been clearly demonstrated. A negative correlation between the frequency of goiter and the 24-h urinary excretion has been observed in Central America [18], Slovenia [19], and elsewhere (Fig. 4.1). In both studies the highest prevalence of goiter corresponds to median UIC below 25 μgr/L.

The presence of goitrogens in the diet, (for example cassava and cruciferous vegetables, which contain thiocyanate, an inhibitor of thyroidal iodine uptake) or in the environment (such as sedimentary rocks rich in organic matter or humic substances) may exacerbate the thyroidal effects of iodine deficiency [20–22].

Pathophysiology

Elevated serum TSH levels are observed where the iodine supply is severely reduced [4, 5, 23–26]. The immediate consequence of TSH overstimulation is increased proliferation and hyperplasia of thyrocytes, leading to hypertrophy of the thyroid gland. Initially, goiters are characterized by diffuse homogeneous enlargement, with abundant parenchyma, large amounts of follicular epithelium, and reduced colloid. At later stages, due to chronic TSH overstimulation, there is an abnormal proliferation of thyrocytes, and nodules often develop. The prevalence of nodularity increases as a function of age, and is higher in women than in men [27, 28]

Fig. 4.2 (**a**) Six year-old boy with difuse goiter. (**b**) Sixty year-old woman with multinodular goiter. These subjects were from a severely iodine deficient area in the Peruvian Andean Mountains.

(Fig. 4.2). Many thyroid nodules derive from somatic mutations and are of monoclonal origin. However, polyclonal and monoclonal thyroid nodules may coexist within multinodular goiters [29]. Morphologic modifications observed in patients with endemic goiter are mainly nodular enlargement of the gland with striking macroscopic and microscopic heterogeneity [30]. Autonomy can develop in nodular goiters, a condition that favors the occurrence of iodine-induced hyperthyroidism when iodine prophylaxis programs are implemented [31]. A significant decrease in goiter rate from 86 % to 52 % 18 months after treatment with iodized oil injections inversely corresponding to a sharp increase in serum thyroxine (T4) levels was observed in a severely iodine deficient region [10]. Similarly, a progressive decline in the prevalence of toxic nodular goiter was reported in Switzerland following the implementation of universal iodized salt consumption [32].

Hypothyroidism

The prevalence of hypothyroidism is higher in areas with severe iodine deficiency than in areas of optimum iodine intake. Most important, however, is the impact of severe iodine deficiency during pregnancy and childhood [33–36].

Maternal Hypothyroidism and Reproductive Failure

Iodine requirements in pregnant and lactating women are higher (150–250 μg/day) than in the general population due to increases in thyroid hormone secretion, to cover the iodine needs of the developing fetus, to compensate for increased renal iodine losses during gestation, and to cover the needs of the growing infant during lactation. This increased demand for iodine, however, cannot be met in regions of severe iodine deficiency. Consequently, hypothyroidism, elevated serum TSH, and enlargement of the thyroid (by 10–50 %) are common during pregnancy. A high prevalence of maternal overt hypothyroidism was observed in Ubangi [35], and rates as high as 73 % have been reported in the severely iodine deficient Andean Mountains area, where the mean UIC is 17.2 μg/gr creatinine and the total goiter rate is 83 % [33]. Severe iodine deficiency in the mother impairs the availability of thyroid hormone and iodine for the fetal thyroid function and development. A very high prevalence of congenital hypothyroidism has been observed in the endemic goiter areas of Zaire, Ubangi [35], Uttar Pradesh and Kerala, India [37] and in the Andean Mountains [33].

Maternal iodine deficiency is associated with additional reproductive risks including abortion, miscarriages, stillbirths, and neonatal mortality. Several epidemiological surveys have demonstrated an increased risk of unsuccessful pregnancy with endemic goiter. Increased neonatal mortality and anomalies of the central nervous system associated with severe iodine deficiency have been observed in Nepal [38], and proportionally more stillbirths and neonatal deaths occurred among the offspring of iodine deficient women in Papua New Guinea [39]. The influence of iodine

deficiency on reproductive failure is clearly demonstrated by the fact that when iodine is administered to women before pregnancy obstetric outcomes improve. Prenatal iodine supplementation in Tasmania reduced the rate of stillbirth from 20/1000 to 12/1000 [40], in Zaire from 18/1000 to 9/1000 [41]. In Algeria prenatal supplementation reduced the rates of prematurity, stillbirth, and abortions, whereas placental and birth weights increased [42]. In Western China following the addition of KIO3 to irrigation water the infant mortality rate was halved over several years [43]. A review of the effects of iodine deficiency on reproductive failure was published by McMichael et al. [44].

Cretinism

Endemic cretinism is the most severe manifestation of dietary iodine deficiency. It is classically seen in individuals born and living in areas of severe iodine deficiency and endemic goiter, who exhibit irreversible anomalies of intellectual and physical development not explained by other causes than the environmental factors responsible for goiter. Recognition of the disorder is based on epidemiological considerations, especially the juxtaposition of suspect subjects and severe endemic goiter.

When McCarrison described cretinism in north-western India during the first decade of the 20th century [45], he delineated a neurologic form, with predominantly neuromotor defects, including strabismus, deaf-mutism, spastic diplegia, and other disorders of gait and coordination. These individuals usually had a goiter. The other form, which he called the myxedematous form, manifested as severe hypothyroidism, short stature, and markedly delayed bone and sexual maturation. These patients usually had a thyroid which was normal in size and position, and were seldom deaf. In some regions one of the two types of cretinism may predominate, but in other areas a combination of the two syndromes can occur.

Pathogenesis and Clinical Manifestations

The clinical picture of endemic cretinism results from the product of two pathophysiologic events. Both events share a common feature, namely iodine deficiency, but act at different points in time. The first event occurs in all individuals with cretinism and represents the prenatal action of thyroid hormone deficiency on fetal brain development. A consistent pattern and intensity of neurological, intellectual, and audiometric deficits is common to and equally present in all types of endemic cretinism. The nature of these deficits points to an intrauterine insult to the developing fetal nervous system around the time of the mid second trimester. The second event represents the postnatal action of thyroid hormone deficiency on somatic as well as brain development. Whereas previous investigators attributed differences in the clinical presentation of endemic cretinism exclusively to the presence or absence

of prenatal hypothyroidism, the distinction between the types of endemic cretinism is additionally related to the length and severity of postnatal thyroid hormone deficiency. Individuals with endemic cretinism with predominant neurological features have only transient hypothyroidism in the postnatal period. The prevalence of goiter in these individuals is high and clinically they are euthyroid, although subclinical hypothyroidism with elevated TSH may occur. In some severely involved individuals, leg muscles are thin and undergrown, and feet are weak. This reflects a loss of anterior horn cells in the spinal cord. Within the broad syndrome of neurological endemic cretinism, the severity of particular features may vary widely. Deafness may be minimal or may be complete; spasticity may be prominent or subtle; speech may be impossible, or may be functional and only mildly dysarthric [46–48].

By contrast, cretinous individuals with marked myxedematous features have permanent and severe postnatal thyroid hormone deficiency. Their clinical characteristics, including growth retardation, bone age, and degree of intellectual impairment, are highly correlated with their degree of hypothyroidism. Other fundamental characteristics are relatively low radioiodine uptake and an absence of goiter in populations where goiter prevalence is very high. This is attributed to thyroid failure and atrophy. The serum concentrations of T4 and T3 are typically undetectable, with very high levels of serum TSH. In addition to signs of neurological damage, these individuals typically have dwarfism, are sexually immature, and have marked clinical features of myxedema. Whether the thyroid gland's morphologic response to iodine deficiency is goiter or thyroid atrophy, dictates the final clinical outcome. In conclusion, our hypothesis states that the clinical expression of endemic cretinism is determined both by fetal hypothyroidism, which results in neurological damage, and the duration and magnitude of postnatal hypothyroidism, which dictates the final clinical appearance [49]. The two phenotypes overlap in some regions.

Thyroid hormone treatment of patients diagnosed with cretinism does not improve intellectual development or intellectual performance, but does lead to definite acceleration in tooth development and linear growth [50]. In addition, improvements in facies, general appearance, and activity levels have been noted.

Cognition and Motor Function

Endemic cretinism constitutes only the most extreme expression of a spectrum of abnormalities of physical and intellectual development and in the functional capacities of the thyroid gland. Many cross-sectional studies have shown clear evidence of the adverse effects of iodine deficiency during pregnancy, such as reduced intellectual function and motor skills [51–55], and language and hearing deficiency [36] in children born to iodine deficient mothers. A meta-analysis of 18 studies, comprising 2214 subjects, concluded that iodine deficiency lowered the mean intelligence quotient by 13.5 points [56]. In regions of severe deficieny, iodine supplementation is highly effective in preventing the neurological damage, and improving intellectual

and psychomotor performances [57–59]. Correction of iodine deficiency during the second trimester reduced neurological abnormalities, increased head growth, and improved the development quotient in a severely iodine-deficient area of Western China [60, 61].

The Relationship Between Iodine, Iron and Vitamin A

In developing countries the prevalence of multiple overlapping micronutrient deficiencies is high, particularly in young children and pregnant women. Coincidentally, iodine deficiency disorders may also be prevalent in these regions. Deficiencies of iron and vitamin A may influence the metabolism of thyroid hormones and potentially exacerbate IDD, and may also reduce the efficacy of iodine prophylaxis.

Iron Deficiency

Deficiencies of iron and iodine are a major public health problem, which together affect about 30 % of the global population. A national screening study in Iran found that goiter was 3.8 times more prevalent in school children with low serum ferritin (SF) levels than in children with normal SF concentrations [62]. Iron deficiency anemia (IDA) reduces thyroid hormone concentration. A significantly lower T3 concentration has been reported in anemic women as compared to healthy controls [63] and it has been observed that the relative increases in TSH, T4, and T3 after cold exposure were smaller when the iron balance was negative than when it was positive [64]. Experimental studies in rats demonstrate that IDA blunts the TSH response to cold exposure and impairs the T4 to T3 conversion [65]. Another possible reason for this interaction is that iron deficiency may lower thyroid peroxidase activity and interfere with thyroid hormone synthesis [66]. The mechanisms by which iron influence thyroid metabolism have been reviewed by Hess [67].

A high prevalence of IDA may limit the effectiveness of iodine intervention programs in regions where these deficiencies coexist. It has been shown that the therapeutic response to oral iodized oil is impaired in goitrous children with iron deficiency anemia, compared to goitrous children who are not anemic [68].

Vitamin A Deficiency

Human studies have shown an association between thyroid function and vitamin A metabolism. A negative correlation between palpable goiter and serum retinol concentration was reported in Senegal [69], and significantly lower serum retinol levels were found in Ethiopian children with visible goiters than in children without

goiters [70]. In a recent investigation in children with severe iodine deficiency from Northern Morocco, thyroid volume, TSH, and thyroglobulin, were all higher with increasing severity of vitamin A deficiency [71].

Vitamin A deficiency (VAD) decreases thyroidal iodine uptake, impairs thyroglobulin synthesis, and increases the risk of goiter [72–74]. Increased thyroid weights in vitamin A-deficient animals have been seen by some investigators [70, 75]. Increased concentrations of circulating thyroid hormones in VAD rats, with a negative correlation between the amount of free T3 and serum vitamin A, have been observed in some studies [76, 77].

The interaction between thyroid metabolism and vitamin A deficiency is partially attributed to the low concentrations of retinol-binding protein observed in vitamin A-deficient rats [78]. This is important for the transport of retinol as well as T4 and T3, as it forms a complex with T4-binding prealbumin, called transthyretin. The change in plasma transport consequently causes a change in plasma concentrations of thyroid hormones. An increase in hypothalamic TRH and pituitary TSH content in vitamin A deficiency has been found, which implies that vitamin A deficiency may also modulate T4 feedback of TSH secretion [79]. A more detailed review of the association of vitamin A on thyroid function has published by Hess [67].

Conclusions

The most extreme consequence of severe iodine deficiency is endemic cretinism. Children born to mothers who are iodine deficient are also at risk of subclinical deficits including impaired neurological and intellectual development. An increased risk of abortions, stillbirths, miscarriages, and neonatal deaths is also associated with severe iodine deficiency. The interaction of iron and vitamin deficiency may aggravate the impact of IDD. Another consequence of severe iodine deficiency is a very high prevalence of goiter and thyroid nodules, which are prone to iodine-induced hyperthyroidism. Iodine prophylaxis, mainly through universal salt iodization, is the most cost effective strategy for preventing these consequences.

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Chapter 5
Mild to Moderate Iodine Deficiency

Creswell J. Eastman and Mu Li

Abstract Measurement of iodine excretion in urine is the accepted surrogate marker for dietary iodine intake. Results of these measurements are used to classify and report the spectrum of iodine deficiency in a population as mild, moderate or severe, but the evidence supporting these definitions is imprecise and questionable. The current practice of describing a population as being iodine deficient is based on single spot urine iodine excretion measurements, rather than measuring habitual iodine intake. We examine and question current practices of extrapolating spot urine iodine results, obtained in school-age children, to other segments of a population as being representative of iodine deficiency in the population as a whole. We suggest that the time has come for a review of definitions and a revised classification system for iodine deficiency rather than repeating the historical imprecise descriptors of mild, moderate and severe iodine deficiency.

While the crippling, adverse consequences of severe iodine deficiency are indisputable, the frequency and extent of damage – the iodine deficiency disorders (IDD) – caused by the currently accepted definitions of mild to moderate iodine deficiency remains uncertain. Enlargement of the thyroid gland in response to continuing iodine deficiency is a normal physiological adaptation designed to maintain normal secretion of thyroid hormones and prevent deficiency disorders. It only becomes a pathological entity when the body can no longer compensate for inadequate iodine intake and irreversible pathological changes occur. Underpinning our understanding of IDD is the assumption that all of the damage to the central nervous system and other organs occurring in association with iodine deficiency is a consequence of deficient thyroid hormone secretion and action. There is evidence for this assumption in populations suffering from severe iodine deficiency but a paucity of good evidence for any significant effect in mild to moderate iodine deficiency. Of particular interest is the recent findings, in the United Kingdom and Tasmania

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Australia, of neurocognitive impairment in the offspring of children born to mothers who were documented to have mild iodine deficiency during pregnancy. While we cannot readily explain these findings as no data was collected on maternal and fetal thyroid function, good clinical practice should ensure that iodine intake during pregnancy is optimised while we await the outcome of randomised controlled trials of iodine supplementation during pregnancy.

Abbreviations

ADHD	Attention-deficit hyperactivity disorders
ALSPAC	Avon Longitudinal Study of Parents and Children
EAR	Estimated Average Requirement
IDD	Iodine deficiency disorders
IQ	Intelligence quotient
RCT	Randomized clinical trial
RDI	Recommended dietary intake
SAC	School-aged children
TSH	Thyroid stimulating hormone
UIC	Urinary iodine concentration
WHO	World Health Organization

Introduction and Historical Aspects

Iodine deficiency disorders (IDD) in humans comprise a wide spectrum of disorders, expressed as damage in most organ systems, but the most pronounced and irreversible consequences occur in the human brain [1]. IDD specifically targets the developing central nervous system in the fetus and infant. The best known association between iodine deficiency and human disease is endemic goiter, recognised for generations by many different societies. The underlying mechanism for the IDD is believed to be decreased thyroid hormone production and action in target tissues as a consequence of lack of dietary iodine. There is no evidence that lack of iodine *per se* causes any direct tissue damage. Although many populists espouse, most commonly via Internet posts, direct biological actions of iodine on tissues such as the brain and the breast, there is no convincing scientific evidence for this speculation.

The critical issue in an individual that determines adverse outcomes from iodine deficiency is the adequacy of the total body iodine stores. These stores reside mostly as protein bound iodine in the thyroid gland and also to a lesser extent as iodine stored in extrathyroidal tissues [2]. This issue is frequently overlooked or ignored in discussions about iodine deficiency, probably because body iodine stores are so difficult to measure. Several different iodine balance studies have shown thyroidal iodine stores to be approximately 10–20 mg in euthyroid adults living in iodine sufficient environments [2, 3]. Assuming an average of 15 mg, the iodine-replete euthyroid adult stores

100 times the recommended daily iodine intake, without consideration of extrathyroidal iodine stores contained in circulating thyroid hormones and their metabolites.

The severity of IDD at particular times in the human life cycle, especially during growth and development, appears directly related to the degree and duration of the iodine deficiency [4]. Logically the degree of iodine deficiency should be reflected in clearly quantified decreases in circulating levels of thyroid hormones and compensatory increases in circulating thyrotropin (TSH) concentrations. However, this is not always the case, or alternatively the changes are too subtle to be readily measured.

Classification and Characterisation of Mild, Moderate and Severe Iodine Deficiency in Humans

How we view and describe the spectrum of mild, moderate and severe iodine deficiency is imprecise and is derived from observational studies lacking a solid evidence base. For generations the term "endemic goiter" has been considered synonymous with iodine deficiency. Enlargement of the thyroid gland is an adaptation to iodine deficiency and is explained by decreased thyroid hormone synthesis and secretion in response to a lack of iodine supply. The compensatory increased TSH secretion stimulates hyperplasia and hypertrophy of the thyroid cells to maintain normal thyroid function. In populations suffering mild to moderate iodine deficiency there is a paucity of evidence demonstrating significant abnormalities in thyroid function, raising the possibility of the participation of other hormonal or growth factors, in addition to TSH, stimulating the development of goiter.

The original classification of the severity of iodine deficiency into mild, moderate and severe was derived from epidemiological goiter surveys. Determination of goiter size and prevalence in school-age children (SAC), usually 6–12 years of age, within affected communities has been extrapolated to the community as a whole. The underlying assumption for these studies has been that the volume of the thyroid gland varies inversely with the iodine intake, while appreciating that there may be a long lag-response phase (months to years) in this relationship. The most useful definition of the term goiter accepted by the WHO is that the thyroid gland is enlarged, and further described specifically as "a thyroid gland each of whose lobes have a volume greater than the terminal phalanges of the thumb of the person being examined will be considered goitrous" [5]. Grade 0 is no palpable or visible goiter, Grade 1 is a thyroid gland that is palpable but not visible when the neck is in the normal position and Grade 2 is a clearly visible swelling when the neck is in the normal position and consistent with an enlarged thyroid when the neck is palpated. It is accepted that specificity and sensitivity of the palpation method is poor and exacerbated by the level of inexperience and lack of training of the observer. Our view, formed from extensive fieldwork experience, is that conclusions based on such epidemiological studies may be misleading and at times of no value. In the modern era, goiter surveys should be performed by ultrasonographic measurement of thyroid volume by trained operators. Despite these serious limitations, the total goiter rate was the original basis for the development of the criteria for determining the severity of IDD and

Table 5.1 Epidemiological criteria for assessing the severity of IDD based on prevalence of goiter in school-age children

	Degree of IDD as percentage of total number surveyed			
Total goiter rate	None	Mild	Moderate	Severe
	0.0–4.9 %	5.0–19.9 %	20.0–29.9 %	>30 %

Adapted from WHO 2007, Ref. [5]

remains in current use as a marker of iodine deficiency in a population as shown in Table 5.1 [5]. SAC have been the preferred target group for goiter surveys for several reasons, including the ready availability and cooperation of children of this age and the ease of access to schools for examining children. In addition, at these ages they are mostly pre-pubertal and any increase in thyroid volume is more likely to represent the effects of the current status of iodine nutrition or recent habitual iodine intake in that community. By contrast, endemic goiter in adults usually represents past events that have caused irreversible changes to the thyroid gland. Unfortunately, data collected from SAC goiter surveys have traditionally been extrapolated, frequently without adequate validation, to conclusions about other segments of the community such as pregnant women, infants, and younger children. Of course, the more severe the iodine deficiency the more likely there will be highly prevalent and readily detectable enlarged thyroid glands in that community (Table 5.1).

As previously mentioned, the critical issues are first the habitual daily iodine intake and the underlying quantity of iodine stored in the thyroid, which are the determinants of thyroid function; and second the compensatory thyroidal and non-thyroidal mechanisms an individual utilises to protect from the tissue damage caused by thyroid hormone deficiency. Unfortunately, because there is no simple way of measuring thyroidal iodine stores this critical parameter is generally overlooked or ignored.

Classifying IDD as mild, moderate and severe on the basis of goiter rates in a community is a very arbitrary descriptive definition. It was useful for documenting goiter rates in remote populations when iodine deficiency in a population was viewed as being synonymous with endemic goiter. With the development of a new public health paradigm by Hetzel [1] moving the emphasis from endemic goiter to the wider spectrum of IDD, and more particularly brain damage, the measurement of urinary iodine concentration (UIC) became the accepted marker for the diagnosis of iodine deficiency in a population. Subsequently the classification of mild, moderate and severe iodine deficiency based on goiter rates was transferred to median levels of iodine excretion in the urine, measured by spot UIC.

Role of Goitrogens in the Biological Expression of Iodine Deficiency

Goitrogens are environmental substances, occurring in foodstuffs and drinking water, which interfere with iodine uptake or utilisation by the thyroid. In communities with an adequate iodine intake these substances probably have little or no effect

on thyroid growth and function, but become relevant when there is coexisting iodine deficiency [6]. Malnutrition and poor living conditions probably also contribute to their negative effects on thyroid function. Besides ingestion of foods containing goitrogens, the most ubiquitous environmental goitrogenic factor is tobacco smoking due mainly to inhalation of thiocyanates in the tobacco leaf [7].

Dietary Reference Intake for Iodine

To identify and understand the spectrum of mild to severe deficiency first requires quantification of the average dietary iodine intake necessary to maintain normal thyroid function and thyroid volume at all stages of the life cycle. Many different countries and international organizations have established dietary intakes for iodine [5, 8, 9]. Adequate Intake (AI) is the average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group, or groups, of apparently healthy people that are assumed to be adequate; the Estimated Average Requirement (EAR) is the daily nutrient level estimated to meet the requirements of 50 % of the healthy individuals in a particular life stage and gender group and; the Recommended Dietary Intake (RDI) is the daily intake that is sufficient to meet the requirements of nearly all (>97 %) healthy individuals in a particular life stage and gender group. The RDI is equal to the EAR + 2SD of the EAR.

The EAR and RDI were developed for adults using thyroidal iodine accumulation and turnover data published many decades ago [3, 10]. These data were derived from very small numbers of normal volunteers; for example Fisher and Oddie [3] studied 18 adult euthyroid volunteers and De Groot [10] studied only 4 euthyroid adult volunteers in addition to small numbers of patients with thyroid disorders.

Data for children and adolescents (ages 8–18 years) were determined from a Belgian study published in 1969 in which the researchers stated *"The purpose of these investigations was to determine whether euthyroid people living in a relatively iodine-poor dietary environment (a) are usually in negative iodine balance and (b) whether or not an"obligatory"excretion of iodine can be demonstrated where dietary Iodine is low"* [11]. Optimal intakes for younger children were derived by extrapolation from adult EAR values based on body weight [12]. While convenient, this practice is poorly validated and not well supported by evidence. Many national agencies have set levels of intake that are considered optimal for maintenance of good health, particularly good thyroid health and prevention of deficiency disorders [13, 14]. Most of these recommendations are comparable with one another, which is not surprising given that recommendations are essentially based upon the same source material [14]. In a recent thoughtful publication discussing evidence needed to inform the next dietary reference intakes for iodine, Trumbo makes the point that the EARs and RDIs were set for adults using data published in the 1950s and 1960s based on thyroidal iodine accumulation and turnover studies as indicators of daily iodine needs [12]. Clearly, the time has come for a reassessment of these dietary intake recommendations, and more research needs to be undertaken to validate them (Table 5.2).

Table 5.2 Recommended daily iodine intake by age or population groups

WHO/UNICEF/ICCIDD recommended daily iodine intake (RNI)		Institute of Medicine recommended daily iodine intake (RDA)	
	Iodine intake (μg/day)		Iodine intake (μg/day)
Children 0–5 years	90	Infants 0–12 months	110–130
Children 6–12 years	120	Children 1–8 years	90
		Children 9–13 years	120
Children > 12 years and adults	150	Children ≥ 14 year and adults	150
Pregnant women	250	Pregnant women	220
Lactating women	250	Lactating women	290

Adapted from WHO 2007 and IOM 2001, Refs. [5, 8]

When data from UIC levels are used to extrapolate to dietary requirements it is either the EAR or the RDI that is used as the reference point. Trumbo [12] states that the EAR and not the RDI should be used to estimate the prevalence of inadequate intake in groups, since using the RDI to assess populations will overestimate nutrient inadequacy [15].

Estimation of iodine intake by documentation of food composition assessment is frequently confounded by variations in food iodine content and lack of information in country specific food composition tables. Nonetheless it is used as an alternative to calculations based on UIC and UIE to provide an assessment of dietary iodine intake [16].

Assessment of Iodine Intake and Degree of Iodine Deficiency by Measurement of Urinary Iodine Concentration (UIC)

Dietary iodine is readily absorbed from the upper gastrointestinal tract and transported in the circulation as iodide. It is cleared from the circulation predominantly by the thyroid and kidney, but also by salivary glands and the lactating mammary gland. Absorption of dietary iodine and iodate from the gastrointestinal tract is on average approximately 90 % [8]. Not much is known of the relationship between the degree of absorption and the level of thyroidal iodine stores. This is usually ignored in most research publications. Further, little is known about factors compromising bioavailability of iodine in iodine containing foods.

Excretion of iodine in the urine is not simply a function of dietary intake but is subject to multiple variables including gender, body weight, hydration, urine flow and volume, pregnancy, ethnicity, climate, seasonal and other endogenous and exogenous factors such as environmental goitrogens. The quantity of iodine excreted in the urine has become the proxy for calculating iodine intake and monitoring the response of populations to iodine supplementation programs. The usual practice is to measure

Table 5.3 Epidemiological indicators and criteria for assessing and defining iodine deficiency based on UIC

Median UIC (μg/L)	Iodine intake	Iodine nutrition status
School-aged children (≥6 years) and adults		
<20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Adequate iodine nutrition
200–299	Above requirements	More than adequate intake, may pose a slight risk in general population
≥300	Excessive	Risk of adverse health consequences
Pregnant women		
<150	Insufficient	–
150–249	Adequate	–
250–499	Above requirements	–
≥500	Excessive	–

Reference [17]

UIC in a spot sample of urine and then extrapolate this result to make an estimate of 24 h urine volume to calculate the 24 h Urinary Iodine Excretion (UIE). The following formula is recommended by the Institute of Medicine (IOM) to calculate iodine intake in epidemiological studies and as a substitute for standardised dietary assessment methods [8]. Spot urinary iodine (UIC μg/l) × 0.0235 × body weight = daily iodine intake. For example, a spot UIC of 100 μg/l for a person of average body weight of 65 kg would yield an intake of 153 μg/day. This is the basis for the quoted relationship between a UIC (100 μg/l) and RDI of 150 μg/day. A different value for UIE is obtained from the more commonly used calculation of spot UIC of 100 μg/l × 0.92 × 1.5 (urine volume in litres) = 138 μg/day intake. This calculation assumes an average adult daily urine output of 1.5 litres, but takes no account of body weight, level of hydration or other factors that may influence urine output (Table 5.3).

To calculate the dietary intake of iodine in children, age and body weight and specific urine volumes should be employed, but many ignore this requirement when reporting survey data. When corrections for urine output are made in children the calculations are usually based on a single source reference for urine volumes published in 1995 [18]. These data refer only to British children and may not be applicable to different ethnic races in vastly different environments and climates around the world. If the quoted median urine flow value of 0.9 ml/h/Kg body weight is used from the above report, it should be noted that the corrected urine output levels may vary several fold between individuals, suggesting the potential errors in using spot UIC to estimate UIE are so huge as to make the data questionable or even invalid. It is of concern that while these methods are currently used by workers in the field to estimate iodine intake from UIC and UIE, particularly on spot urine samples, there are few research studies across the range of iodine intakes from very low to very high to validate these methods [19].

Relationship Between UIC and UIE

UIC is estimated in spot urine samples because of the difficulty in obtaining reliable 24 h urine collections. Expressing the result with reference to urinary creatinine excretion (UIC μg/l per gram creatinine), rather than μg/l, was thought to be the best way to compensate for variability of urine volumes as daily creatinine excretion was assumed to be relatively constant. However, due to day-to-day variations in urinary creatinine excretion and low excretion rates in populations with inadequate dietary protein intake, it has been argued that this method does not provide any advantage over simply expressing UIC as μg/l [20]. Perhaps we have been too premature in abandoning this method. A recent study from China assessing UIE in iodine sufficient pregnant women found that using the conventional spot UIC spuriously increases the prevalence of iodine deficiency during pregnancy and that UI/Cr better reflects the 24 h urinary iodine excretion [21]. The underlying variable is the increased glomerular filtration rate and increased urine volume during pregnancy leading to a dilutional effect with a lower UIC per litre, but not an overall decrease in urine iodine over a 24 h time-period [21]. In a study comparing different methods of reporting iodine content in the same urine sample Als and colleagues reported that using the iodine excretion/24 h sample (UIE) as the reference standard, both UIC measured as μg iodine/g creatinine and μg iodine/l clearly underestimated the iodine intake in subjects with adequate dietary protein intake [19].

Returning to the most important question of "how well does the spot UIC reflect UIE and hence daily iodine intake"? This relationship has been explored in a number of studies in different population groups [21–25]. What emerges from most of these studies is that extrapolation of spot UIC measurements to determine UIE, and hence an estimation of daily iodine intake, is fraught with error and often misleading in determining the iodine nutritional status of any given population.

In a recent systematic review aimed at identifying studies that had investigated iodine intake and biomarkers, Ristic-Medic and colleagues performed a meta-analysis to estimate the dose-response relationship between iodine intake and iodine status [26]. Their analysis indicated that within the iodine intake range of 120–500 μg/day, doubling the daily intake of potassium iodate increased the UIC by 97 % in adults, 81 % in pregnant women but only 26 % in children. These discrepancies are difficult to explain and call into question the validity of current methods employed in this field. Zimmermann and colleagues [15] addressed the issue of the importance of habitual iodine intakes in populations and emphasised the difficulty of obtaining an accurate estimate of iodine intake in an individual because the day to day variation in iodine intake may be high.

Evidence for UIC and UIE Underpinning the Current Classification of the Severity of Iodine Deficiency in a Population

The UIC has now largely replaced total goiter rate in epidemiological studies defining population ID status and positive responses to salt iodisation programs. Despite all the limitations we have pointed out the UIC is the most widely studied and

accepted biomarker of iodine nutritional status recommended by international authorities [5, 8, 9]. In essence, the iodine concentration in urine reflects recent iodine intake – the past few days – but not the habitual intake over the past months. This is why population studies of UIC yield large variations from person to person. The more homogeneous the population and greater consistency of daily dietary iodine intake the smaller the spread of results in UIC levels [15].

The WHO epidemiological criteria for classification of mild, moderate and severe iodine deficiency, based on median UIC levels in school-aged children, is shown in Table 5.3. Severe iodine deficiency is a UIC <20 μg/l, moderate is 20–49 μg/l and mild is 50–99 μg/l. These definitions are usually quoted and accepted without question. But, what is the evidence underpinning these definitions that correlate mental and physical disorders with specific median population UIC levels? In our view the evidence is very difficult to find and at best weak. Laurberg and colleagues in an excellent review of iodine intake as a determinant of thyroid disorders in an iodine deficient population reproduced the data from population studies undertaken in South America recording the association between frequency of goiter and UIE [27].

These data confirm that goiter prevalence is common when UIE (calculated as μg/day) is less than 30–40 μg, but less common when UIE is between 40 and 60 μg and almost non-existent in those with a UIE >60 μg per day. These data suggest that a reasonable cut-off point for iodine deficiency causing goiter is a UIE of approximately 60 μg/day. This is roughly equivalent to a UIC of 40 ug/l, assuming a daily urine output of 1.5 litres. It is difficult to reconcile these estimates with published UIC limits and recommended daily intakes from WHO, IOM, and other international agencies [5, 8, 9]. Indeed, the data in Fig. 5.1 suggests that there is little evidence to continue to use the current classification of mild, moderate and severe iodine deficiency. We are unable to find better published data using goitre prevalence and UIC. In summary, the evidence base underpinning the measurement of UIE, especially from measurements of spot UIC, and extrapolation to iodine intakes and classification of populations as suffering mild, moderate or severe iodine deficiency is based on questionable data and premises.

Adverse Biologic Effects of Mild to Moderate Iodine Deficiency

The adverse effects on the brain and body of moderate to severe iodine deficiency are well known and not disputed [1]. There is a large body of literature documenting the wide spectrum of disorders in populations living with long-standing moderate to severe iodine deficiency. It should be noted that the most populations suffering from severe IDD reside in impoverished environments with sub-standard nutrition and are likely to suffer from multiple micronutrient deficiencies that could contribute to the biological expression of the consequences of iodine deficiency. For example, a coexisting selenium deficiency may contribute to goiter development in iodine deficient populations [28].

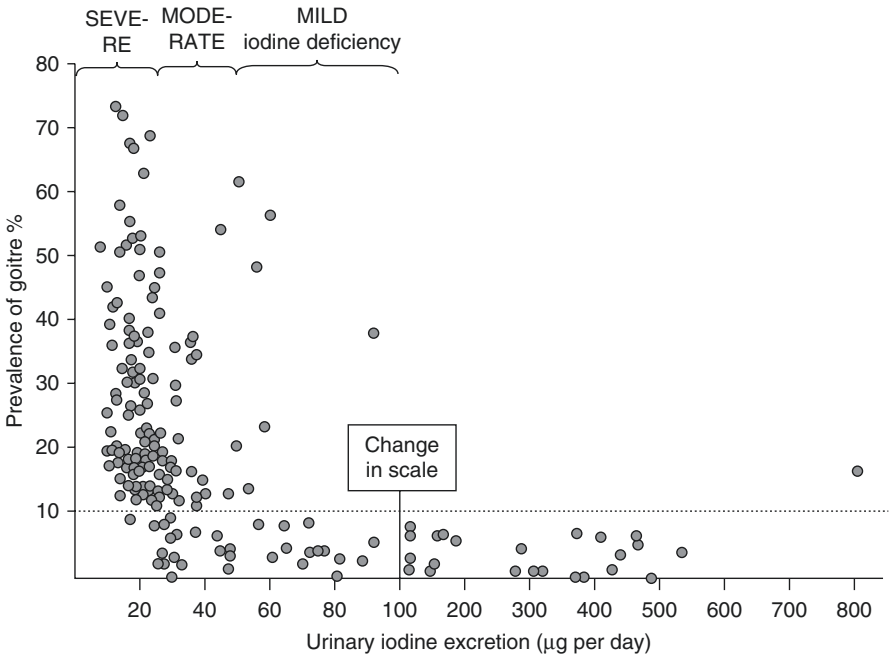

Fig. 5.1 Average urinary iodine excretion (UIE) and prevalence of goiter in the general population of 186 localities in Central America during the period 1965–1967. Each point represents an average of values from subjects of 20 randomly selected families. Goiter and UIE were measured in 21,611 and 3,181 subjects, respectively [27] (Reproduced with permission from Elsevier; the figure was kindly provided by the late Professor Peter Laurberg)

Endemic Goiter and Thyroid Dysfunction

There is no debate that severe iodine deficiency causes goiter and predisposes to hypothyroidism. There is a wealth of evidence to support a cause-and-effect relationship. Iodine deficiency decreases thyroid hormone synthesis by impairing iodination of the thyroglobulin molecule in the thyroid cell with a consequent fall in the serum thyroxine level, leading to increased pituitary TSH secretion and greater stimulation of the thyroid that responds by cellular hypertrophy and hyperplasia. This is believed to be a compensatory phenomenon to maintain normal circulating thyroid hormone concentrations at the expense of an enlarged thyroid gland. Of course, if the thyroid fails to compensate then hypothyroidism will likely result. In time the thyroid responds to chronic iodine deficiency by enlarging further and developing nodular changes. These nodules may become autonomous and if exposed to increased iodine intake may paradoxically cause hyperthyroidism [29]. It is generally accepted that the risk of goiter increases with the degree and chronicity of iodine deficiency. However, scientific evidence from long-term prospective studies is lacking to provide specific levels of deficiency at which this is likely to occur. In addition, as previously mentioned, iodine deficiency frequently coexists

with other micronutrient deficiencies and the effects of intake of goitrogens such as tobacco smoking in adults may magnify the expression of the underlying iodine deficiency.

Brain Damage and Neurocognitive Impairment

The WHO says that iodine deficiency is the single most important cause of preventable brain damage in our world today [5]. To be precise, this statement refers more correctly to iodine deficiency occurring during pregnancy, infancy and possibly early childhood causing irreversible damage to the developing brain. In a comprehensive study of the neurological damage caused by moderate to severe iodine deficiency as the cause of neurological cretinism – the most egregious manifestation of severe iodine deficiency – Halpern and colleagues in 1991 [30] proposed that maternal hypothyroxinaemia, occurring early in pregnancy from iodine deficiency, reduces placental transfer of maternal thyroxine and so deprives the developing fetus of adequate thyroid hormone for optimal brain development. While the brain damage is global, it is manifested most prominently in structures such as the cochlea, basal ganglia, and cerebral cortex that commence development in the first trimester with maximal growth in the second trimester [30]. Therefore, prenatal thyroid hormone deficiency – caused by decreased placental thyroxine transfer from the mother, compounded by impaired fetal thyroid hormone synthesis later in gestation from maternal iodine deficiency – offers an explanation for fetal brain damage independent of any direct effect of iodine deficiency on brain development [4, 30]. In communities affected by severe iodine deficiency inhabitants show lower intelligence quotient (IQ) scores compared with iodine replete communities [31, 32]. These lower IQ scores are often associated with other signs of neurological deficit such as impaired hearing and gait disorders or may occur independently of any other overt signs of brain damage [4, 30].

The important question that needs to be considered is the likelihood of neurocognitive impairment in young children living in environments classified as having mild to moderate iodine deficiency. It has been well established that impaired neurodevelopment occurs in the children born to iodine sufficient women with mild thyroid hormone deficiency during pregnancy due to diminished placental transfer of thyroid hormone to the fetus [33]. It has been assumed from poorly controlled observational studies that mild to moderate iodine deficiency during pregnancy may impair neurocognitive development in the offspring, presumably by the same mechanism of reducing the quantity of thyroxine delivered to the developing fetus [34]. Impaired neurocognitive development and attention-deficit hyperactivity disorders (ADHD) have been reported in the children born to mothers with mild to moderate iodine deficiency during pregnancy [35, 36]. In these latter studies no evidence has been produced for decreased circulating levels of thyroxine in the mothers of the children, so the evidence for adverse effects is circumstantial. In reviewing the evidence on iodine deficiency in pregnancy and the effects of maternal iodine supplementation on offspring, Zimmermann stated that the potential adverse effects of mild-to-moderate iodine deficiency during pregnancy remain unclear [37].

In a systematic review of randomized controlled trials and the Cochrane Register of Controlled Trials, Zhou and colleagues highlighted the paucity of evidence for improvement in childhood intelligence and other growth and development outcomes from iodine supplementation in pregnant women [38]. In another systematic review, Taylor et al reported that there was a lack of convincing evidence from randomised controlled trials (RCT) for beneficial effects of gestational iodine supplementation on infant neurodevelopment [39]. However, they concluded from a pooled analysis of two RCTs measuring cognitive function in school age children that there were modest benefits resulting from iodine supplementation.

Two recent studies have attempted to confirm or exclude adverse effects from mild to moderate maternal iodine deficiency on neurocognitive outcomes in their offspring. In a mother-child pair study, conducted in a region of mild iodine deficiency in south west England (Avon Longitudinal Study of Parents and Children – ALSPAC), the investigators studied the effects of maternal iodine deficiency on the IQ of the offspring tested at 9 years of age [40]. After adjustment for confounders, they found that children born to women with an iodine to creatinine ratio of 150 μg/g during pregnancy were more likely to have IQ scores in the lowest quartile for verbal IQ, reading accuracy and reading comprehension, compared with children born to mothers with ratios of 150 μg/g or more. These IQ scores declined progressively with decreasing UIC values [40]. In a similar study conducted in Tasmania Australia, Hynes and colleagues sought to determine whether children born to mothers with a UIC <150 μg/l during pregnancy (defined as mild to moderate iodine deficiency) had poorer educational outcomes compared with peers whose mothers had a UIC >150 μg/l (iodine replete group). After adjusting for confounding factors, they found significant reductions of 10 % in spelling, 7.6 % in grammar and 8.7 % in English literacy in children of the iodine deficient mothers, compared with the iodine sufficient mothers, when children were tested at age 9 years [41]. While both the British and Australian studies provide persuasive evidence for adverse effects of mild iodine deficiency during pregnancy on brain development and cognitive function in the offspring, neither study demonstrated any evidence for impaired maternal thyroid function and both studies lack the convincing degree of evidence that comes from randomised controlled trials. Nonetheless, good clinical practice requires that mild-to-moderate iodine deficiency, as currently defined by median UIC levels <150 μg/l in pregnant women, be addressed at both public health and individual patient levels to prevent impaired neurocognitive outcomes in children born to iodine deficient mothers [42].

Discussion

The original epidemiological criterion for assessing the severity of IDD in a population was based on the prevalence of goiter in school-age children, categorising a population into mild moderate or severe, depending on the goiter rate, and it continues to be recommended as an impact indicator [5]. While historically useful,

especially for assessing populations living in remote regions, this time-honored method has largely been replaced by measurement of UIC in spot urine samples. In recommending this methodology the WHO states *"in individuals the urinary iodine excretion can vary somewhat from day to day and even within a given day, however this variation tends to even out among populations – and studies have convincingly demonstrated that a profile of iodine concentrations in morning or other casual urine specimens (child or adult) provides an adequate assessment of a population's iodine nutrition if a sufficient number of specimens are collected*" [5]. Again, close scrutiny of the evidence underpinning this recommendation reveals that reliance on casual spot urine specimens yields an imprecise assessment of an individual's urinary iodine excretion. The assumption that day to day variations in UIC can be cancelled out by increasing the sample size is questionable, particularly if other confounding factors have not been controlled in the collection process. Further, as we have discussed, it has been difficult to find evidence to support categorisation of populations into mild, moderate and severe iodine deficiency on the basis of UIC in spot urine iodine samples as recommended by the WHO. Most reports in the literature, providing UIE data extrapolated from spot UIC results, without reference to control of the multiple variables influencing UIC, remain open to question.

The median population UIC level of 100 μg/l, recommended by WHO and other national and international agencies to determine a cut-off point for iodine deficiency, corresponds approximately to an iodine intake of 150 μg/day which is the RDI for adults. Mild iodine deficiency is defined as a median UIC of 50–99 μg/l and moderate as a median UIC of 20–49 μg/l [5]. These numbers translate approximately to daily iodine intakes of between 75–150 μg and 30–75 μg, respectively. By inference severe iodine deficiency would represent a daily iodine intake of less than 30 μg/day. These assumptions are of questionable validity as calculations or extrapolations from spot and 24 h urines are not equivalent [21–27, 43]. It is quite clear that more precise methods are required to define the iodine nutritional status of a population to improve upon the current UIC classification of mild, moderate and severe iodine deficiency. As the implementation of salt iodisation programs progress globally, it is important that we explore more precise measurements of population iodine nutrition. UIC measurements obtained from a sample of school age children are frequently extrapolated inappropriately to other population groups such as infants, preschool children, adults and pregnant women.

While these definitions have been useful, what we need to know is the habitual iodine intake with reference to the EAR or RDI for defined population groups based upon age, sex, reproductive status and possibly ethnicity to ensure optimal iodine nutrition and prevent adverse effects from iodine deficiency or excessive intake. How can we achieve this? Has the time come for a new definition and classification system for iodine deficiency, rather than repeating the historical, imprecise descriptors of mild, moderate and severe deficiency, derived from median UIC levels in school-age children? The information we require to determine iodine deficiency or excess is an estimation of habitual iodine intake, not a "one off" urine test of iodine excretion that essentially reflects only recent iodine intake over the preceding few days and the correlation of intake with well-being and adverse outcomes.

In their Nutrition Reviews article in 2012, Zimmerman and Anderson proposed a new approach in which UIE data are extrapolated to iodine intakes [44]. This was the approach we proposed when estimating the daily iodine supplement for Australian women to take during pregnancy to reach the recommended RDI and ensure that >97 % of pregnant women would have an optimal iodine intake [16]. In defining the iodine status of a population, the emphasis needs to change from simply quoting a median UIC, frequently undertaken without reference to age, gender, body weight, hydration, ethnicity, reproductive status and dietary habits, and then comparing that median with a similar study in other differently constituted populations. More recently Zimmermann in collaboration with researchers from several different countries used the data from national and regional spot UIC studies and calculated daily iodine intake from the relation between body weight and 24 h urine volume and the within person variation by using repeat UIC measurements [15]. They used within person variance proportions to obtain the prevalence of inadequate or excess usual iodine intake by using the EAR. This approach has merit and warrants consideration to replace the current UIC method.

In addition to the development of more precise evidence-based methods to quantify urinary iodine excretion and dietary iodine intake, the time has also come to review the qualitative terminology of mild, moderate and severe iodine deficiency. On the basis of available evidence it is difficult to reconcile quantitative data of median UIC levels in school-age children with the qualitative terminology ascribed to degrees of deficient habitual dietary iodine intake. There is little doubt that severe iodine deficiency will cause the physical and mental consequences described as IDD. While it is likely that there is a spectrum of manifestations of iodine deficiency in any afflicted population, the terminology of mild moderate and severe has little evidence to support it and at times it is misleading. A more appropriate terminology is a quantitative description of iodine intake and how that is interpreted in the context of the EAR or RDI. The time has come for international agencies to accept the challenge of developing and testing new methodologies and definitions to describe the iodine nutritional status of populations.

Most recent and current articles appearing in the medical and scientific literature are documenting the prevalence of mild to moderate iodine deficiency in diverse populations and the UIC responses to salt iodisation or iodine supplementation programs. Severe iodine deficiency is now quite uncommon, if not rare. More research is needed to define an optimal range for iodine intake and a focus on this to prevent both inadequate and excessive iodine intakes.

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Chapter 6
The Effects of Iodine Excess

Angela M. Leung

Abstract Iodine is a necessary micronutrient and essential for the synthesis of the thyroid hormones. Iodine exposure may also occur as a result from iodine fortifications programs (through salt iodization, fortification of foods, or other routes), medications, dietary supplements, topical iodine antiseptics, radiographic iodinated contrast media, and other sources. Excess iodine exposure, particularly among individuals with underlying thyroid disease, has the potential for inducing hyperthyroidism and hypothyroidism. Iodine-induced thyroid dysfunction can be transient or permanent. With the exception of specific medical indications for the use of supraphysiologic iodine, excessive iodine ingestion and/or exposure should be avoided.

Abbreviations

AIH	Amiodarone-induced hypothyroidism
AIT	Amiodarone-induced thyrotoxicosis
CT	Computed tomography
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
IGN	Iodine Global Network
KI	Potassium iodide
LOAEL	Lowest observed adverse effect level
NIS	Sodium/iodide symporter
NOAEL	No observed adverse effect level
RDA	Recommended Dietary Allowance
SSKI	Saturated solution of potassium iodide
TSH	Thyroid stimulating hormone

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TUL	Tolerable upper level
UF	Uncertainty factors
UIC	Urinary iodine concentration
UNICEF	United Nations Children's Emergency Fund
WHO	World Health Organization

Introduction

Iodine is an important micronutrient that is crucial for thyroid hormone production. As it is naturally present as a trace element primarily in coastal areas, iodine deficiency was historically and still continues to be a significant public health issue in many regions of the world. It is taken in primarily through the diet, and universal salt iodization and iodine fortification of foods have been adopted worldwide to prevent the adverse effects of iodine deficiency. The U.S. Institute of Medicine, the World Health Organization (WHO), the United Nations Children's Emergency Fund (UNICEF), and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) [since renamed the Iodine Global Network (IGN)] recommend a daily iodine intake of 150 μg in adults [1, 2].

However, in addition to the diet, iodine exposure can also occur incidentally from medical procedures or medications and other sources, often in concentrations much higher than the recommended daily intake levels. Excess iodine intake or exposure, particularly if acute, can have adverse consequences, due to its potential for inducing thyroid dysfunction, and both iodine-induced hypothyroidism and hyperthyroidism can result. Based on limited supporting data for the threshold for iodine levels that would be deemed unsafe, the U.S. Institute of Medicine has set a Tolerable Upper Level (TUL) (the approximate threshold below which significant adverse effects are unlikely to occur in a healthy population) for iodine at 1,100 μg/day in adults [1], while the WHO, UNICEF, and IGN advise that pregnant and lactating women ingest no more than 500 μg of iodine per day [2] (Table 6.1).

Population Measures of Excess Iodine Exposure

Because of significant variations in dietary iodine intake, the iodine status of a given individual cannot be reliably measured [3]. Thus, iodine nutrition can only be measured in populations, which has historically been done using median urinary iodine concentrations (UIC). Median UICs are a good biomarker of iodine intake. As defined by the WHO, UNICEF, and IGN, median UICs greater than 300 μg/L are consistent with excessive iodine status among 6–12 year old children [2].

Alternatively, thyroglobulin levels measured from dried blood spots may potentially also serve as a measure of iodine status among school-aged children. In one

Table 6.1 Tolerable upper limits for daily iodine intake

U.S. Institute of Medicine [1]		World Health Organization (WHO), United Nations Children's Emergency Fund (UNICEF), International Council for the Control of Iodine Deficiency Disorders (ICCIDD) [2]	
Age	μg/day	Population Subgroup	μg/day
0–12 months	Unknown	Infants	180
1–3 years	200	Pregnancy	500
4–8 years	300	Lactation	500
9–13 years	600		
14–18 years	900		
19–50 years	1,100		

report, the mean dried blood spot thyroglobulin concentration was significantly higher in healthy 6–12 year old children in whom the median UIC was greater than 300 μg/L, suggesting that dried blood spot thyroglobulin levels may serve as a sensitive marker for iodine excess in this population [4].

Thyroidal Response to Iodine Excess

The normal physiologic adaptation to excess iodine exposure is known as the acute Wolff-Chaikoff effect. From experiments during the 1940s, it was recognized that rats exposed to high amounts of iodide through the peritoneum have a reduction in thyroid hormone synthesis that persists for approximately 24 h [5] and thus a corresponding decreased risk for the development of iodine-induced thyrotoxicosis. Although the exact mechanism for this decrease in thyroid hormone production (the acute Wolff-Chaikoff effect) is not completely understood, it has been postulated that several compounds, including intrathyroidal iodolactones, iodoaldehydes, and/or iodolipids, on thyroid peroxidase activity, are formed and work to inhibit thyroid hormone synthesis in the thyroid follicular cell [6]. Furthermore, there may also be a reduction of deiodinase activity within the thyroid, as a result of the excess iodine exposure, which contributes toward decreased thyroid hormone production.

The physiologic phenomena of the acute Wolff-Chaikoff effect and decreased thyroid hormone production are transient in most individuals, as escape from the acute Wolff-Chaikoff effect occurs and normal thyroid hormone production resumes within a few days [7]. The mechanism for the escape was elucidated in 1999, when Eng and colleagues reported that there is a marked decrease in expression of the sodium-iodide symporter (NIS) present on the basolateral membrane of thyroid follicular cells 24 h after the excess iodine exposure occurs [8]. NIS is a 13-transmembrane glycoprotein which mediates the active transport of iodine from

the circulation into the thyroid [9], and decreased thyroidal NIS expression thus results in lower intrathyroidal iodine concentrations. The reduction in intrathyroidal iodine stores results in decreased formation of the iodinated inhibitory substances on thyroid hormone synthesis, thereby enabling the resumption of normal thyroid hormone production.

However, there are certain instances in which the acute Wolff-Chaikoff effect or escape from the effect do not occur, resulting in iodine-induced thyrotoxicosis or iodine-induced hypothyroidism, respectively. Predisposing factors include those which result in dysregulation of the thyroid follicular cell. Thus, individuals with a history of Hashimoto's thyroiditis, Graves' disease (even if treated), postpartum thyroiditis, subacute thyroiditis, partial thyroidectomy, or use of lithium (which traps iodine in the thyroid gland), may be particularly susceptible. The developing fetus or neonate (in whom thyroid development is still occurring) is also particularly vulnerable. In these instances, the iodine-induced thyroid dysfunction may be transient or permanent.

Iodine-Induced Hyperthyroidism

In certain susceptible patients, the excess iodine load provides a rich substrate for increased thyroid hormone production. Iodine-induced hyperthyroidism (the Jod-Basedow phenomenon) was initially described in the early 1800s, when thyrotoxicosis was observed to be more common among those with endemic goiter treated with iodine supplementation, compared to non-goitrous individuals. The frequency of iodine-induced hyperthyroidism varies by the degree of endemic iodine deficiency in the local region and timecourse of iodine exposure; a summary by country has been published [10]. The development of hyperthyroidism following excess iodine exposure can occur within days to weeks [11].

Iodine-induced hyperthyroidism may be transient or permanent, and risk factors include nontoxic or diffuse nodular goiter, latent Graves' disease, and longstanding iodine deficiency [12, 13]. Endemic iodine deficiency predisposes to but not is not necessary for the development of iodine-induced hyperthyroidism, as it has also been described among euthyroid patients with nodular goiter in iodine sufficient areas [13, 14].

Iodine-Induced Hypothyroidism

The underlying mechanism of iodine-induced hypothyroidism is inhibition of thyroid hormone synthesis due to failure to escape from the acute Wolff-Chaikoff effect, but hypothyroidism may also be due to the development of autoimmune thyroiditis resulting from the iodine load. Some data suggest that exposure to high iodine concentrations may also decrease thyroid hormone synthesis and release, as reported in several small studies which show mild decreases in serum thyroid

hormone levels and increases in the serum TSH level to the upper limit of the normal range [15–17]. The development of iodine-induced hypothyroidism can occur as early as weeks following exposure to excess iodine [18].

The developing fetus and young infant are particularly vulnerable to the effects of iodine excess, as normal thyroid function is critical for neurodevelopment and somatic growth. It is thought that the ability to fully escape the Wolff-Chaikoff effect does not mature until around 36 weeks gestation, so that although pregnant women who receive a large iodine load might be able to maintain normal thyroid function, their fetuses could become selectively hypothyroid. One recent case series described three newborn infants who were found to be profoundly hypothyroid (serum TSH concentrations ranging up to 419 mIU/L) following maternal ingestion of an iodine-rich supplement (12.5 mg/day) daily during pregnancy [19]. However, although this is not routinely used (see section below regarding "Medical Uses of Excess Iodine"), there is experience in Japan with using high-dose iodine (as potassium iodide, KI) for the treatment of maternal Graves' hyperthyroidism with few, if any, adverse outcomes. One report demonstrated no observed fetal thyroid dysfunction among 283 women treated with KI in the first trimester of pregnancy [20].

Iodine-Induced Thyroid Autoimmunity

Iodine status has also been thought to be an important contributor toward the development of thyroid autoimmunity in a dose-dependent manner that acts through both cellular and humoral responses [21]. In a study of three regions in China with mildly deficient iodine intake, more than adequate iodine intake, and excessive iodine intake, the prevalence of autoimmune thyroiditis was 0.2 %, 1.0 %, and 1.3 %, respectively [22]. Similarly, in the 4–5 years after the introduction of a mandatory program of salt and bread iodization Denmark in 2000 there was an increase in serum thyroid peroxidase and thyroid anti-thyroglobulin antibody positivity, compared to the period prior to the program [23]. The increase was seen in all age groups studied, but was particularly frequent among young women. Most individuals developed only low titers of the serum thyroid antibodies.

Potential Sources of Excess Iodine Exposure

Iodine can be present in concentrations of up to several thousand-fold higher than the recommended levels [1] from several common sources. These may include iodine-containing foods, medications, supplements, and as iodinated contrast agents used for radiologic studies. Estimates for the iodine content in some common foods and medical agents are shown in Table 6.2. Ingestion or exposure to iodine-rich substances can, in some susceptible individuals, result in thyroid dysfunction from the excess iodine load.

Table 6.2 Potential sources of excess iodine ingestion or exposure

Source	Iodine content (μg)
Kelp (per gram)	16–8,165
Bread (per slice)	2–587
Milk (per 8 oz)	88–168
Fish (per gram, dry)	0.73
Iodized salt	Variable
Prenatal multivitamins (per daily serving)	75–200
Amiodarone (per 200 mg tablet)	75,000
Iodinated contrast (free iodine per CT scan)	13,500
Topical (povidone) iodine	1–10 % (10 % contains 85 mg/ml) [11]
Saturated solution of potassium iodide (SSKI) (per drop)	50,000

Adapted from: Leung and Braverman 2014, Ref. [86]

Iodine Fortification

Iodine fortification has been the primary method of ameliorating iodine deficiency, the most common cause of preventable intellectual impairment, on a global scale over the past century. Small amounts of iodine have been administrated as iodized oil orally and intramuscularly, introduced into the water supply, used in crop irrigation, incorporated into animal fodder, and introduced into food through salt iodization, bread iodophors, and other products [24]. Goyle et al reported the successful use of fortified micronutrient biscuits in raising the median urinary iodine levels of Indian schoolgirls [25].

Although iodine supplementation and food fortification efforts have decreased the number of those at risk for iodine deficiency and its associated sequelae, particularly in the most recent decades, the use of iodine has also led to concerns regarding excessive iodine exposure in selected individuals.

Iodine supplementation and food fortification have also been shown to be associated with increased incidences of thyroid dysfunction, thyroid autoimmunity, and in some reports, thyroid cancer. Subclinical hypothyroidism was more common in those supplemented with a 400 μg iodine daily tablet, compared to placebo, in a study of over 200 Chinese adults [26] similar to the results of other studies in Denmark [27] and New Zealand [28], which also showed an increased prevalence of transient hyperthyroidism. There has also been an increase in the incidence of thyroid autoimmunity [29] and thyroid cancer, particularly papillary thyroid cancer, following iodine supplementation in some studies. The rise in thyroid cancer over the past few decades is multifactorial, but has been discussed as perhaps a consequence of changes in iodine nutrition from many countries that have analyzed the trend before and after various iodine fortification programs [30–33].

Diet

National market surveys in the U.S. show that dairy products, some breads, seaweed and other seafood, and iodized salt are the most common sources of dietary iodine nutrition [34]. Salt iodization is viewed to be one of the safest and most effective methods of achieving population iodine sufficiency. Iodine fortification of all food-grade salt is mandated in approximately 120 countries, although the enforcement and degree of implementation of these efforts in individual countries are unknown [35]. Salt is not generally considered to be a source of iodine excess as long as appropriate monitoring of salt iodization programs is conducted.

The iodine content in some grain products stems from the use of iodate dough conditioners, which help to preserve the shelf stability of bread. In Tasmania, bread iodation was introduced in 1966 as a prophylactic measure against iodine deficiency and endemic goiter [36]. However, in the initial few years following this intervention, several reports demonstrated an increase in the incidence of thyrotoxicosis that was thought to result from excess iodine exposure [37, 38]. In the U.S., bread iodation was thought to be associated with the decreases in thyroidal radioactive iodine uptake values nationally during the 1960s [39]. In Australia, due to previous reports of low iodine status, iodization of bread was mandated in 2009, which resulted in a modest increase of the median urinary iodine concentration among pregnant women [40]; there are no known reports of iodine-induced thyroid dysfunction as a result of this action in this population.

One example of an iodine-rich food is seaweed, and the iodine content of seaweed can vary widely [41]. Cases of iodine-induced thyrotoxicosis have frequently been reported among seaweed users, including one woman who drank kelp-containing tea for four weeks [42], another patient who had a longstanding history of using kelp-containing dietary supplements [43], and a woman who was consuming a kelp-based diet plan [44]. Recently, Kasahara et al reported a case of delayed onset congenital hypothyroidism in an infant with a mutation in the dual oxidase (DUOX2) gene, which is known to be associated with transient congenital hypothyroidism, which was exacerbated by maternal ingestion of excessive seaweed during pregnancy [45]. In other reports, both short-term and chronic seaweed ingestion has been reported to be associated with modest elevations of serum TSH without overt thyroid dysfunction [46–48]. Seaweed soup is commonly ingested by postpartum women as a cultural practice in some regions and contains over 1,700 μg per 250 mL serving [49]. Japanese reports have shown the positive correlation between maternal iodine intake of seaweed soup during pregnancy and elevated serum TSH concentrations of their newborn infants [50, 51], similar to several Australian cases of neonatal hypothyroidism arising from maternal ingestion of seaweed soup and of soy milk manufactured with seaweed during pregnancy [52].

Amiodarone

Amiodarone is an iodine-rich medication which has been in use since the 1960s and which was approved for the management of ventricular tachyarrhythmias in the U.S. in 1985 [53]. It has a high iodine content (37 % by weight), so that one 200 mg tablet contains 75 mg iodine, equivalent to several thousand times the recommended daily requirement of 150 μg in adults [1]. Amiodarone has a long half-life (approximately 100 days) and can accumulate in adipose tissue, the liver, and the lungs.

Due to the its high iodine content, amiodarone use is associated with type 1 amiodarone-induced thyrotoxicosis (AIT) in 4–28 % of patients [54, 55], depending on whether preexisting thyroid disease is present and overall iodine status from nutritional intake. The two types of AIT are important to distinguish, as their recommended management is different. Type 1 AIT is iodine-induced and is associated with increased thyroid hormone synthesis and treated with thionamides, beta-blockers, and if available, perchlorate, while type II AIT is characterized by a destructive thyroiditis and usually managed with corticosteroids if it is severe [56]. Type 1 AIT is more commonly seen in individuals with underlying nodular goiter or Graves' disease, whereas Type 1 AIT is more frequent in individuals residing in iodine-sufficient areas [56].

Amiodarone use can also result in iodine-induced hypothyroidism. Amiodarone-induced hypothyroidism (AIH) is more common than AIT in iodine-sufficient regions, and particularly among individuals with chronic lymphocytic thyroiditis [53]. As in other examples of iodine-induced hypothyroidism, AIH may spontaneously remit or become permanent.

Iodinated Contrast Media

Iodinated contrast media is a common iodine-rich substance used in radiographic diagnostic imaging, and a typical dose contains 13,500 μg of free iodide and 15–60 g of bound iodine [57], amounts which are equivalent to several hundred times the daily recommended intakes. Both ionic and nonionic contrast media contain approximately 300–370 mg iodine/mL [58]. Several case reports have demonstrated the effects of thyroid dysfunction arising after iodinated contrast use [59–61]. Studies in Germany and the U.S. showed that a small proportion of patients who received either coronary angiography or an iodinated CT scan developed subclinical hypothyroidism approximately one week after the exam [62, 63]. In a Turkish study of 101 patients who underwent coronary angiography, there was a small increased risk of subclinical hyperthyroidism at up to 8 weeks following the iodine exposure [64]. However, one small study showed that administration of intravenous iodine contrast during pregnancy did not result in a significantly increased incidence of fetal thyroid dysfunction [65].

Several large population studies have also examined the associations between iodinated contrast media use and the development of thyroid dysfunction. In a nested case-control study of adult patients at a Boston hospital over 20 years, there

were significantly increased risks for both incident hyperthyroidism and hypothyroidism following iodinated contrast media exposure [57]. These findings were also confirmed in a community-based Boston cohort [66] and two general population cohorts in Taiwan [67, 68].

The effects of iodinated contrast media use in diagnostic imaging may not be immediate. In a prospective study of 54 euthyroid adults who received elective outpatient iodinated computed tomography (CT) scans, the mean time to achieve peak urinary iodine concentration (UIC) was 1.1 ± 0.5 weeks, and normalization of UIC was not achieved until 5.2 ± 4.0 weeks [69]. In this report, 22 % of the subjects developed incident thyroid dysfunction over the up to three months of follow up in the study. The effects of iodinated contrast media on inducing potential thyroid dysfunction are particularly important in the neonate. One case series reported three neonates who presented with profound hypothyroidism (serum TSH concentrations ranging from 30–175 mIU/L) within one month of having undergone cardiac catherization(s) which utilized iodinated contrast [70]. Another study analyzed pediatric patients (<18 years old) with thyroid dysfunction, matched 1:1 to euthyroid controls by age, sex, and race, and reported a three-fold increased risk of incident thyroid function abnormalities among those who had a history of iodinated contrast media exposure, with nearly 11 months as a the mean time period between iodine exposure and thyroid dysfunction [71]. These data confirm the several case reports that have been made known to the U.S. Food and Drug Administration concerning the potential for hypothyroidism resulting from use of iodine-containing contrast agents in infants [72].

Guidelines by the Contrast Media Safety Committee of the European Society of Urogenital Radiology advocate that high-risk patients be monitored for thyroid dysfunction following iodinated contrast use [73]. There are currently no guidelines for screening or following at-risk patients receiving iodinated contrast in the U.S.

Topical Iodine

The development of thyroid dysfunction related to transdermal iodine use has been most commonly reported in hospitalized neonates. A recent study in Israel reported significantly higher serum TSH concentrations in preterm neonates who had received topical iodinated antiseptic cleansers, compared to the preterm neonates who received alcohol-based topic cleansers (15.4 vs. 7.8 mIU/L, $p<0.01$) [74]. However, most neonatal intensive care units in the U.S. have phased out routine use of topical iodine given the concerns regarding excess iodine iodine exposure in this population [75]. Iodine is also commonly used as a topical antiseptic in many surgical settings (including mediastinal irrigation [76]) and among burn victims, whose ability to absorb topical iodine may be increased. Iodine-induced thyrotoxicosis and a review of the differential diagnosis was also described in a paraplegic woman in the U.S. who had applied topical povidone-iodine prior to urinary self-catheterization several times daily for many years [6].

Drinking Water

The iodine content of drinking water has also been a reported source of excess iodine exposure. Among Sahawari refugee children in the Algerian desert, where the median iodine content of household drinking water was 108 μg/L (interquartile range 77–297 μg/L) during a 2007 assessment, the median UIC was 565 μg/L (interquartile range 357–887 μg/L) [77]. Naturally high concentrations of iodine in drinking water have also been reported in some regions of China; one region of Hebei province reported a median UIC of 518 μg/L (interquartile range 347–735 μg/L) among children residing in the area [78].

Reversible elevations in serum TSH have been observed among U.S. astronauts drinking iodinated water [79] and individuals ingesting water purified by iodinated tablets [80]. In the 1990s, due to use of a faulty iodine-based water filtration system, small increases in serum TSH concentrations were detected in American Peace Corp workers in Niger; these changes resolved following discontinuation of the iodinated water source [81].

Miscellaneous Sources of Excess Iodine Exposure

Other sources of potentially excessive iodine exposure include various expectorants, vitamins and supplements, food preservatives, prescribed medications, parenteral preparations, topical antiseptics, mouthwashes [82], and vaginal douches [16]. Iodine-containing expectorants were historically a potentially concerning source of iodine excess, particularly in patients with cystic fibrosis who were treated with these agents routinely. However, iodine-containing expectorants are now longer regularly in use, and a recent study shows that overt iodine-induced thyroid dysfunction among cystic fibrosis patients is uncommon [83].

Medical Uses of Excess Iodine

There are specific clinical settings in which supraphysiologic iodine is medically indicated. Saturated solution of potassium iodide (SSKI), or Lugol's solution, for which the generic formulation contains 1,000 mg potassium iodide (KI) per mL, can be used for the rapid treatment of hyperthyroidism. Use of SSKI is usually reserved for patients with thyroid storm or in patients who are managed preoperatively for Graves' disease and administered in conjunction with antithyroidal and other therapies. In such patients, pharmacologic doses of iodine should be administered after a thionamide has been first dosed to block thyroid hormone synthesis. Also, supraphysiologic iodine ingestion may be recommended following a nuclear emergency to prophylax against the exposure to radioactive iodine.

Recommendations Cautioning Against Excess Iodine Exposure

TUL thresholds have been defined by U.S. Institute of Medicine as the highest average daily intake level of a nutrient which is unlikely to pose any adverse health effects (defined as a significant alteration to the human structure or its function) in the majority of population [1]. The range of intake between the Recommended Dietary Allowance (RDA) and TUL is not one in which there is a possible beneficial effect, but it is likely biologically tolerable. At chronic daily intakes above the TUL, adverse effects may increase. The RDA and TUL for iodine are 150 μg/day and 1,100 μg/day in adults, respectively [1] (Table 6.1).

The derivation of the TULs for any given nutrient is based on risk assessment models, in which the probability of ingestion/exposure to the nutrient having adverse health effects in human is systematically evaluated using both qualitative and quantitative available data from the animal and human literature [1]. Risk assessment of nutrients must acknowledge the scientific uncertainties of the information that may be present and make explicit the basis for judgments. Models are based on identifying the potential hazard, assessment of a dose response, assessment of the nutrient intake in humans, and characterization of the risk. This process involves identification of a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL). The LOAEL values which informed the US TUL were based on two small dose-response studies [17, 84]. The NOAEL is the most sensitive measure of a nutrient's toxicity and takes into account areas of uncertainty (termed uncertainty factors [UF]) in the available literature. The TULs of all nutrients are based on the assumption of chronic daily exposure from all sources, including food, water, and supplements.

The WHO, UNICEF, and IGN also advise that pregnant and lactating women ingest no more than 500 μg of iodine per day [2] (Table 6.1). Recognizing that many iodine-containing supplements contain excessive iodine amounts, the American Thyroid Association advises against the ingestion of iodine supplements containing more than 500 μg of iodine per day in the general population [85].

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Chapter 7
Salt Iodization into the Modern Era and Beyond

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Abstract Following from the history described in Chap. 1, the present chapter describes the scientific basis for, and the worldwide acceleration of, national IDD prevention programs from the continuous expansion of salt iodization strategies in country upon country starting from the mid-twentieth century. The vision of global IDD prevention and control was first formulated in 1960 by the World Health Organization (WHO). Commitments made by the heads of state and government at the World Summit for Children in 1990 prompted a 10 year period of multisector collaborative actions especially in the developing world, which raised the coverage and access of adequately iodized consumer salt to 70 % worldwide by 2000. The period after the year 2000 witnessed a slower but continued increase in the worldwide iodized salt supplies, along with a steady reduction in the number of countries still considered deficient. The chapter outlines the up-to-date insights into the modern methods and approaches to establish true universal salt iodization (USI). Again in 2014 and based on a meta-analysis of research findings, WHO strongly recommended the mandatory iodization of all dietary salt to prevent iodine deficiency disorders (IDD). Current program management concerns include an increase in the salt intake from processed foods that occurs with economic development and the challenges in aligning the two salt-based strategies of salt intake reduction and salt iodization. The chapter ends with a premonition that the sustained prevention of IDD requires assurance that USI has become established as a habitual norm in iodine nutrition policy and practice worldwide.

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Abbreviations

ICCIDD	International Council for Control of Iodine Deficiency Disorders
IDD	Iodine deficiency disorders
IGN	Iodine Global Network
INCAP	Institute of Nutrition in Central America and Panama
PAHO	Pan-American Health Organization
UNICEF	United Nations Children's Fund
USI	Universal salt iodization
WHA	World Health Assembly
WHO	World Health Organization
WSC	World Summit for Children

Salt Iodization into the 1960s

Chapter 1 has described the discovery of iodine and the early scientific evidence that adding iodine intake is an effective method for goiter prophylaxis. During the period leading into the 1960s, the use of salt as a "carrier" foodstuff to deliver a measured additional amount of dietary iodine started expanding throughout Europe and beyond. Salt at that time was a very basic product, principally obtained from the mining of ancient underground salt deposits or by evaporation of water from the sea or salt lakes [1]. Except for some grinding and cleaning, little effort was yet being made to improve upon the chemical and physical characteristics of the raw product; esthetically, salt was not particularly pleasing. Typically, common salt was sold in paper or cardboard packages of varying size and shapes, mostly depending on the preference of the salt companies and their associated traders, and the supply channels were largely determined by traditional trade relations. Also, the salt markets for industrial food manufacturing hadn't yet taken off and so, there was little incentive for diversification, except for the salt used by pharmaceutical companies. Coinciding during this time period was a steady increase in scientific discoveries regarding the roles of dietary vitamins and minerals in maintaining human health. Each exciting new finding was disseminated by the popular press. The list of dietary deficiencies being long, each new discovery was typically positioned around yet another nutrient, with the effect that iodine deficiency became only one among a variety of potential nutritional health factors that competed for priority public attention. And most importantly, the serious devastation from World War II slowed down scientific progress and returned much of society to subsistence food provisioning. Consequently, the large-scale diffusion of theory and knowledge on goiter prevention, and the integration of the simple approach of salt iodization into public health practice did not take off in true force until after the 1950s arrived.

Immediately after World War II ended in 1945, one of the visions of world leaders at the formation of the United Nations was to set up a global health organization. The World Health Organization (WHO) adopted a constitution in 1948 and

established its headquarters in Geneva, Switzerland. Regional WHO offices spread over the world, each connected to the Ministries of Health of the WHO member states. Initially, the priority at WHO was directed at guiding the development of health service systems worldwide, but important attention was also given to defining and documenting the extent and severity of existing nutritional conditions such as endemic goiter, as well as to an exploration and validation of improved manufacturing methods for iodized salt [2, 3]. The use of iodate as a chemical compound in animal feeds was already known and to reduce the instability and sizable losses when iodine was mixed in the form of iodide into impure salt in tropical countries, laboratory studies in England [4] demonstrated that iodate could be used instead and was safe when given in large doses to mice and rabbits over a 1 year period. In 1956, further research at the Institute of Nutrition in Central America and Panama (INCAP) showed that the iodization of sea salt with potassium iodate resulted in only 3.5 % loss of iodine when stored for 1 year without protection against the typical adverse environmental conditions of this area [5]. Shortly thereafter, INCAP produced evidence of an immediate, society-wide fall in goiter prevalence among schoolchildren in Guatemala following the iodization of the entire national edible salt supply with potassium iodate [6].

An exhaustive monograph on endemic goiter, published in 1960, was a particularly outstanding result of the WHO efforts at that time [7]. This key publication accumulated all the accessible data and information on the worldwide prevalence, severity, and extent of common goiter up to this time, citing no less than 1,369 scientific references and covering the sources of knowledge from as far back as the early 1800s. Aside from the US and Switzerland, salt iodization was already being put into practice in Canada, parts of Italy, the Netherlands, New Zealand, Poland, and certain areas in Germany. Somewhat later salt iodization followed in a growing number of states in Central and South America. Contrary to most infectious diseases and other major nutritional disorders, endemic goiter appeared to be present as a significant public health problem in almost all WHO member countries and was not confined to the so-called developing world only. The monograph's introductory chapter which dealt with the history of goiter [8] stated that the worldwide nature and importance of endemic goiter "focuses attention to its etiology and methods of mass prophylaxis" and the author of the chapter added: "Today, we possess an abundance of reports from all parts of the world on the favorable effects of iodine prophylaxis, and if this method were universally adopted, it would appear possible at least to achieve a great reduction in endemic goiter in the world, if not to eradicate it completely." This forward-looking vision expressed the idea of global conquest of IDD for the first time in history.

The Period to 1990

While the practice of iodizing salt for human consumption continued expanding to a growing number of countries [9], a major impetus during these years was leveled at improvements of scientific methods and techniques for population assessment and more accurate estimates of the true IDD burden. The Pan-American Health

Organization (PAHO) took a leading role by the stimulation of periodic meetings of scientists who chiefly worked on refining the etiology of goiter and a better understanding of its consequences, which during the 1970s lead to acceptance that prevention efforts were needed to address "Goiter and Cretinism" rather than "Endemic Goiter" only. During the first scientific meeting in 1969, the PAHO Regional Nutrition Advisor reported that 17 governments of its 25 state members in the region had declared goiter prevention as a priority concern, that some countries had also noted that cretinism existed, and 15 had already enacted legislation to compel salt iodization [10]. The report was structured along the now-familiar steps of designing a national program, namely establishment of baseline evidence and extent, enactment of legislation/regulation for salt iodization, distribution of roles and responsibilities to guarantee supply and arrange its oversight, and building of ongoing systems to quality assure the iodized salt supply and to measure population outcomes. The Advisor's report was particularly insightful for a clear description of the various common obstacles and barriers encountered in successfully managing these elements, thereby foreshadowing the essential need for effective public-private partnership. The publication from the second scientific meeting in 1974 [11] showed a clear change in the understanding of the true human burden and an ongoing shift toward more priority attention for the steps in national programming.[1] The number of Health Ministries that responded to the standard questionnaire about program developments had not increased, but the status of iodization was reported in considerably more detail. Significant improvements had resulted from more oversight of the iodized salt supplies and from monitoring of associated health outcomes, i.e., goiter and urinary iodine, particularly in the Central America area. WHO issued a booklet in 1979 [12] with two contributions by UNICEF on the technical and legislative aspects of salt iodization. The legislative chapter cites ongoing salt iodization efforts in 43 countries and voluntary availability of iodized salt in another nine countries. Salt iodization laws and/or regulations had been enacted in 37 countries, a major part of which were covering the whole country and half of which specified iodide and the other half iodate as the permitted fortificant. The defining feature of this publication was that it positioned iodine deficiency as a global issue of worldwide significance. Nevertheless, it was left to the WHO member states to select a national strategy from a choice between the two options of salt iodization for all or iodine supplementation for vulnerable groups only. A meticulous scientific publication in 1980 under the leadership of John Stanbury and Basil Hetzel [13] provided a detailed update of the 1960 WHO monograph and included 30 chapters on new insights in etiology and pathology, analyses of endemic cretinism and impaired intellectual development associated with endemic goiter, as well as several summaries of prevention efforts with their problems and successes.

[1] The 1969 report consisted of 34 manuscripts, only one of which focused on programming of salt iodization strategies. In the 1974 report – only 5y later – the 32 manuscripts included two updates on the status of salt iodization in the region, three papers on technical issues and programmatic guidance and another three reports from country-based supply and outcome monitoring systems.

The capstone issue of the PAHO-stimulated publications in 1986 [14] reported on a meeting that convened health officials from Latin America together with staff from PAHO/WHO and UNICEF and academicians in endocrinology and public health from around the world. This time, the majority of the reports from countries in the PAHO region contained information about ongoing programs based on salt iodization and/or targeted iodine supplementation. Some reports were also included from countries in Asia and Africa, where the development of programs had only recently been gathering momentum. The recommendations on assessment methods from this meeting formed the technical basis for a later WHO world-wide inventory on the global prevalence of iodine deficiency disorders, i.e., the baseline for a world-wide conquest of IDD, a vision expressed a quarter of a century before in the 1960 WHO monograph.

Although dietary iodine shortfall had long been recognized as the main underlying cause of goiter, evidence of the myriad effects of iodine deficiency had been mounting throughout this period. Effects on fetal and post-delivery neurological development were increasingly being recognized, as were the facts that these effects weren't just confined to narrow geographical areas and that the consequences weren't restricted to only the most vulnerable life periods of pregnancy, infancy and childhood. These critical insights were described in great clarity in a prominent article by Basil Hetzel in the prestigious medical journal *The Lancet* of 1983 [15]. Basil S. Hetzel, an eminent Australian scientist and global public health advocate, completed his medical degree in 1944, followed by postgraduate training in Adelaide and New York, and endocrinology specialization at St Thomas's Hospital in London. During his tenure as professor at Universities in Adelaide and Melbourne, Hetzel instigated a number of collaborative studies of severe goiter and cretinism in the highland villages of Papua New Guinea, which culminated during 1966–1969 in a double-blind trial of iodized oil injections in pregnant women which proved that supplemental iodine, when given before conception, prevented the mental disability spectrum characteristic of cretinism [16]. The ambition of addressing iodine deficiency worldwide became a life-long passion of Professor Hetzel. Together with like-minded colleagues from around the globe, he founded the International Council for Control of Iodine Deficiency Disorders (ICCIDD) in 1987 and, in collaboration with the WHO nutrition section in Geneva, he developed a plan to tackle IDD worldwide. This plan was endorsed by the United Nations technical Subcommittee on Nutrition and offered a sound, practice-oriented foundation that the World Health Assembly (WHA) adopted in May 1990 as a resolution to accelerate national programs for prevention and control of IDD in all countries by the year 2000 [17].

1990 to 2000: Feverish Action

The final decade of the last millennium became characterized by an escalating, widespread, collaborative mission to reach the goal of global IDD elimination, a vision coined in the 1960 monograph by WHO on endemic goiter and more recently

underpinned by the WHA-adopted global action plan. Commitments at the highest levels of government were pledged at the World Summit for Children (WSC) in September 1990 by including the virtual elimination of IDD among 27 priority health and social development goals for the decade [18]. This Summit set off a sequence of events designed to stimulate global success. In Montreal, 1 year after the WSC, the Policy Conference on Hidden Hunger translated the political promises into realistic policy guidelines [19] and in Rome, another year later, the International Conference on Nutrition, co-organized between WHO and the Food and Agricultural Organization of the United Nations, agreed on outline frameworks for national planning [20]. Further, as basis for future reference, WHO, UNICEF and ICCIDD jointly put together a databank of the global IDD prevalence in 1990 [21], documenting that the populations of 110 countries had inadequate iodine intakes. The infrastructure for action was delineated and a baseline was ready. However, an agreed-upon preferred strategy that could be incorporated into the national plans of each country was not yet clear, despite the broad documentation of the efficacy of appropriate daily deliveries of iodine through common salt [22]. Thus, in January 1994, the UNICEF-WHO Joint Committee on Health Policy met in a special session and resolved to recommend Universal Salt Iodization (USI) as the most feasible, cost-effective, and equitable approach, defining USI by the iodization of "all salt for human and animal consumption, including salt for food processing (Universal Salt Iodization) in all countries where Iodine Deficiency Disorders (IDD) are a public health problem" [23].

UNICEF, a worldwide United Nations program initiated after World War II, provided direct material, technical, and training assistance to the key national partners in IDD programs, based on its experience from previous work in the Western Hemisphere [11, 14] and started wielding its significant convening influence in the public, private, and civic sectors to speed up policy-making for salt iodization strategies in many parts of the world. Supported and funded by donor agencies and charitable sources, UNICEF increased the financial, technical, training, and communications assistance to accelerate national USI strategies in countries of Africa and South and Southeast Asia [24]. The USI message was communicated and assistance provided to the salt producing industries and, consequently, deliveries of iodized salt expanded in country after country. By the year 2000, an estimated 70 % of the world's households were using iodized salt, compared with fewer than 20 % in 1990 [24].

Important lessons from this period of extraordinary progress [25] included the realization that an approach to overcome iodine deficiency at a scale that matches the nature and magnitude of the problems in society needs more than a health-sector service delivery. Instead, the progress in country after country took place from mutually supportive public-, private- and civic-sector actions that rested on partnership, joint coordination, and collaborative oversight of progress and outcomes. A related lesson was that because iodine deficiency became positioned as a national and not a local issue, iodization of salt needed to be universal, i.e., aimed at the

steady delivery of additional dietary iodine for the entire population. It is not likely that the massive gains of extra iodine into the common diet would have taken place without legislative mandates. With a voluntary approach, the producer who decides to bear the extra work and expense of supplying iodized salt remains unprotected in the market against the competition that elects to ignore the appeal from their national leaders. Finally, because iodization at the source requires responsible producers, capable of proper standard operating practices that ensure the quality of products, the decade also typified a normative shift in partnership balance by the increase in acceptance of a pivotal responsibility for the pursuit of success by the salt industry and their allied traders [26].

Sustaining Success

Salt Iodization Strategies

Similar as for other food fortification initiatives, iodizing salt requires national legislation because attempts to establish regional and/or voluntary approaches typically remain feeble or fail to succeed [27]. The setting of a standard for iodine content in iodized salt is a critical element for the enactment of proper regulations, which accompany the principal legislation. Ideally, the overarching food or industry law should address the iodization mandate, i.e. the legal requirement that the salt intended for human consumption should be iodized, while an attendant regulation should specify the required range of salt iodine content that the producers and importers in the country are expected to deliver. Other required elements in the legal and regulatory framework are that the authority for enforcement of the salt iodine standard should be defined and that a procedure to modify the salt iodine standard, if and when necessary, should be made clear. The regulations, finally, should also address requirements for packaging, labeling, hygiene and maximum levels of humidity and contaminants.

In 1996, WHO, UNICEF and ICCIDD issued a recommendation for the setting of salt iodine standards [28], taking as reference an average adult salt intake of 10 g per day, an average iodine loss of ±40 % from iodized salt between production and consumption, and the recommended dietary allowance of 150 μg iodine per day for adults. Taken together, these factors yielded a recommendation for salt iodine content at production in the range from 20 mg to 40 mg iodine per kg salt. When salt used in processed foods is also iodized, the lower limit (20 mg iodine/kg salt) was deemed applicable.

Importantly, this recommendation aimed to cover the average salt iodine levels considered sufficient in most situations; the 20–40 mg/kg range did not represent the standard salt iodine content applicable or recommended for adoption in each situation. For deciding on a standard range of salt iodine content for the national

regulation, therefore, each country needed to examine its own average (adult) salt intake, the typical expected loss of salt iodine content during the turnover period between the supply and use of iodized salt and, most importantly, the common practical capacity of the salt companies that serve the country's markets. While these underlying factors can vary appreciably across different continents, climates, salt supply situations and stages of technology development in the world, the 20–40 mg/kg guidance for mean national salt iodine supply has nevertheless stood the test of time rather well.

That said, however, the key weakness of the approach was that salt iodization strategies are designed to provide supplemental dietary iodine, i.e., in addition to the already existing iodine intake from native iodine content in common foods, while the recommendation assumed that the iodized salt supply needed to cover the entire iodine intake. Practical experience in a number of countries, for example in the Balkan area of Southeast Europe [29], shows that a standard for salt iodine content below the 20–40 mg/kg range can very well bridge a shortfall of iodine intake when the complete salt supply is iodized. This is generally to be expected in those situations where the background, native-source iodine intake of the population does not fall too far below the minimum threshold for iodine deficiency.

With the continuous increase of industrial food manufacturing around the world, the type of salt selected for iodization has become a critically decisive factor in deciding on an effective national standard for salt iodine content. Despite the original intent [23] and the underlying assumption by the agencies in 1994 [28] that salt iodization should encompass all the types of salt intended for human consumption, the legislation in many countries in fact addresses only the salt for direct consumer use, while it does not reference or compel the iodization of salt destined for commercial food manufacturing. In less industrialized countries, especially in rural populations, the consumption of commercially processed foods is small or negligible and in such cases, a law that addresses only edible salt for consumer use can very well be effective. In contrast, the amount and proportion of salt intake in a population from industrially manufactured food rises with urbanization and technological development and in the Western world, up to 75–80 % of the total salt intake in the adult population derives from commercially produced foods. In such situations, a salt iodization law that singles out only the salt for use in the households will increasingly become marginal in providing additional dietary iodine intake.

To address anticipated variations in mean (adult) population salt intakes from efforts to reduce the salt contents in common foods, WHO recently issued a more detailed guideline on salt iodine content for the mandatory fortification of salt with iodine [30]. Note that, as before, these amounts are meant for mean recommended salt iodine contents. And also as before, note that each country needs to establish its own appropriate range for the permissible variation in iodine content at production.

Salt consumption estimate, gram per day[a]	Average amount of iodine to add,[b] mg per kg salt
3	65
4	49
5	39
6	33
7	28
8	24
9	22
10	20
11	18
12	16
13	15
14	14

[a]This includes consumption as table salt as well as salt from processed foods
[b]Calculated from the mean adult dietary allowance of 150 μg iodine per day, plus 30 % loss during turnover between production and consumption, and 92 % iodine bioavailability from the diet

The crucial distinction between the two salt supply channels, i.e., salt for use in the food industry and consumer salt, has implications for an effective supply monitoring system. First, at the production sites, inspections are typically conducted under authority of a Ministry of Trade & Industry, and in many countries the results of such annual audits are connected with the certification and licensing of the factory. Where this part of a national monitoring system which functions well, the licensed factory is authorized to issue a certificate of conformity to its customers who, in turn, sell the salt products to the food industries and the market outlets for consumers. The conformity certificate is particularly useful for inter-country trade as it often forms the basis on which the customs authority of an importing country permits the entry of salt shipments, thereby providing a measure of confidence by the importer in the proper quality of the salt purchase.

Second, market monitoring is commonly a function under the Food (Control) Agency, connected to the authority of the Ministry of Health. While health inspectors visit and examine the type(s) of salt for sale in consumer outlets such as markets and shops, such inspections of the salt quality in food processing enterprises, restaurants, and worker canteens is not frequent in most countries. An obstacle for regular inspections in food factories (e.g., bread bakeries, milk and meat processing plants, etc.) is that the measurement of the iodine content in the end product is a complex and, thus, costly task.

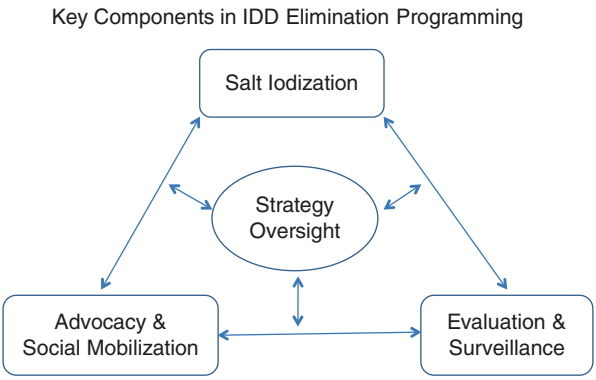
Third, surveillance of the iodine content in consumer salt takes place in many countries as part of periodic population-based surveys, such as the Demographic Health Surveys or Multiple Indicator Cluster Surveys, where the salt in a representative selection of households may be tested “on the spot” [31] or salt samples collected for measuring the iodine content in a laboratory. As a general guideline,

where more than 90 % of households are using table salt with iodine content ≥15 mg/kg, the country is considered to have reached the USI target [30].

National Partnership

A design rationale for programming IDD prevention and control by the USI strategy reflects a grown experience of health planning [32], which identifies the key components on which health strategies are built. Accordingly, a USI strategy characteristically consists of four key components, three of which are technical: iodization, communications, and monitoring, and one managerial: oversight (See Figure below).

Having adequate capacity in each organization that collaborates in the USI strategy is a necessary but not sufficient condition to achieve success. Also, having full capacity established for each component among the stakeholders does not automatically mean that the overall strategy will inevitably perform well, become habitual practice and, therefore, attain success. Shortfalls of strategy performance can be successfully addressed and overcome by a national oversight arrangement, devised to make sure that the iodization, communication and monitoring activities continue to yield their expected results. The mutual relationships for accountability among stakeholders forecast the essential need for "partnership collaboration" in executing the USI strategy, in which each stakeholder is in agreement on their specific individual and collective roles and responsibilities. Adequate capacity and mutual answerability then serve to avert external dependence, augment national ownership, and buttress continuous progress. These are the pillars for sustainability [33].



The remarkable progress witnessed during the 1990s clearly established the advantage of ever-closer collaborations, both nationally and internationally, among the public, private, civic, scientific, and other groups that learned to act as one cohesive force in channeling and coordinating the actions aimed at the USI target. It also demonstrated that anchoring of national "ownership" is a key to making the national

successes endure. Where persistent national ownership became manifest, iodine deficiency disappeared while systems became built and put in place to self-sustain the success of USI into the future. Underlying this self-sustaining process was the fact that national lead partners – government ministers of industry and health, captains of salt industry, and leaders from civic society and scientific bodies – in each case formed a coalition that ensured that salt iodization in their country would endure. Such national coalitions, or "National Watches," served to provide assurance and oversight that high quality iodized salt continues to be produced, that the salt companies sell only iodized products to its customers, i.e., the food manufacturing companies and the consumer markets, that each partner periodically renews its political commitment and promises to end iodine deficiency forever, and that society remains informed of the dangers of iodine deficiency and the benefits from exclusive iodized salt supplies.

International Collaboration

At the World Salt Symposium in the year 2000 [26], top salt industry executives held a side meeting with leaders of government, non-governmental organizations, and scientific organizations, and directors of multilateral agencies and charitable organizations, with an aim to discuss how they could continue the partnership collaboration model that had grown and flourished during the past decade. An agreement was reached to form a global coalition to support the national efforts to achieve IDD elimination and help sustain it, by jointly promoting the collaboration among the national stakeholders in lagging countries. The Iodine Global Network (IGN) [34], a successor to the ICCIDD, a non-profit, non-government global organization dedicated to USI as the most cost-effective solution for sustained IDD prevention, ultimately arose from this agreement of 15 years ago. IGN's mission – to be the authoritative source for advice on iodine nutrition – rests on the considerable body of knowledge and experience among its public, private, civic and scientific memberships. When it tackles a particularly challenging national situation, IGN typically mounts a joint collaborative effort that draws on the range of specific expertise accessible from among its members, thereby providing an international example of the partnership collaboration also required at the national level.

The 25-year period after the WSC witnessed considerable learning from the many national practices to eliminate IDD with salt iodization and monitoring its disappearance. Highlights and lessons consolidated from this period include the further refined guidance for building national monitoring systems [35], global updates on the progress of preventing IDD by national USI strategies [36], a comprehensive iodine review on biomarkers for development [37] a meta-analysis of research, leading to renewal of the recommendations for mandatory USI [30] and a guideline for alignment and joint monitoring systems between the two salt-related strategies of salt intake reduction and salt iodization [38]. Examples of recent technical advances are the development of more refined frameworks for the analysis

of population surveys [39], an increase in the research focus on populations that are lagging most in progressing toward the global goal [40], and documentation of a steady drop in the number of countries still affected [41].

Conclusions

Goiter and cretinism was a scourge of humankind since time immemorial. It lasted a century from the discovery of the nutrient iodine to arrive at the first demonstration that iodization of salt is the solution, and it took another 50 years to arrive at the high-level political commitments during the WSC to forever eliminate IDD worldwide. The 25 years since the historic WSC have witnessed the adoption and scaling-up of national salt iodization strategies in country after country to the present point in time when the vision of global elimination has become tantalizingly close. The previous Director-General of the World Health Organization, Dr. Gro Harlem Brundtland, stated that "Overcoming iodine deficiency, the single-most preventable cause of needless brain damage in the world, will be a major public health triumph comparable to the eradication of smallpox and polio."

Among food fortification strategies, salt iodization is truly unique. Currently, the successes of the USI strategy in preventing IDD encompass almost a century of steadily expanding experience in more than 100 countries. In contrast to other micronutrient deficiencies, success in addressing all grades of severity among all groups of a population is attainable by the fortification of only a single dietary ingredient. Salt is an omnipresent meal ingredient by itself and it is a regular item in the recipe of various commercially prepared foods; these facts make the impact of USI superbly equitable. The properties of salt in better taste and prevention of food spoilage are appreciated by consumers everywhere. Salt intakes across populations are remarkably stable, both short-term and with the changes of seasons; its consumption is self-limited and salt is a relatively price-insensitive market item. The matchless dietary characteristics and properties of salt, and the proven effectiveness and unparalleled global track record of the USI strategy are factors that argue for a future in which the mandatory iodization of all salt becomes the habitual norm for preventing iodine deficiency-related brain damage worldwide.

Presently, the key barriers in the remaining countries with deficient populations are no longer technical, but political. The governments of these countries were among those who made high-level commitments to the IDD elimination goal at the historical Summit in 1990. The past 25 years of worldwide progress has taught the vital lesson, however, that national success demands that the stakeholders must decide to coalesce around a jointly shared mission of delivering protection against the threat of iodine deficiency-caused brain damage for the entire population. Such national partnerships require genuine political courage and determination in each sector of society with true, resolute guidance from government leaders at the highest level. Leadership for such a simple, equitable, and proven solution to an age-old scourge will be remembered by each future generation.

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Chapter 8
Non-salt Food Fortification Programs

Peter Laurberg and Lone Banke Rasmussen

Abstract Both high and low population iodine intake increase the risk of thyroid disease in a population. This should be taken into account when planning iodine fortification programs. A number of methods are available to adjust iodine content of diet, among them the most important non-salt targets for fortification are bread and dairy products. Monitoring and adjusting population iodine intake is important for public health.

Introduction

Iodine is necessary for thyroid hormone production and therefore essential for healthy daily living and for successful reproduction. In most parts of the terrestrial world, iodine content of the natural diet is quite low, compared with the iodine required for thyroid hormone production. To adapt, a series of physiological mechanisms have developed to assist in keeping thyroid hormone production adequate despite low iodine intake. On the other hand, various mechanisms protect against excessive thyroid hormone production after a sudden high iodine intake from e.g. seaweed. This is an efficient, but also a complicated system that may lead to disease if not in sufficient balance. Moreover, the thyroid gland is often affected by

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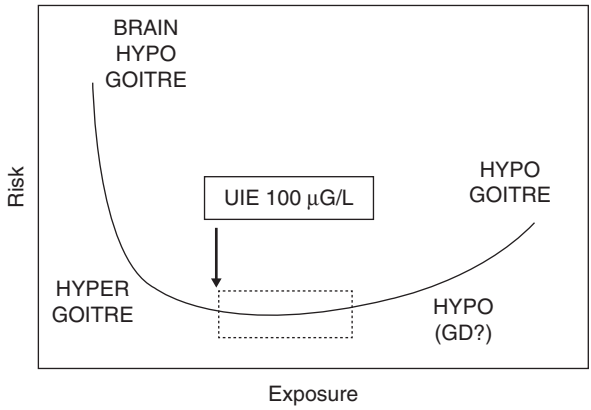

Fig. 8.1 Relationship between exposure to a certain iodine intake level over a long period of time and the risk of developing disease: hypothyroidism, brain damage and goiter in severe iodine deficiency; multinodular toxic goitre and non-toxic goiter in mild/moderate deficiency; autoimmune hypothyroidism and hyperthyroidism as well as diffuse non-toxic goitre in excessive iodine intake. The *dotted box* indicates the level at which median population urinary iodine concentration is optimal. The urinary iodine excretion (UIE) of 100 µg/L indicates the lower level of adequacy for groups of people as proposed by the WHO/UNICEF/IGN [23]. At this level, iodine deficiency disorders are minimized [3], and there is apparently no need for individual iodine supplementation in pregnancy [52, 53]. Iodine intake should be maintained at a level where iodine deficiency disorders are prevented, but no higher (The figure is modified from Laurberg [54])

autoimmunity that may lead to both excessive and insufficient thyroid gland function with clinical hyper- or hypothyroidism, and the risk of such diseases changes with a change in the iodine intake level. Hyper- and hypothyroidism are common disorders that may have serious effects in pregnant women [1], and may increase the risk of future disease in the child [2]. Moreover, these disorders may considerably affect the health and quality of life of individual patients and be an economical burden for society. Monitoring and adjusting population iodine intake to optimal level is an important part of public health services.

When discussing iodine fortification of food, an important factor to take into account is that optimizing iodine intake in a population is not a simple task. A public iodine fortification program should not only focus on average iodine intake in the population, but it should aim at optimizing iodine intake of individual members of society. Iodine intake in every pregnant woman and young child should be at a level where there is no risk of developmental damage from severe iodine deficiency. In addition, iodine nutrition should in general be at a level where the risk of thyroid disease from deficient or excessive iodine intake is as low as possible [3].

Figure 8.1 illustrates the association between iodine intake level and the risk of thyroid disease. Severe iodine deficiency is associated with hypothyroidism and risk of developmental brain damage. Milder iodine deficiency is not associated with hypothyroidism as might be expected, because compensatory mechanisms are activated, with up-regulation of iodine trapping and utilization by the thyroid. However, the compensatory mechanisms may lead to goiter and to the development and

growth of nodules in the thyroid with autonomous hormone production and clinical hyperthyroidism. In a Danish population study of 68 year-old individuals living in a moderately iodine deficient area, the frequency of goiter was high, and 11 % of the women had signs of thyroid hormone overproduction with low serum TSH (not caused by L-T4 intake). Three percent of the women had biochemical overt hyperthyroidism [4]. According to guidelines [5], many of these women should be treated for hyperthyroidism, mostly using radioiodine. The prevention of such disorders by adjusting iodine intake is better than administering radioiodine to considerable part of the population.

At the other end of the risk curve (Fig. 8.1) a more than adequate iodine intake increases the risk of diffuse goiter and of hypothyroidism caused by autoimmunity. In addition, hyperthyroidism caused by Graves' disease may manifest at a young age, and the disease may be more difficult to treat [3].

Changes in iodine intake, even within a relatively narrow range, may have considerable effects on public health. This is an important concern when discussing methods to fortify food with iodine.

Goals of Iodine Fortification

As detailed above, the goal of iodine fortification is to increase the intake in all members of an iodine deficient society and not just to increase the mean intake. The 'how to' and 'how not to' are illustrated in Fig. 8.2. An even better outcome than a uniform increase in iodine intake would be that iodine fortification of food predominantly increases iodine intake in the portion of the population having the lowest iodine intake.

Ever since public iodization programs started nearly a century ago, iodine fortification of salt has been widely used [6]. All members of society consume salt and therefore it is a good vehicle. However, efforts are now being made in many countries to reduce salt consumption because high salt intake is regarded unhealthy, as it may increase the risk of high blood pressure [7]. One solution to adjust iodine intake if the intake of iodized salt is reduced is to increase the amount of iodine added to salt, but alternative fortification practices must also be considered.

Fortification and Biofortification

There are two ways to fortify food, direct fortification and biofortification. Fortification of salt is an example of direct fortification, where iodine is added to the food. Biofortification is an indirect way to fortify a product. As an example, milk may be biofortified with iodine by adding iodine to cow fodder, and vegetables may be biofortified with iodine by adding iodine to irrigation water. The strategy to follow depends on the type of food.

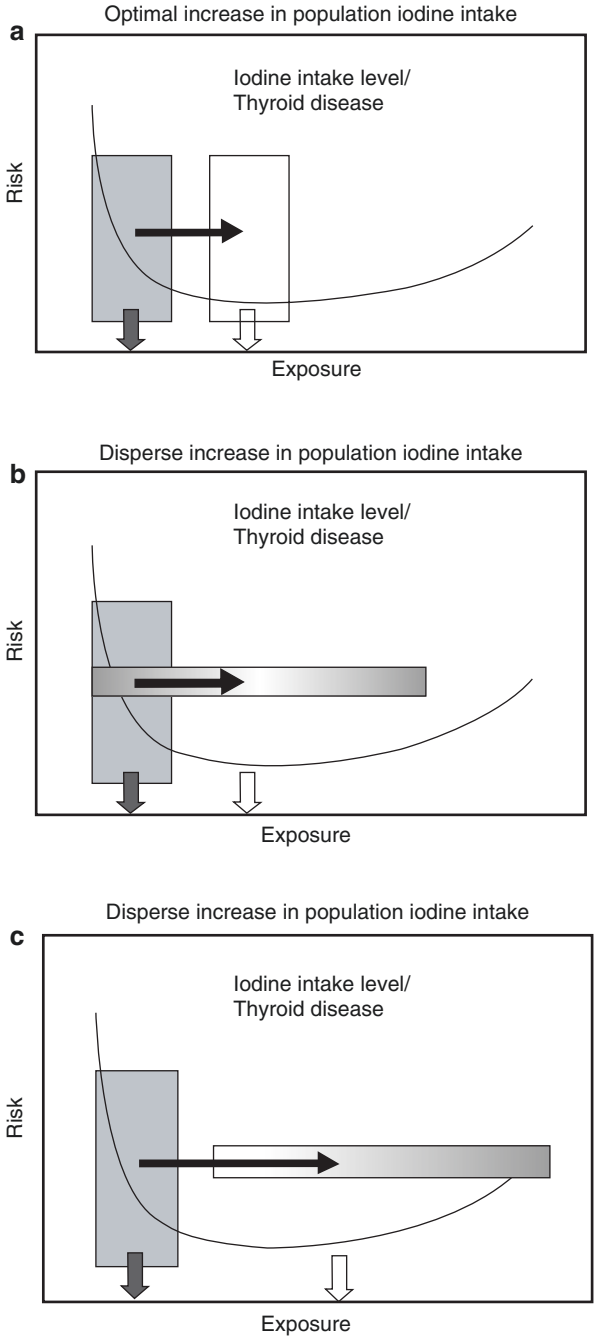

Fig. 8.2 (**a**–**c**) 'How to' and 'how not to' increase iodine intake in an iodine deficient population. *Boxes shaded grey* are non-optimal iodine intakes (low or high). *White boxes* are optimal iodine intakes. *Vertical arrows* indicate median iodine intake of the population before and after intervention. The *upper panel* illustrates a situation where an iodization program increases iodine intake equally in all members of society, thus increasing iodine intake from low to adequate in all individuals. The *middle panel* depicts a situation where some members of the population change to a diet with high iodine content, but other members remain insufficient. Thus, median intake increases from low to adequate, but many individuals have inadequately low or excessively high iodine intakes. The *lower panel* illustrates how a program such as the one introduced in the *middle panel* has to overdo iodine intake in many individuals to avoid iodine deficiency in part of the population.

The Planning of Fortification

When considering which foods may be suitable for iodine fortification, it is important to have good knowledge of the natural sources of iodine in the population, and also of the intake distribution of foods that may be candidates for fortification.

Figure 8.3 shows the main sources of iodine intake in a Danish population study performed before the initiation of the Danish iodization program [8]. The study evaluated iodine sources based on a semi-quantitative food frequency questionnaire including food items known from previous Danish studies to contribute around 90 % of the iodine in the diet [9]. As illustrated, the main dietary source of iodine was dairy products, which contributed about 40 % of dietary iodine intake in the population investigated.

The reason that milk products are good iodine sources is that the cells of the lactating mammary gland contain a very active sodium iodide symporter (NIS), similar to NIS in the follicular cells of the thyroid gland [10]. NIS transports iodide from blood into the cells of the mammary gland, where it is excreted into milk. As opposed to the thyroid gland, where NIS activity is autoregulated with a decrease in iodine uptake when iodine intake is high, there is little autoregulation in the mammary gland. Accordingly, the iodine content of dairy milk varies considerably with the iodine content of cows feed [11].

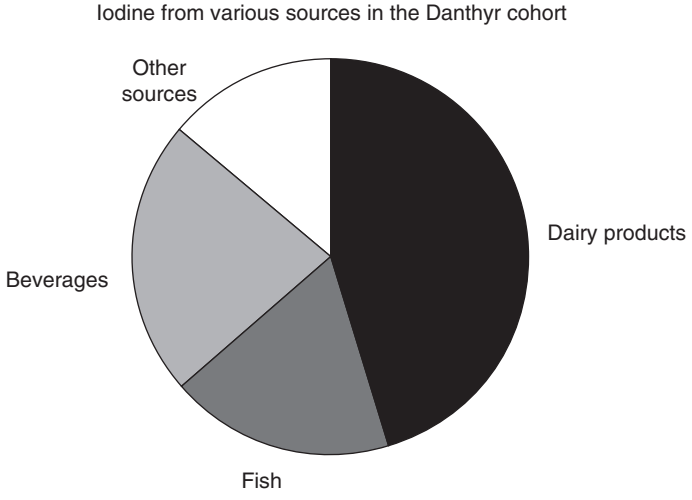

Fig. 8.3 Dietary iodine sources in the DanThyr cohort investigated before the introduction of the Danish iodine fortification program (n = 4649 adults from the population). Median urinary iodine concentrations in sub-cohorts were 45–70 μg/L. Dietary sources were estimated from a food frequency questionnaire [9]. Iodine intake from vitamin/mineral supplements is not included (Data are from Rasmussen et al. [8])

Dairy Products and Iodine Biofortification

Dairy products are technically simple targets for iodine biofortification. It is a matter of increasing the iodine content of cattle feed. Historically such increases have led to considerable improvements in iodine nutrition in many countries, with a reduction in diseases caused by iodine deficiency. However, this has not to date been part of a planned intervention. As described by Philips [12] in his article 'Iodine, milk, and the elimination of endemic goitre in Britain: the story of an accidental public health triumph,' the increase in the iodine content of British milk was not intended to improve human health, but was caused by farmers' attempts to increase their herds' reproductive performance and milk production by increasing iodine in feed. Similar increases in iodine content of cattle feed have occurred in many other countries [13]. However, in many regions iodine content of cattle feed has again decreased, and thereby dairy milk iodine content has become lower. Moreover, milk consumption has recently decreased in many regions.

We know of no good example of regulated iodine content of consumer's milk as part of a public program to adjust population iodine intake. The EU has recently proposed regulations on iodine content of cattle feed [11]. An important detail in this field is that certain substances may competitively inhibit NIS transport of iodide into milk and thereby lower iodine content of milk. One such substance is thiocyanate, and thiocyanate from rapeseed in cattle feed considerably decreases milk iodine content (Fig. 8.4) [14]. Thus, both the iodine content of feed and the use of rapeseed (canola) feed affect milk iodine content [15]. In reality, it may be simpler

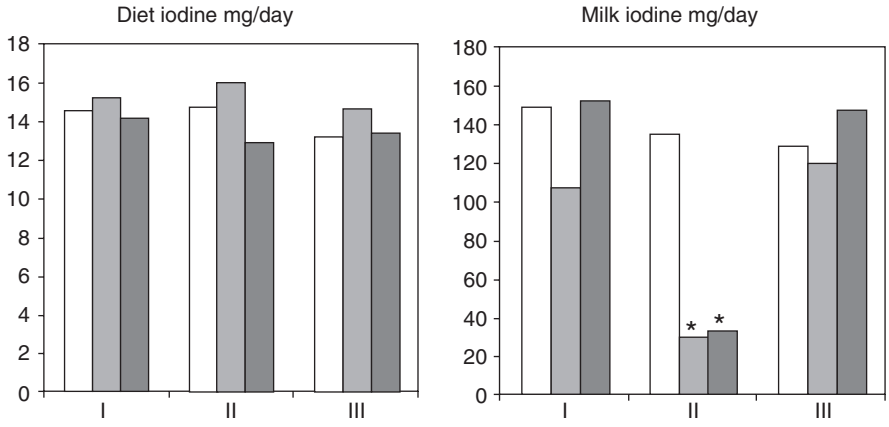

Fig. 8.4 Effect of rapeseed meal on the iodine content of cows' milk (n = 15). Cows were investigated over three time periods (I–III). During periods I and III all cows received soybean meal. In period II cows were randomized to be feed with soybean meal (*white columns*) or two types of rapeseed meal (*shaded columns*). The *left figure* shows the unaltered iodine content of feed, and the *right figure* illustrates the profound inhibition of milk iodine excretion invoked by rapeseed feeding (Data are from Papas et al. [55])

to measure iodine in batches of dairy milk and adjust the iodine content by adding KI (direct fortification) than to try to balance biofortification via cattle feed.

Another problem with dairy products as the dominant source of iodine in a population is that the distribution of milk intake may be skewed, as illustrated in Fig. 8.5. In the Danish population some people have no intake or a very low intake, and some have a very high intake of dairy products [16]. Thus, an increase in iodine content of milk will have minimal effects on part of the population and it could result in excessive intakes in others.

The importance of milk intake for individual iodine status is illustrated in Fig. 8.6. When participants of a Danish population study (n = 4649) were stratified according to average daily milk consumption, urinary iodine excretion showed considerable differences, with nearly 50 % higher mean values in people consuming >3 glasses of milk per day compared to non-consumers (Fig. 8.6, upper panel) [8]. Such differences in milk and iodine intake led to a difference in the concentration of thyroglobulin in serum (Fig. 8.6, lower panel) [17]. Thyroglobulin is a large protein that plays a major role for thyroid hormone synthesis and storage in the thyroid gland. Small amounts of thyroglobulin are released from the thyroid gland into

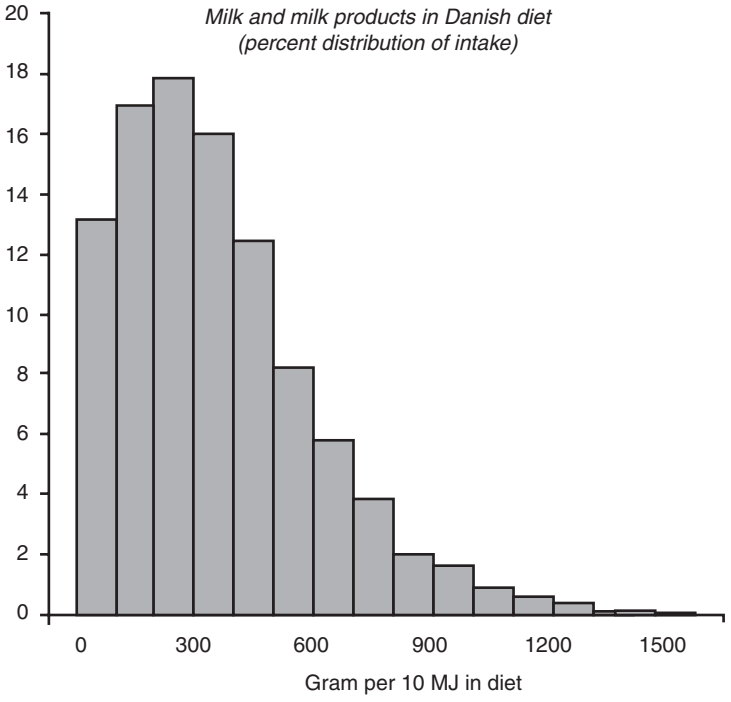

Fig. 8.5 Distribution of the intake of milk and milk products in grams per day per 10 MJ in the diet in Denmark. 10 MJ is the approximate daily energy intake of an adult Dane. Columns indicate the proportion of the investigated 3,946 individuals aged 4–75 years who had the indicated milk intake. Intake of food and drink was estimated from food recordings for seven consecutive days (Data are from Pedersen et al. [16])

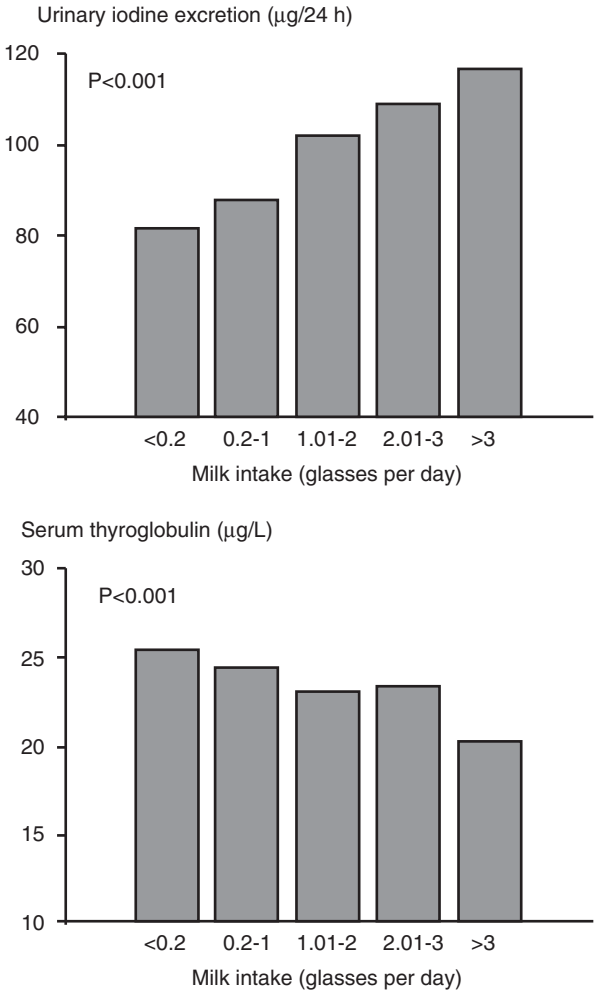

Fig. 8.6 Geometric mean urinary iodine excretion (*upper figure*) and serum thyroglobulin (*lower figure*) in adult Danes (n = 4649) stratified according to milk intake (Data are from Rasmussen et al. [8, 17])

blood, depending on a variety of factors [18]. Overall, elevated thyroglobulin in blood is a good marker of iodine deficiency in a population [19, 20].

Dairy products are important sources of iodine in many populations. However, even if dairy products contribute importantly to iodine nutrition, the level of milk intake is somewhat heterogeneous and the iodine content of dairy milk is often not regulated and declared. Thus, relying nearly entirely on dairy products for iodine nutrition in a population is not optimal.

Biofortification of Fish?

Generally, iodine is considerably more abundant in the sea than in the terrestrial world, with very high levels present in some types of seaweed. Where seaweed is common in the diet, as it is in Japan [21] and Korea [22], population iodine

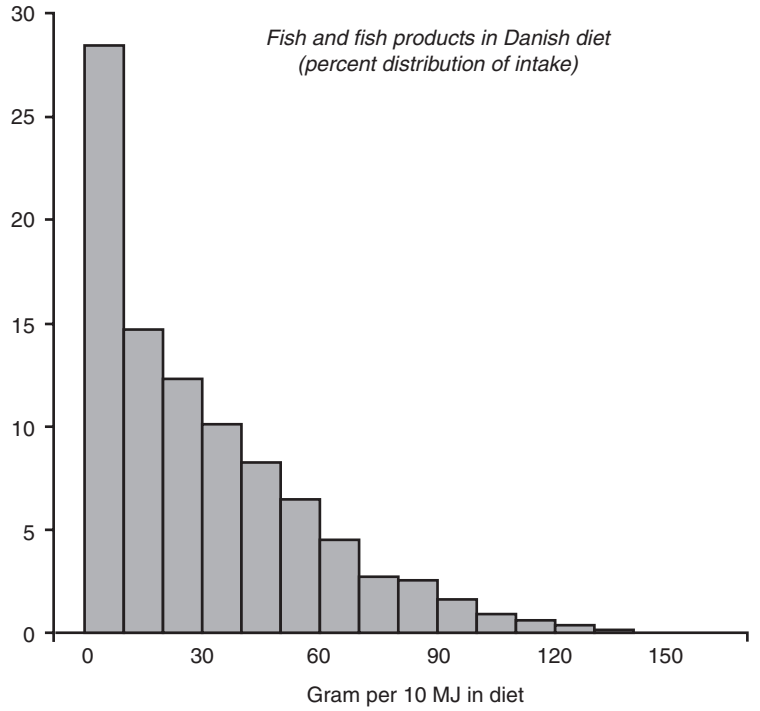

Fig. 8.7 Distribution of the intake of fish and fish products in grams per day per 10 MJ in the diet in Denmark. 10 MJ is the approximate daily energy intake of an adult Dane. Columns indicate the proportion of the investigated 3,946 individuals aged 4–75 years who had the indicated fish intake. Intake of food and drink was estimated from food recordings for seven consecutive days (Data are from Pedersen et al. [16])

intakes may be more than adequate or even excessive, as evaluated by WHO guidelines [23]. However, seaweed is not a common part of the diet in most populations.

Fish may be a good source of iodine. One problem is that the iodine content varies substantially between species. In a Polish study [24], the average amount of different types of fish required to cover daily iodine requirements varied between 14 g and 145 g. Catching wild fish for human consumption is widespread, but more and more frequently consumption is dominated by farmed fish. The iodine content of farmed fish depends on the iodine content of the fish feed, and in principle, farmed fish could be biofortified with iodine.

A major problem with fish as a source of iodine in the population is the skewed intake distribution, as illustrated in Fig. 8.7 [16]. In this Danish dietary survey, nearly 30 % of the population had practically no fish consumption. Thus, any program of fortification based on fish products would distribute iodine quite unevenly in the population, with some people still suffering from insufficiency, while others might have a more than adequate iodine intake. Fish products may contribute to iodine intake in a population, but the fish intake is so uneven that fish is not optimal as the main source of iodine.

Water and Other Beverages

In the Danish study of dietary iodine sources, the third important source was beverages (Fig. 8.3). In Denmark, nearly all water used for consumption is ground water. A substantial amount is consumed as coffee and tea, and water iodine content is preserved during preparation. In Denmark, major geographical differences exist in the iodine content of the ground water [25, 26]. These differences allowed ecological studies on the importance of relatively minor systematic differences in iodine intake for the development of thyroid diseases in the population, and such differences were considerable [27]. In particular, more goiter was observed in areas with moderate iodine deficiency and very low water iodine content (a few micrograms per liter) compared with only mild iodine deficiency (iodine around 20 μg/l water), and the prevalence of sub-clinical and overt hyperthyroidism caused by thyroid autonomy was much higher in the regions with the lower drinking water iodine content. On the other hand, the incidence of overt autoimmune hypothyroidism was 50 % higher when iodine deficiency was only mild compared with moderate [28].

The highest iodine content of Danish ground water (140–150 μg/l) was observed in the small city of Skagen, where the content of iodine-rich humic substances in water was high [29]. One problem with a national program of iodization is that regional differences in iodine intake may persist, and that some areas may be at risk for more than adequate iodine intake. Thus, iodization programs have to be initiated with caution. If small areas have high water iodine content, a change of the drinking water supply may be needed. If large areas have high groundwater iodine content, such areas may optimally be exempted from the iodization program.

Considerable differences in thyroid disease epidemiology depending on ground water iodine content have also been shown in other areas of the world [30, 31]. In some areas, aquifers are so iodine rich that the proper intervention is a decrease in the use of such water for consumption.

Iodination of drinking water has been tried in various villages in Africa [32] and in a town of Sicily [33]. Elnagar et al. [32] found an increased urinary iodine excretion and a decreased goiter rate 2 years after a system of water iodination using silicon matrices containing 30 % sodium iodide was introduced in the wells in four villages. Likewise, urinary iodine increased in a goiter endemic area in Sicily after introduction of iodine into a public water supply [33]. However, in societies with centralized water supplies, such fortification is rarely, if ever, feasible.

Bread as a Source of Iodine

Before the Danish iodization program, bread did not contribute significantly to iodine intake, but intake of bread is distributed very well in the population (Fig. 8.8) [16]. This makes bread well suited to be a vehicle for iodine, and it is the

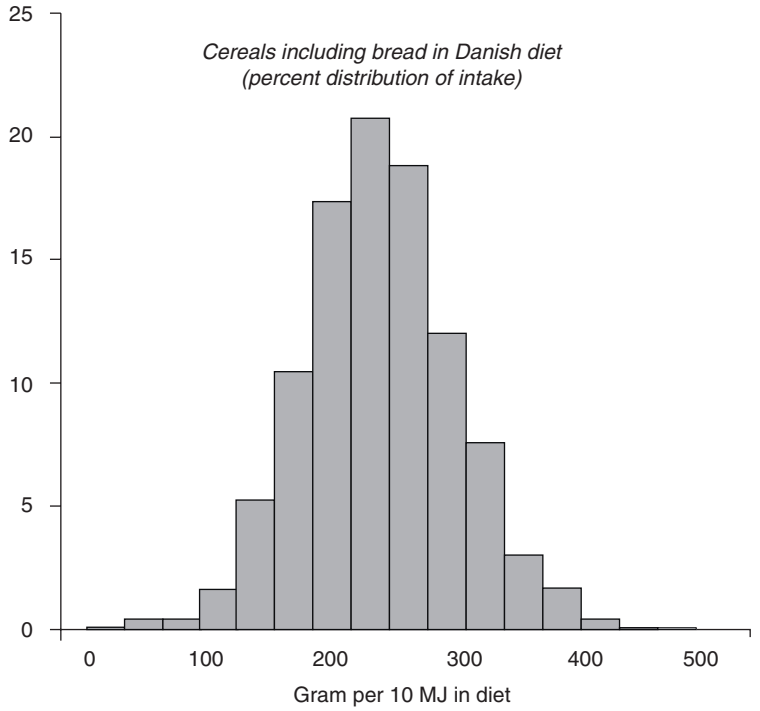

Fig. 8.8 Distribution of the intake of cereals including bread in grams per day per 10 MJ in diet in Denmark. 10 MJ is the approximate daily energy intake of an adult Dane. Columns indicate the proportion of the investigated 3,946 individuals aged 4–75 years who had the indicated intake. Intake of food and drink was estimated from food recordings for seven consecutive days (Data are from Pedersen et al. [16])

background for the current Danish program of iodine fortification of bread, introduced in the year 2000. In addition to salt used for bread production by factories and smaller bakeries, household salt is iodized [27], which ensures that families baking their own bread will be covered.

Several other countries such as The Netherlands [34], Australia [35], and New Zealand [36] have introduced iodization programs based on iodine fortification of bread. In principle, the iodine might be added to any component of bread, but for practical reasons salt used for production of bread is the common choice.

Based on knowledge of the salt content of bread, bread intake (Fig. 8.8), and the use of household salt, the amount of iodine to add to obtain a certain increase in average iodine intake in the population can be estimated. In Denmark, it was decided to initiate the iodization program cautiously, with an average increase in daily intake of 50 μg iodine (added to salt as KI) to minimize the risk of side effects from the increase in dietary iodine. The average intake of salt in bread and household salt was estimated to be 4 gram per day. Thus, the amount of iodine added to salt was set at 13 μg per gram salt (13 ppm).

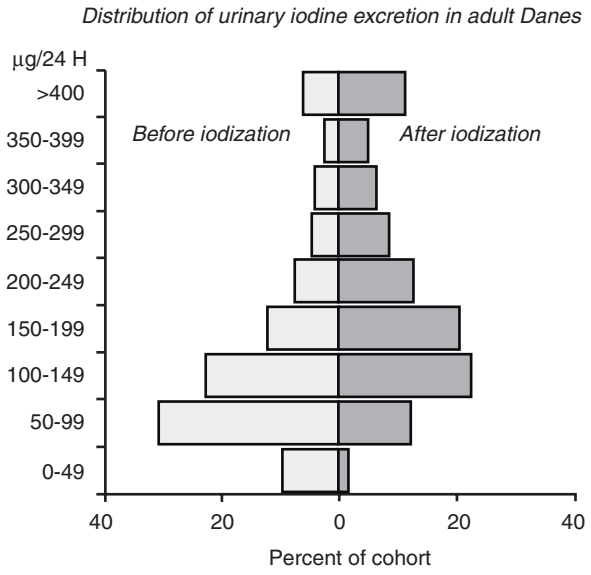

Fig. 8.9 Distribution of urinary iodine excretion (µg/24 h) in adult Danes before (*left panel*) and after (*right panel*) the Danish iodization program (mandatory 13 ppm iodization of salt used for commercial bread production and household salt). Two identical population studies were performed (C1a, 1997–1998, n = 4649; C2, 2004–2005, n = 3570). 24 h urinary iodine excretion was estimated from measurements of iodine and creatinine in spot urine samples [37]

After starting the mandatory iodization program, the observed increase in iodine intake estimated from urinary iodine excretion was close to this value [37]. Thus, the Danish experience demonstrates that such type of fortification can work as planned and that it can lead to a general increase in iodine intake, as illustrated in Fig. 8.9. In the Danthyr C1a cohort, investigated before the iodization, 63 % of participants had estimated 24 h iodine excretion below 150 µg/24 h (~100 µg/L in spot urine [38]), and 10 % had iodine excretion <50 µg/24 h. In the Danthyr C2 cohort investigated some years after iodization, 36 % had iodine excretion <150 µg/24 h and 1 % <50 µg/24 h. Moreover, the Danish program has reduced the occurrence of iodine deficiency disorders in the population [39]. Various reports on such type of iodine fortification from other countries have also been positive [34–36], but as seen in Fig. 8.9, the number of people with a high urinary iodine excretion tends to increase.

In countries where dietary intake of bread is high and consumption is uniformly distributed in the population, iodine fortification of bread is convenient and effective.

Experiences with Biofortification

Biofortification of eggs [40] has been considered, and meat is to some degree biofortified from iodine feeding of pigs and cattle [41], but the main focus has been on biofortification of vegetables [42–47]. In an Italian study by Tonachera et al. [44], vegetables (potatoes, cherry tomatoes, carrots, and lettuce) were biofortified with iodine by spraying iodine on the plants through fertilization during the growing season. The plants assimilated the iodine, and the amounts of accumulated iodine were 45–52 µg per 100 g. During two weeks 50 volunteers consumed 100 g of biofortified vegetables daily. Urinary iodine concentration increased from 98 (64–142) µg/L to

118 (78–180) μg/L (P = 0.035). Thus, biofortification of vegetables is possible. Cerretani et al. [46] tested how well biofortified vegetables would preserve their iodine content during cooking, and concluded that preservation varied from reasonable to good. On the other hand, Smolén et al. [48] found that iodine biofortification of carrots might under some circumstances reduce the vegetable quality.

In a study by Lawson et al. [49] iodine was added to the soil as potassium iodide or potassium iodate before planting. Potassium iodate resulted in a high iodine concentration in both lettuce and kohlrabi in the first growing season, without influence of the quality of the product. Supplying potassium iodide, on the other hand, resulted in a lower amount of iodine and impairment of plant growth. In the same study, the efficiency of the method involving adding iodine to the soil was also compared with foliar fertilization. Foliar fertilization (applying fertilizer directly to plant leaves) most efficiently increased the iodine content in lettuce, whereas soil fertilization resulted in higher iodine content in kohlrabi. In another study from Xinjiang Province of China potassium iodate was dripped into irrigation water canals [50]. This increased iodine concentration in soil and crops, as well as in human urinary iodine.

Biofortification of vegetables may potentially be a tool for increasing the iodine intake of a population. However, there are many technical details to consider.

Conclusion

Universal salt iodization has been the recommended method to eradicate iodine deficiency. This method was introduced at a time when most food was homemade and salt intake was relatively high. Iodization of household salt has been common, whereas iodization of salt used by the food industry has been uncommon in many countries. Various attempts have been made to iodize a series of different food items as reviewed in detail by Mehra and Srinivasan [51], but documentation for effects at the population level is only available for the iodization of bread. Reports on bread fortification have in general been positive, but bread intake should be common and well distributed in the population.

The classical example of biofortification is dairy products, but experiences are mostly retrospective. The increase in cattle feed iodine was introduced to benefit farm production and not to improve human health.

A fundamental basis for creating and sustaining optimal iodization programs is knowledge of the iodine content of food consumed by the population and of the contribution of various food items to the diet.

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Chapter 9
Iodine Supplementation

Peter N. Taylor and Onyebuchi E. Okosieme

Abstract Iodine is essential for thyroid hormone production. Many areas of the world are at least mild-moderately iodine deficient with some regions still severely iodine deficient. Iodine supplementation, particularly through universal salt iodization, can be an extremely effective and relatively inexpensive method of correcting iodine deficiency. The benefits of correcting iodine insufficiency, particularly in pregnant women and children, can have dramatic positive effects on childhood cognitive development and other key outcomes such as growth. While the benefits of correcting iodine deficiency in severely iodine deficient regions are clear, the evidence for correcting mild-moderate iodine deficiency is less robust. Iodine supplementation requires careful introduction and monitoring to prevent over-replacement, which would mitigate against any benefits.

List of Abbreviations

KI	Potassium Iodide
KIO_3	Potassium Iodate
IQ	Intellectual Quotient
PDI	Psychomotor Development Index
PPTD	Postpartum Thyroid Dysfunction
TPOAB	Thyroid Peroxidase Antibodies
TV	Thyroid Volume
UIC	Urinary Iodine Content
USI	Universal Salt Iodization
WHO	World Health Organization

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Introduction

Iodine is key for the synthesis of thyroid hormone and was identified in the thyroid gland as long ago as 1895 [1]. As far back as 1917, it was demonstrated that goiters were caused by iodine deficiency and could be prevented by iodine supplementation [2]. However it was not until much later that actively correcting iodine deficiency became a public health concern. In 1980 the first global assessment of iodine status by the World Health Organization (WHO) determined that potentially 20–60 % of the world population was iodine deficient. Controlled studies in iodine-deficient regions demonstrated that iodine supplementation eliminated new cases of cretinism, reduced infant mortality, and improved cognitive function [3]. Iodine deficiency has been identified as one of four key risks to global childhood development [4].

More recently economic assessments identified that in the developing world, the annual potential losses attributable to iodine deficiency are approximately $35.7 billion compared to an estimated $0.5 billion annual cost for iodine supplementation through salt iodization [5]. In areas of mild-moderate iodine deficiency economic advantages are still apparent; a recent UK study [6] demonstrated that iodine supplementation in pregnancy resulted in a societal cost-savings of £4476 per woman with a net gain of 1.22 intellectual quotient (IQ) points in the offspring.

Given the clear potential benefits from a low-cost intervention such as universal salt iodization (USI), elimination of iodine deficiency has become an integral part of many national nutrition policies [7, 8]. However there are notable exceptions where policy is lacking [9]. In addition, programs to prevent iodine deficiency disorders may not remain effective due to unforeseen changes in government policy, commercial factors, and human behavior [10]. Regular ongoing monitoring and outcome studies are therefore required to maintain effectiveness of iodine supplementation and fortification programs.

Iodine Supplementation Strategies for School-Aged Children

In iodine deficient countries, whenever possible, iodine should be routinely added to complementary foods for weaning infants to provide approximately 90 μg of iodine per day [11]. The benefits of iodine supplementation observed in school-aged children are highly relevant to health policy makers. European children are increasingly micronutrient deficient [12]. Although the potential benefits of iodine supplementation in childhood vitamins may be substantial, data are lacking at present. Further research is urgently needed in this area.

Iodine Supplementation Strategies for Pregnancy and Lactation

Correction of severe iodine deficiency in pregnancy is economically advantageous and results in better clinical outcomes, including a reduction in cretinism and infant mortality rates [3, 13]. USI is the most widely used strategy for sustained prevention of iodine deficiency in pregnancy [14]. Iodine requirements are increased ≥50 % during pregnancy due to increased renal iodine losses and the need for a higher maternal free thyroxine to maintain euthyroidism [15]. Iodine deficiency in pregnancy can therefore still occur despite sufficiency in the general population [16]. In iodine-deficient countries where there is limited availability of iodized salt (<90 % house hold availability), and the median UIC is less than 100 μg/l in schoolchildren, iodine supplements should be given to pregnant/lactating women and infants [17]. The WHO recommends that individual countries assess their salt iodization programs, then decide whether supplementation is necessary [17]. Ideally, given regional variations in diets and use of iodine supplements, countries should target advice and guidance to the subnational level.

Iodized oil, although inferior to USI, still has a role. In particular the use of iodized oil is recommended in remote areas of iodine deficiency, where communications are poor or where there are numerous small scale salt producers [8]. Iodized oil also has a role at the beginning of USI control programs when iodized salt is not widely available and also in areas where universal salt iodization has previously failed [18]. Iodized oil can be given orally or via the intramuscular route but oral administration is more common because it is simpler. The usual dose provided by iodized oil is between 200 and 400 mg iodine/year. [17]. Disadvantages are an uneven level of iodine in the body over time and the need for direct contact with individuals with the accompanying increased costs compared to USI [8].

Both European and American Thyroid association guidelines [19, 20], recommend that women who are pregnant, lactating, or planning pregnancy who are at risk of iodine deficiency take iodine supplements (150 μg/day strength). The WHO [14] and the Endocrine Society [21] endorse the need for a target intake of 250 μg of iodine a day although a specific supplement dose is not indicated. It is noteworthy that both the European and American Thyroid associations recommend 150 μg daily for iodine supplements, even though the USA is more iodine sufficient than most of Europe. Ideally, given the key differences between nations in iodine status and local fortification strategies, national guidelines are essential. However, it is unclear whether targeting iodine supplementation in pregnant women and infants in areas with USI policies will lead to excessive iodisation in the rest of the population. It is straightforward to target pregnant women to receive iodine supplementation in high income countries with no USI program and evidence of low median UIC levels in pregnancy. What is less clear is whether pregnant women should also be targeted to

Table 9.1 Summary of key guidelines for iodine supplementation in pregnancy

Guideline	Guidance
American Thyroid Association [19]	To achieve a total of 250 μg iodine ingestion daily in North America all women who are planning to be pregnant or are pregnant or breastfeeding should supplement their diet with a daily oral supplement containing 150 μg of iodine
Endocrine Society [21]	Pre-conception and during pregnancy and breastfeeding, women should increase their daily iodine intake to 250 μg. Iodine intake during pregnancy and breastfeeding should not exceed 500 μg per day
European Thyroid Association [20]	Women who are pregnant, lactating, or planning a pregnancy should ingest daily supplements containing 150 μg iodine
WHO [14]	Women who are pregnant or breastfeeding should take a daily oral iodine supplement so that the total daily intake is 250 μg

receive iodine supplementation in areas with USI in place but where median UIC in pregnancy is still low, especially in low resource countries where the challenges of curtailing excessive iodisation could have devastating health consequences.

To address these controversies the Salt Iodization: Meeting the Needs of Pregnancy, Lactation and Infancy (SIMPLIFY) study (NCT 02196337) was undertaken and recruited women from China, Croatia, the Philippines and Switzerland. The objective of this study is to test whether USI alone can meet the dietary requirements of iodine in women of reproductive age, as well as pregnant women, lactating women and infants up to 2 years of age. Furthermore, it will assess whether this can be achieved without causing excess iodine intake in school children and non-pregnant non-lactating women. The results of this study will provide invaluable data on whether pregnant women or women planning pregnancy need additional targeting even if USI is available, and whether USI can meets the increased dietary requirements of pregnant women without causing excess iodination to the general population (Table 9.1).

Patient education is crucial and greater awareness of the importance of adherence to these recommendations is needed. Iodine supplementation may need to be started well in advance of pregnancy for maximum benefit. An observational study by Moleti et al. [22] demonstrated that consumption of iodized salt for more than 2 years before pregnancy was associated with lower TSH and lower rates of gestational hypothyroidism than supplementation which commenced only in pregnancy. This suggests that prolonged use of iodized salt is associated with better maternal thyroid function, probably due to greater intra-thyroidal iodine stores to utilize during pregnancy. A further study by the same group reported higher TSH concentrations in women who took iodine supplements from early gestation compared to women who consumed iodized salt alone from 2 years before conception or those who took no supplements at all [23].

Pregnant women at risk of iodine deficiency may be predictable, although some risk factors likely vary by region. In a cross-sectional study, milk intake, maternal age, and iodine-containing prenatal supplement use were all strongly positively associated with the estimated 24 h urinary iodine excretion in pregnant women in the UK [24]. In contrast, women with obesity are at increased risk for iodine deficiency in pregnancy [25].

Pregnant women who take supplements should also be reminded to continue supplementation while breast feeding as iodine requirements during lactation may be even higher than in pregnancy [26]. A study in Germany determined that women who received 200 μg of oral iodine daily had significantly higher mean iodine concentrations in breast milk than untreated women [27]. Pretell et al. [28] and others [29] have reported similar findings. These studies demonstrate that iodine supplementation in breastfeeding women can substantially increase the iodine available to newborns. More recently in a randomized double blind placebo controlled trial in Morocco [30] (an area of moderate to severe iodine deficiency without effective USI in place) healthy breast feeding women and their newborn babies were randomized (N = 241) to receive either one dose of iodine to the mother with placebo to the infant (indirect supplementation) or placebo to the mother and iodine to the infant (direct supplementation). At 3 months and 6 months of age, median infant urinary iodine concentration in the indirect infant supplementation group was sufficient (>100 μg/l) whereas in the directly supplemented group sufficiency was only attained at 6 months. This work would suggest that direct supplementation is less effective than indirect supplementation in optimizing iodine status in early life.

Summary of the Evidence of Benefit of Iodine Supplementation in Severely Iodine Deficient Regions

In Papua New Guinea, a blinded controlled trial by Pharoah et al. demonstrated that iodine supplementation in pregnancy reduces the prevalence of cretinism fourfold [31, 32]. A similar study in Zaire also revealed substantial benefits of iodine supplementation; notably this study showed benefits even if supplementation was commenced as late as 28 weeks gestation [33]. However due to high losses to follow-up this result has to be regarded with caution. In a Chinese study, the prevalence of moderate or severe neurological abnormalities among infants whose mothers received iodine in the first or second trimester was only 2 %, compared with 9 % among infants whose mothers received iodine during the third trimester or who received iodine only after birth [34]. Furthermore, maternal iodine supplementation initiated before the third trimester predicted higher psychomotor test scores for children relative to children of mothers provided with iodine later in pregnancy [35].

A randomized control trial in three villages in Peru [36], which had a baseline rate of cretinism of 3 %, assessed women who had received iodized oil either prior to or during pregnancy. The initial analysis did not indicate any improvement in cognitive function in offspring whose mothers received iodine supplementation. However, subsequent re-analysis based on whether children were iodine sufficient or iodine deficient did demonstrate that the iodine sufficient group had a mean 11 point higher IQ. This may reflect the need for ongoing iodine sufficiency in childhood to maintain benefits. A controlled trial in two villages in Ecuador revealed that the IQ of offspring of women who received iodine in pregnancy was 10 points higher than that of controls by the first year of school [37]. Subsequent analyses indicated that benefits were only seen in women treated early in pregnancy or prior to conception [37]. The outcomes of these five key intervention trials are summarized in Table 9.2.

Table 9.2 Summary of key iodine supplementation trials in severe iodine deficiency

Trial location	Design	Outcome	Effect of iodine supplementation	Substantial limitations
Papua New Guinea [31]	Alternate families received iodized oil	Prevalence of cretinism at 4- and 10-year follow-up	Age 4: Relative risk of cretinism 0.27 (0.12–0.60). Age 10: Relative risk of cretinism 0.17 (0.05–0.58)	–
Zaire [33]	Two groups, one received iodized oil the other just vitamins	Psychomotor development scores at 72 months of age	Higher mean psychomotor development scores. Significantly fewer children with low psychomotor scores – 0.5 % vs 9.7 %	Average recruitment was at 28 weeks gestation. Substantial losses to follow-up
China [34]	Oral iodized oil given to pregnant women. Children already born served as controls	Prevalence of moderate and severe neurological abnormalities	Reduced moderate and severe abnormalities if supplementation in first/second trimester (2 % vs 9 %)	–
Peru [36]	Iodized oil injections vs.no treatment	Cognitive development at age 1–4 years	No difference seen	Many children were iodine deficient. Improvements seen when only iodine sufficient children were studied
Ecuador [37]	One village received iodine oil supplementation, one did not	Cognitive development over childhood	IQ higher by 10 points	–

The Effect of Iodine Supplementation on Infant Mortality in Severely Iodine Deficient Regions

In severely iodine deficient regions there is a well-established inverse relationship between maternal free thyroxine levels in pregnancy and infant mortality [38]. Substantial decreases in infant mortality of up to 65 % have been observed with maternal iodine supplementation in pregnancy [33, 39, 40]. Infant survival may also be enhanced by iodine supplementation of newborns. In a presumed iodine deficient region of Indonesia, there was a 72 % decrease in risk of infant death [41]. Overall these studies strongly suggest that iodine supplementation in pregnant women and children in severely iodine deficient regions may reduce the infant mortality rate by over 50 %.

The Impact of Iodine Supplementation in Severely Iodine Deficient Regions on Growth and Childhood Cognition

Severe iodine deficiency in *utero* increases the risk of dwarfism. Supplementation even in areas of moderate iodine deficiency can increase birth weight by up to 200 g [42]. It is less clear, however, whether iodine supplementation also influences postnatal growth. Data from severely and moderately iodine deficient regions indicate that iodine supplementation significantly increases total thyroxine, IGF-I, IGFBP-3, as well as weight-for-age Z scores, and height-for-age Z scores [43]. Cross-sectional analyses have also repeatedly demonstrated reduced cognitive function and impaired motor skills in children from iodine-deficient areas, especially severely iodine deficient regions [8]. It is, however, difficult to assess the impact of iodine supplementation if undertaken prior to conception as a substantial proportion of the benefits likely will be from enhanced iodine status in utero.

A meta-analysis of observational data in China [44] does indicate that there appear to be only modest benefits of providing ongoing iodine supplementation to children even if they were iodine deficient in utero. This meta-analysis compared children living in naturally iodine-sufficient areas with children in: (i) severely iodine-deficient areas; (ii) iodine-deficient regions born before the introduction of iodine prophylaxis; and (iii) iodine-deficient areas born after the introduction of iodine prophylaxis. Children in iodine sufficient regions had higher IQ of 12.45, 12.3, and 4.8 IQ points, respectively indicating that the majority of the potential benefits are in *utero*. However further studies are needed to establish whether iodine supplementation in childhood can substantially improve cognitive development.

Four randomized, controlled trials in school-aged children have tried to measure the effect of iodized oil supplementation on cognition in severely iodine deficient or goitrous regions [45–48]. Only one study [46] showed potential benefit, however substantial methodological problems were present in all studies. In particular, in

two studies there was a substantial improvement in iodine status in the control group [45, 48] whereas in the other two studies the treated group remained iodine deficient on re-testing [46, 47].

Evidence for the Benefits of Iodine Supplementation in Areas of Mild-Moderate Iodine Deficiency

The evidence for the benefits of correcting iodine supplementation in areas of mild to moderate iodine supplementation is less clear. This has been addressed in a limited number of studies with mixed results. A recent meta-analysis of studies in pregnancy and children comprising seven randomized controlled trials in pregnancy and two trials in children [49] showed that iodine supplementation may be beneficial even in areas of mild-moderate iodine deficiency. In particular there may be improvements in maternal thyroid indices during pregnancy and cognition in school age children. However more data are needed before firm recommendations can be made [49].

The Impact of Maternal Iodine Supplementation on Maternal Thyroid Function and Maternal Thyroid Volume in Areas of Mild-Moderate Iodine Deficiency

Seven randomized controlled trials in European countries with mild to moderate iodine deficiency [50–57] have been undertaken to explore the effects of maternal iodine supplementation on maternal thyroid function. These have all been small studies with a combined total of number of participants of 641 of whom 370 received supplementation. Various doses of iodine ranging from 50–300 μg daily were administered in these studies and were compared with either placebo or a lower dose of supplement. The trials are summarized in Table 9.3. Compliance was good in the trial settings and iodine supplementation appears to be effective in increasing iodine intake as all seven studies showed appropriate increases in urinary iodine in women who received iodine supplementation.

Three studies demonstrated a discernible rise in TSH levels, albeit within the normal pregnancy related reference range in untreated controls, an effect which was not observed in women receiving iodine supplements [52–54]. However Antonangeli et al. found no change in TSH levels in women who received two different daily doses of iodine (50 μg vs 200 μg) [50]. Having access to iodized salt may also prevent the need for targeted iodine supplementation. Santiago et al. reported no difference in TSH between women who took iodized salt only and those who took 200 μg or 300 μg of iodine daily [56]. Furthermore, starting

Table 9.3 Randomized controlled trials on the impact of iodine supplementation in mild-moderate deficiency on maternal and neonatal outcomes

Study	Intervention	Maternal outcomes[a]				
		UIC	TSH	T4	Serum Tg	Thyroid volume
Romano et al. [30] 1991, Italy	120–180 µg iodine/day from 1st trimester (n = 17); control (n = 18)	Increased by 170 % in iodine group and by 64 % in controls	No change in either group	Not assessed	Not assessed	Increased by 16 % in controls only
Pedersen et al. [27] 1993, Denmark	200 µg KI/day from 17–18 weeks (n = 28); control (n = 26)	Increased by 90 % in KI group; decreased by 20 % in controls[b]	Increased by 21 % in controls; no change in KI group	Decreased in both groups	Increased by 50 %[b] in controls; reduced in KI group	Increased by 31 % in controls and 16 % in KI group
Glinoer et al. [31] 1995, Belgium	100 µg /day KI (n = 60);100 µg KI+100 µg LT4/day (n = 60); placebo (n = 60)	Increased by 120 % in KI and KI+LT4 groups; decreased by 30 % in controls[b]	Increased by 120 % in controls and 67 % in KI; decreased by 40 % in KI+LT4	Decreased by 10 % in controls and KI, increased by 17–23 % in KI+LT4 group	Increased by 50 % in controls; decreased by 30 % in KI and by 50 % in KI+LT4[b]	Increased by 30 % in controls, by 15 % in KI, and 8 % in KI+LT4
Liesenkotter et al. [32] 1996, Germany	300 µg/day KI from 1st trimester (n = 38); control (n = 70)	Increased by 113 % in KI group; no change in controls	No change in either group	No change in either group	No difference between groups	No difference between groups
Nohr et al. [33] 2000, Denmark	150 µg/day iodine from 1st trimester (n = 42); placebo (n = 24)	Increased by110% in iodine group; no change in controls	Increased by 29 % in controls and by 4 % in iodine group	Decreased in both groups	Increased in controls; decreased in iodine group	Not assessed

(continued)

Table 9.3 (continued)

Study	Intervention		Maternal outcomes[a]			
		UIC	TSH	T4	Serum Tg	Thyroid volume
Antonangeli et al. [26] 2002, Italy	200 μg/day (n = 32); 50 μg/day iodide (n = 35) from 10–16 weeks gestation.	Increased by 153 % in 200-group and 95 % in 50-group	No change in either group	No change in either group	No change in either group	Increased by 3 % in 200-group and 10 % in 50-group
Santiago et al. [34] 2013, Spain	IS only (n = 38); 200 μg/day KI (n = 55); 300 μg/day KI (n = 38) from 1st trimester	Increased by 43 % in 200-group and 55 % in 300-group	No change in all three groups	No difference between groups	No difference between groups	No difference between groups
			Neonatal Outcomes			
Pedersen et al. [27] 1993, Denmark	200 μg KI/day from 17–18 weeks; control (n = 54)	–	No difference between: controls and KI;	No difference between controls and KI:	Higher in controls than KI: median Tg 67 vs. 38 $P = 0.005$	Not assessed
Glinoer et al. [31] 1995, Belgium	100 μg KI/day (n = 60);100 μg KI + 100 μg LT4/day (n = 60); placebo (n = 60)	–	No difference between groups:	No difference between groups:	Higher in controls: median Tg 113 (control) vs. 65 (KI) vs. 56 (KI+LT4); $P = 0.0001$	Larger in controls: mean TV1.05 (control) vs. 0.76 (KI) vs. 0.75 (KI + LT4) $P = 0.0001$
Liesenkotter et al. [32] 1996, Germany	Intake of 300 μg KI/day from 1st trimester (n = 38); control (n = 70)	–	Not assessed	Not assessed	Not assessed	Larger in controls than KI: median TV 0.7 vs.1.5; $P < 0.004$

Santiago et al. [34] 2013, Spain	IS (n = 38); 200 µg/day KI (n = 55); 300 µg/day KI (n = 38) from 1st trimester	–	No difference between groups:	Not assessed	Not assessed	No difference between groups:

Table adapted from Taylor et al. Ref. [49].
UIC urinary iodine concentration, *KI* potassium iodide, *LT4* levothyroxine, *TPOAb* thyroid peroxidase antibody, *PPTD* postpartum thyroid dysfunction, *TV* thyroid volume, *IS* iodized salt, *KI* potassium iodide, *NA* not assessed
[a]Maternal outcomes are presented as percentage change in thyroid indices at the end of pregnancy relative to baseline
[b]values are approximate estimates from figure in original paper. Baseline median urinary iodine (UIC) concentrations were as follows: Romano et al. 31 µg/24 h in controls and 37 µg/24 h in intervention group; Pedersen et al. 51 µg/l in controls and 55 µg/l in intervention; Glinoer et al. 36 µg/l; Liesenkotter et al. 64 µg/l; Nohr et al. 50–52 µg/l in intervention and control groups; Antonangeli et al. 74 µg/g creatinine; Santiago et al. 109 µg/l

iodine supplementation well before embarking on pregnancy is likely to have added advantages as one observational study revealed that long-term prophylaxis with iodized salt was associated with higher FT4 levels than prophylaxis initiated during pregnancy [22]. Surprisingly, one observational study reported higher FT4 concentrations in control subjects than in those who received iodine supplementation, although the control group also had higher TSH levels [57]. The implication of this somewhat paradoxical finding remains unclear and merits further study.

Iodine supplementation may also potentially reduce the risk of goiter during pregnancy. Three of these randomized controlled trials reported an increase in thyroid volume in untreated women with a lower magnitude of increase observed in women who received supplements [51, 52, 54]. Only one study showed no difference in thyroid volume between supplemented and untreated groups [55]. No differences in thyroid volume were observed between groups of women who took iodized salt only versus who took 200 or 300 μg KI daily [56] or between those who received 50 μg versus 300 μg of iodine daily [50].

Thyroglobulin is a potential biomarker for iodine deficiency and also appears to be responsive to iodine supplementation [58]. Four randomized control trials have compared maternal serum thyroglobulin levels in treated women with those of untreated controls [52–55]. Three of these showed a rise in thyroglobulin levels in untreated controls while thyroglobulin levels fell in women who received supplements [52–54]. Only one study by Liesenkotter et al. failed to show a difference in thyroglobulin levels between groups [55]. This study also showed no difference in thyroid volume and there was no decline in iodine status in the control group implying that the differences in iodine status between the untreated and treated groups in this study were not sufficient to see an effect.

Four randomized control trials have included data on TPOAb in pregnancy as well as data on postpartum thyroid dysfunction [50, 52, 53, 55]. Of these, no difference in postpartum thyroid dysfunction rates was seen between treated and untreated women, and no excess cases of TPOAb positivity developed in relation to iodine supplementation. However it should be noted that the numbers in these trials were small and not adequately powered to evaluate the impact of iodisation on thyroid autoimmunity.

Effects of Maternal Iodine Supplementation on Neonatal Thyroid Parameters

Four randomized controlled trials have reported on thyroid function in the newborns of women receiving iodine supplements in pregnancy [52, 54–56]. Three studies demonstrated higher thyroglobulin levels or larger thyroid volumes in neonates of women who did not receive supplements [22, 24, 25]. Only two controlled studies assessed neonatal thyroid function in the offspring of treated and untreated women and these showed no difference in TSH or FT4 between the groups [22, 24] although numbers studies were small. Larger studies with adequate power are required.

Maternal Iodine Supplementation in Mild-Moderate Iodine Deficiency and Child Neurodevelopmental Function

One randomized control trial [56] and four observational studies [57, 59–61] have examined the impact of maternal iodine supplementation on child neurodevelopment. Results have been hard to interpret given that variable developmental outcomes were utilized in these studies. Another randomized trial was started but before recruitment targets were reached this trial was recently abandoned due to lack of funding, reflecting the difficult resource requirements for controlled trials in this area [81].

Although these studies generally show beneficial effects of iodine supplementation on offspring neurodevelopmental function there have been some discrepancies between studies. Velasco et al. observed that the children of treated women had better behavioral performance and psychomotor performance than those of untreated mothers [57]. In addition Berbel et al. demonstrated that developmental quotients were higher in children of women who started taking supplementation in early pregnancy (4–6 gestational weeks) and in addition had a FT4 above the 20th percentile compared to infants of mothers who commenced supplements in the second or third trimesters with baseline free T4 between the 0 and 10th percentiles [59]. Delayed neuro-behavioral performance was observed in 25 % and 37 % of children of mothers who started supplements in the second or third trimesters respectively, whereas no offspring of mothers who received supplements starting in early gestation had delayed neuro-behavioral performance [59].

The randomized control trial (N = 131) [56] did not have an untreated group as the groups consisted of women who received: (i) iodised salt in cooking or at the table (ii) 200 μg potassium iodide a day or (iii) 300 μg potassium iodine a day. No differences were observed between groups and childhood neurological development. Surprisingly, a study using self reported supplementary iodine intake revealed that infants of mothers who self-reported a supplementary iodine intake of >150 μg iodine per day scored lower on the psychomotor development index (PDI) than infants born to mothers with intake of <100 μg per day from supplements [61]. The reason for this observation is unclear and whilst there may be a causal association, it may be due to confounding or bias. However the same group demonstrated a significantly lower psychomotor development scale in association with supplementary iodine intake >150 μg per day in three additional areas of Spain [60]. These studies imply caution is still needed when recommending iodine supplementation, and further studies are urgently needed to address these concerns.

Iodine Supplementation in Childhood and Cognitive Function in Areas of Mild-Moderate Deficiency

The WHO recommends a daily intake of iodine of 90 μg for preschool children (up to 5 years) and 120 μg for children aged 6–12 years [17]. This may be difficult to achieve in Western-style diets. Two randomized controlled trials examined

cognitive performance in children living in areas with mild to moderate iodine deficiency. In a double-blind trial, cognitive and motor performance in 310 Albanian children aged 10–12 years (median UIC 44 μg/l), were randomly assigned to receive 400 mg of intramuscular iodine or placebo [62]. Compared with the placebo group, the iodine treated group showed improvements in 4 out of 7 tests of cognition and motor performance, namely rapid target marking, symbol search, rapid object naming, and Raven's Colored Progressive Matrices ($P < 0.0001$) [62]. This indicates that iodine supplementation can have rapid effects and that the negative effects of mild-moderate iodine deficiency are not irreversible.

In a marginally iodine deficient population in New Zealand (median UIC 63 μg/l) 166 children aged 10–13 years were randomly assigned to receive a daily tablet of 150 μg of iodine or placebo for 28 weeks [63]. Children who received iodine supplementation had improved iodine status and in addition scored higher on two out of four subtests for cognitive performance, namely, picture concepts ($P = 0.023$) and matrix reasoning ($P = 0.040$) [63].

While these studies have shown that iodine supplementation can produce substantial and rapid improvement in childhood intellectual development, it should be highlighted that childhood iodine supplementation should be viewed as an extension of maternal iodine supplementation. As indicated above, iodine sufficiency in childhood does not eradicate the consequences of exposure to lower maternal iodine levels in utero [64].

Overview of the Effects of Iodine Supplementation in Mild to Moderate Iodine Deficiency

Correction of mild-to-moderate iodine deficiency prevented increases in maternal and newborn thyroid volume and serum thyroglobulin. The effect of iodine on maternal and neonatal thyroid function was less convincing although still showing potential benefits. Iodine supplementation at dose ranges of 200–300 μg daily was equally effective as iodized salt in optimizing gestational thyroid indices. Long term iodine exposure before pregnancy had more favorable effects on thyroid indices than more recent supplementation and early institution of iodine supplements was more effective than initiation of treatment in late pregnancy.

Risks of Iodine Supplementation

A major concern regarding the potential introduction of iodine supplementation has been the risk of iodine-induced thyroid dysfunction. At the individual level short-term use such as supplementation during pregnancy/lactation appears to be safe with no evidence of an excess of overt thyroid dysfunction in the controlled iodine intervention trials in pregnancy. Furthermore, the incidence of postpartum thyroid

dysfunction observed in these trials does not appear to be higher than the published rates in the general population [65].

Epidemiological studies, however, have raised justifiable concerns. Rapid substantial increases in iodine intake in severely iodine deficient populations can precipitate hyperthyroidism, especially in elderly individuals with longstanding thyroid autonomy [66]. Less striking manifestations have been reported in marginally iodine deficient areas or where iodine prophylaxis was gradually introduced [66–68]. In Denmark and Switzerland transient increases in the incidence of hyperthyroidism were observed immediately following the introduction of iodine supplementation but reversal to baseline rates occurred within several years [69, 70]. Nevertheless, surveys from Denmark, [68] Greece, [71] Sri Lanka [72], China [73] and parts of Africa [74] have all documented increases in the occurrence of thyroid dysfunction or autoimmunity in the wake of iodization. Caution is advised against over-replacement with supplements and current guidance advises against taking more than 500 μg of iodine a day, especially during pregnancy and lactation [21, 75].

Pregnant women with a UIC of 250–499 μg/l have increased odds of subclinical hypothyroidism compared to those with a UIC of 150–250 μg/l. This rise to seven-fold higher in pregnant women with a UIC >500 μg/l [76]. The prevalence of thyroid autoimmunity has a U-shaped relationship to iodine status, with higher prevalences in both iodine deficiency and iodine excess [76]. Data from the INMA cohort indicated that offspring of mothers who consumed 150 μg/day or more of iodine in supplements had higher odds of lower psychomotor scores and an IQ score less than 85 [60], although this was not statistically significant. Another smaller study indicated that maternal intake of ≥150 μg/day, compared with <100 μg/day, of iodine from supplements was also associated with a 5.2-point decrease in the psychomotor developmental index [61]. However, this was an observational study and may be subject to substantial bias and confounding. Given that this analysis was based on the supplement dose rather than an individual's iodine levels it may also reflect other socio-economic or regional differences. There is a concern that Wolff-Chaikoff effect, the adaptive mechanisms used to counteract the thyroid inhibitory actions of an acute iodide load, do not fully develop in the fetus until late gestation [77]. Therefore, it is possible that fetal hypothyroidism could occur due to excessive maternal iodine exposure even when the mother remains euthyroid. Furthermore, the iodine content of food and water [78] is highly variable and some individuals in marginally iodine deficient countries will inevitably be exposed to higher iodine intake than the WHO recommended daily upper limit of 500 μg [79] if they also take supplements.

Taken together, these adverse outcomes demonstrate that close monitoring is essential following iodine supplementation programs as iodine excess may result in adverse outcomes. Nevertheless, this should not deter future efforts at iodine deficiency prevention as the potential adverse effects of iodine deficiency on child development far outweigh the risk of correctable hypothyroidism in a minority of adults.

Summary

It is clear that severe iodine deficiency has substantial adverse health outcomes, particularly severe cognitive impairment and adverse pregnancy outcomes. Even mild-moderate iodine deficiency *in utero* and in childhood results in some intellectual impairment, poor growth, and goiter. Iodine supplementation with periodic monitoring is an extremely cost-effective approach to correcting iodine deficiency. However iodine supplementation can have adverse consequences. Correction of mild iodine deficiency may be associated with a transiently increased risk of overt and subclinical hypothyroidism, as well as a increased risk of autoimmune thyroiditis. While effects may vary between countries, in Denmark, an increase in rates of hypo and hyperthyroidism was observed after correcting mild-to-moderate iodine deficiency. In contrast, in areas of chronic iodine excess in China, increases were observed in the incidence of subclinical hypothyroidism and autoimmune thyroiditis, but not in overt hypo- or hyperthyroidism.

Overall effects are likely to be dependent on local factors such as historic iodine levels, diet, thyroid auto-immunity, genetic predisposition, and a host of other environmental factors. National guidance is therefore essential for optimum outcomes. It appears that achieving optimal iodine intakes (in the range of 150–250 μg/d for adults) can minimize the amount of thyroid dysfunction in populations. Alternative strategies such as combining iodine supplements with folic acid may be of particular value in iodine deficient countries with limited national polices on iodine supplementation such as the United Kingdom. Continued reliance on adventitious and unmonitored sources of iodine is unwise [80] and needs urgent correction in iodine deficient countries where robust supplementation strategies are not in place.

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Chapter 10
Environmental Iodine Uptake Inhibitors

Elizabeth N. Pearce and Lewis E. Braverman

Abstract The anions perchlorate, thiocyanate, and nitrate are competitive inhibitors of the sodium/iodide symporter (NIS). When present in sufficiently high concentrations, these substances decrease the transport of iodine into the thyroid gland, therefore decreasing thyroid hormone synthesis. High intakes of thiocyanate-containing foods may exacerbate the effects of iodine deficiency in endemic goiter regions. Recent studies have examined whether environmental exposure to perchlorate and nitrate might also pose a public health risk by inducing or aggravating underlying thyroid dysfunction. Because of the importance of adequate thyroid hormone for normal development *in utero* and in early life, exposure to NIS inhibitors is of particular concern for pregnant and breastfeeding women. Because of concern about thyroidal effects in vulnerable populations, agencies in some regions are currently considering new limits on allowable amounts of perchlorate in food or drinking water. Ensuring adequate iodine intakes is another strategy for mitigating the effects of environmental NIS inhibitor exposures.

Abbreviations

AIT	Amiodarone-induced thyroxtoxicosis
EPA	Envorinmental Protection Agency
MCL	Maximum contaminant level
NHANES	National Health and Nutrition Examination Survey
NIS	Sodium iodide symporter
TPO	Thyroperoxidase
TSH	Thyroid stimulating hormone
T3	Triiodothyronine
T4	Thyroxine

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Introduction

The anions perchlorate, thiocyanate, and nitrate are competitive inhibitors of the sodium/iodide symporter (NIS). When present in sufficiently high concentrations, these substances decrease the transport of iodine into the thyroid gland, therefore decreasing thyroid hormone synthesis. *In vitro* studies have demonstrated that the affinity of perchlorate for NIS is 15 times greater than that of thiocyanate, 30 times greater than that of iodine, and 240 times greater than that of nitrate [1]. It has been known for decades that high intakes of thiocyanate-containing foods may exacerbate the effects of iodine deficiency in endemic goiter regions [2]. More recent studies have examined whether environmental exposure to perchlorate and nitrate might also pose a public health risk by inducing or aggravating underlying thyroid dysfunction [3–7]. Because of the importance of adequate thyroid hormone for normal development *in utero*, exposure to NIS inhibitors is of particular concern for pregnant women. In addition to inhibition of thyroidal NIS, the NIS inhibitors may also inhibit NIS-mediated uptake of iodine into breast milk [8].

Perchlorate

Sources of Exposure

Perchlorate salts are used as oxidizers in solid propellants for rockets and missiles, road flares, fireworks, matches, and air bag inflation systems. While environmental perchlorate is found in many regions due to industrial contamination, it is also present in the environment in areas of the southwestern US and in Chile due to natural processes [9, 10]. Perchlorate is present in Chilean nitrate fertilizers which have been exported globally. Perchlorate is soluble in groundwater and is highly stable over time in the environment. Following the advent of sensitive testing methods in the 1990s, perchlorate has been detected in the drinking water of communities around the United States and worldwide [11–13]. Perchlorate has also been detected in foods such as lettuce and other produce, grains, cows' milk, eggs, wine and beer, infant formula, infant foods, and multivitamins [14–18]. Indoor dust samples from 12 countries were recently found to contain perchlorate, but this is likely a relatively minor route of exposure [19]. In the U.S., most perchlorate exposure likely occurs through the diet [20, 21]. Low-level perchlorate exposure appears to be ubiquitous. Perchlorate was detectable in all 2,820 urine specimens obtained in the 2001–2002 U.S. National Health and Nutrition Examination Survey (NHANES), with a median urine concentration of 3.6 μg/L [22]. Perchlorate is also detectable in serum, colostrum, cord blood, amniotic fluid, and breast milk [23, 24].

Pharmacologic Effects on Thyroid Function

Health effects of perchlorate are presumed to be mediated via decreased iodine uptake, which in turn leads to decreased thyroid hormone synthesis and secretion. However, a recent rat study has suggested that the thyroid gene expression profiles associated with perchlorate exposure and iodine deficiency may differ [25]. Historically, perchlorate was used as a medication to treat hyperthyroidism [26], although enthusiasm for its use decreased following case reports of aplastic anemia in perchlorate-treated patients [27]. Perchlorate is no longer marketed as a medication in the U.S., although limited use continues in Europe and other regions [28], and it may be used in patients with refractory type I amiodarone-induced thyrotoxicosis (AIT) to inhibit the entrance of excess iodine into the thyroid, the cause of type 1 AIT [29].

Occupational Studies

A U.S. occupational study examined 29 men working in an ammonium perchlorate-producing factory who had been exposed via inhalation to high-level airborne perchlorate in 12 h shifts 3–4 days/week for an average of 3 years [30]. Thyroid function was normal and did not differ at the end of three 12 h shifts compared to after 3 days away from the plant. Thyroid volumes were similar to those of 12 unexposed community controls. A Chinese study of 51 perchlorate factory workers with long-term high-level perchlorate exposure similarly found no differences in thyroid function or serum thyroglobulin levels compared to 41 age-matched non-exposed controls who worked in the same factory [31].

Healthy Volunteer Studies

In a 14-day study, the administration of 3 mg perchlorate to healthy volunteers throughout the day did not affect serum TSH, thyroid hormone concentrations, or the 24-h thyroid ^{123}I uptake [32]. In a follow-up study, ingesting 10 mg perchlorate daily for 14 days similarly had no effect on thyroid function tests in spite of a 50 % decrease in the thyroid ^{123}I uptake [33]. Healthy volunteers who received doses ranging from 0.5–35 mg perchlorate daily for 14 days had no change in serum TSH, T4, or T3 concentrations; there was a slight decrease in the thyroid ^{123}I uptake at the 1.4 mg and higher doses, but not at the 0.5 mg dose [34]. Finally, normal volunteers who received daily doses of 0.5 or 3.0 mg perchlorate for 6 months had no changes in serum TSH, thyroglobulin, T4, free T4 index, total T3, and the thyroid ^{123}I uptake, although this study was underpowered [35].

General Population Studies

Among the 36% of women with urinary iodine values <100 μg/L in the 2001–02 NHANES data set, urinary perchlorate concentrations were positively correlated with serum TSH and inversely correlated with serum T4 values [36]. Among women with urinary iodine concentrations >100 μg/L, there was a positive association between urinary perchlorate concentrations and serum TSH, but there was no association between urinary perchlorate concentrations and serum T4 values. There were no significant associations between urinary perchlorate concentrations and thyroid function values in men, regardless of their urinary iodine concentrations, which remains difficult to explain.

Pregnancy Studies

The developing fetus is likely to be highly vulnerable to adverse effects of perchlorate exposure since thyroidal iodine turnover is highest in fetal life and adequate thyroid hormone is essential for normal neurodevelopment. A study in Chile reported that thyroid hormone and TSH levels in pregnant women and their neonates did not differ among three towns with drinking water perchlorate concentrations of 0.5 μg/L, 6 μg/L, and 114 μg/L, respectively [37]. However, due to elevated drinking water iodine concentrations, the median urinary iodine concentration in this study was 269 μg/L, which may have decreased vulnerability to the adverse effects of perchlorate. In studies from Israel and Iran, neonatal thyroid function did not differ based on maternal consumption of drinking water with high compared to low perchlorate concentrations during pregnancy [38, 39]. No associations were detected between urine perchlorate concentrations and thyroid function among pregnant women in Argentina, the U.S. (Los Angeles, California) [40], Greece [41], and the U.S. Vanguard Study cohort [42]. A modeling study suggested that in women with iodine intakes from 75–250 μg daily, typical environmental perchlorate exposures would not result in thyroid function alterations [43]. However, a study in 200 first-trimester Thai pregnant women demonstrated that the ratio of urine perchlorate to creatinine was positively associated with serum TSH and inversely correlated with serum free T4 [44]. A recent California study in 1,880 pregnant women similarly noted that increasing urine perchlorate concentrations were associated with increased serum TSH and lower free and total T4 [45]. Although a study in mildly iodine deficient pregnant women in Wales and Italy found no associations between maternal urinary perchlorate and thyroid function [46], children of the women with urinary perchlorate concentrations in the highest decile had increased odds for having IQ in the lowest 10 % at the age of 3 years [47].

Lactation

Iodine, which is required for infant nutrition, is secreted into breast milk via NIS [7], a process which may be inhibited by perchlorate. A study measured perchlorate in the breast milk of 36 women from around the U.S. and found detectable levels in

all of the samples (range 0.6–92.2 μg/L) [48]. Breast milk iodide and perchlorate concentrations were inversely correlated only in the six samples with perchlorate concentrations ≥10 μg/L. In a study of 56 Boston-area lactating women, perchlorate was detectable in all breast milk samples (median, 9.1 μg/L) [49], but there were no significant correlations between breast milk iodine and perchlorate concentrations, including in the subset of 23 women whose breast milk perchlorate concentrations were ≥10 μg/L. In a small prospective study in 13 lactating women, initiation of supplements containing 150 μg iodine/day did not significantly alter either breast milk iodine or perchlorate concentrations [50].

Perchlorate itself is transported into breast milk via NIS [51], and breast-fed infants have been reported to have higher perchlorate exposures than infants who are fed either milk-based or soy-based formula [52]. In a study of 92 full-term infants, higher urine perchlorate, nitrate or thiocyanate concentrations were associated with increased urine TSH values [53]. However, urine and serum TSH values were not highly correlated (Spearman correlation coefficient 0.49) in the subset of 50 infants for whom serum testing was performed, and there were no significant associations between perchlorate and serum thyroid function tests in those infants. A study in 64 Boston-area women and their infants at 2 months of age reported no associations between maternal breast milk or infant urine iodine concentrations and infant thyroid function [54].

Thiocyanate

Sources of Exposure

Thiocyanate is a metabolite of cyagenic glucosides present in plant foods such as cassava, cabbage, turnips, broccoli, Brussels sprouts, bamboo shoots, and cauliflower. Some of these vegetables, particularly collards, Brussels sprouts, and some types of kale, also contain glucosinalates which may be metabolized to goitrin, another NIS uptake inhibitor [55]. Cigarette smoke contains cyanide, which is metabolized to thiocyanate.

Thyroidal Effects

Diets high in thiocyanate may contribute to the development of goiter in severely iodine deficient regions [56]. This is typically a public health concern only in isolated regions with limited food diversity. For example, consumption of large amounts of cassava, a staple food in regions of Africa and Latin America, may exacerbate goiter risk in iodine deficient populations [57]. Ingestion of large amounts of bamboo shoot, which is high in thiocyanate, has been linked to endemic goiter in the West Manipur region of India, despite adequate iodine nutrition [58].

The effects of cigarette smoke on thyroid physiology are complex. It has been reported that newborns of women who smoked during pregnancy have lower serum

T4 levels, increased TSH levels, and thyroid enlargement [59, 60]. Among Boston-area pregnant women, free T4 index levels were lower in current smokers than in non-smokers [61]. Maternal cigarette smoking has been shown to decrease breast milk iodine concentrations [62, 63]. Smoking has been reported to be associated with increased thyroid volumes, particularly in iodine deficient regions [64, 65]. These effects are postulated to be related to thiocyanate exposure. However, via other mechanisms, cigarette smoke exposure also appears to decrease the risk for thyroid autoimmunity and thyroid cancer, and to increase the risk for Graves' hyperthyroidism [66].

Nitrate

Sources of Exposure

Nitrate is approximately 240 times less potent than perchlorate as a competitive NIS inhibitor [1]. Nitrates from the decomposition of organic materials occur naturally in soil, groundwater, and plants. In addition, inorganic nitrates are used as fertilizers. Sodium nitrite is added to cured meats and other foods to act as a preservative. In the U.S., the average dietary intake of nitrate in adults is about 75–100 mg daily. Most nitrate intake is from ingestion of vegetables such as beets, celery, lettuce, and spinach, and vegetarians may have nitrate intakes of up to 250 mg daily [67]. Nitrate exposures may also result from drinking water contaminated by human sewage, livestock manure, or by runoff from farmland.

Effects on Thyroid Function

In animal studies, very high nitrate doses will consistently induce thyroid hyperplasia and hypothyroidism, particularly in the setting of low-iodine diets, but the effects of lower exposures are less certain [68]. In a cross-sectional assessment of 3,772 iodine-sufficient adult participants in the Study of Health in Pomerania there was no association between urinary nitrate concentrations and ultrasound thyroid volumes [69]. In a prospective study of 10 healthy volunteers, thyroid function tests and radioactive iodine uptake were not altered following 4 weeks of daily ingestion of 15 mg/kg sodium nitrate, far above typical U.S. dietary exposures [70]. In a cohort of Old Order Amish individuals in Pennsylvania, high-level nitrate exposure from well water was associated with a higher risk for subclinical hypothyroidism in women, but not in men [71]. The effects of high nitrate exposures from drinking water contamination have also been described in Eastern Europe. In a Bulgarian village where the drinking water nitrate concentration was 75 mg/L, the odds ratio for goiter was 3.01 among iodine-sufficient schoolchildren compared to children from a nearby village with drinking water nitrate levels of only 8 mg/L [72]. Another study from Bulgaria reported an odds ratio of 5.3 for thyroid dysfunction among

pregnant women in a village with high drinking water nitrate content (93 mg/L) compared to local women without high nitrate exposures [73]. Finally, sonographic thyroid volumes and the prevalence of subclinical hypothyroidism were significantly higher in iodine-sufficient Slovakian schoolchildren from a region with high drinking water nitrate levels (51–274 mg/L) compared to age-matched children without high nitrate exposure [74]. A recent meta-analysis of two studies did not find a significant association between nitrate exposure and risk for thyroid dysfunction [63].

Combined Effects of NIS Inhibitors

Individuals may be exposed to multiple goitogens and other endocrine disruptors, and studies increasingly are trying to identify the combined effects of exposures to mixtures of compounds. In one recent cross-sectional study in pregnant women from New York, individual urine perchlorate, thiocyanate, and nitrate concentrations were not associated with thyroid function, but the weighted sum of exposures to these three NIS inhibitors was associated with higher serum TSH levels [75]. Using data from NHANES 2007–8, Steinmaus and colleagues found that individuals with both high exposure to perchlorate and thiocyanate, and low urine iodine concentrations had serum thyroxine values 13 % lower than those individuals with low perchlorate and thiocyanate exposure and adequate urinary iodine [76].

Regulation of NIS Inhibitors

Although historically there has been little regulation of perchlorate exposure, agencies in many regions are currently considering new limits on allowable amounts in food or drinking water. Canada monitors perchlorate levels in drinking water and targets a recommended threshold of less than 6 μg/L, although this recommendation is not enforced [77]. The U.S. Environmental Protection Agency (EPA) placed perchlorate on its Candidate Contamination List in 1998. In 2011, the EPA proposed national regulation of perchlorate in drinking water [78], including establishment of a national maximum contaminant level (MCL); this has been under review since 2013 [79]. Several strategies, including membrane filtration, ion exchange, electrochemical reduction, adsorption, and bioreduction, can be used for remediation of drinking water perchlorate levels [7]. A 2013 American Water Works Association report estimated that the likely national cost of perchlorate regulation ($120 million annually, assuming an MCL of 4 μg/L) would be lower than for many other drinking water regulations [80]. In Europe, regulations are being applied to perchlorate content of foods rather than drinking water. In 2014 The European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain established a tolerable daily intake of 0.3 μg/kg body weight per day, based on the inhibition of thyroid iodine uptake in healthy adults [81].

The World Health Organization has defined the safe upper limit for nitrate in drinking water as 50 mg/L [82] and the U.S. EPA has set a maximum contaminant level at 10 mg/L [83]. These thresholds were adopted primarily to protect against methemoglobinemia in bottle-fed infants, rather than because of concerns about thyroid health.

NIS Inhibitors: Mitigation Strategies

Increased iodine ingestion has been proposed as a means of mitigating the thyroidal effects of exposures to NIS inhibitors. The U.S. National Research Council has recommended iodine supplementation for pregnant and lactating women to protect against the adverse effects of perchlorate exposure [84]. Similarly, the American Thyroid Association and American Academy of Pediatrics currently recommend that women who are planning pregnancy or who are pregnant or lactating should ingest a 150 μg iodine supplement daily both to ensure adequate iodine nutrition and to overcome the potential adverse effects of perchlorate [85, 86]. A recent modeling study estimated that adding a low level of iodine to drinking water to achieve increased intakes of a few micrograms daily might offset the thyroidal effects of drinking water perchlorate [87].

Summary

At high doses, perchlorate, thiocyanate, and nitrate can all decrease thyroid hormone production by competitive inhibition of NIS. Exposure to high levels of dietary thiocyanate, especially in iodine deficient regions, may exacerbate risks for hypothyroidism and goiter. The thyroidal effects of ubiquitous low-level environmental exposures to perchlorate and nitrate remains incompletely understood. However, pregnant women and young infants are likely the population most vulnerable to the effects of such exposures, since adequate thyroid hormone is needed for normal neurodevelopment. Additional studies are needed to further elucidate the risk posed by environmental exposure to iodine uptake inhibitors, both separately and in combination. Because of concern about thyroidal effects in vulnerable populations, agencies in some regions are currently considering new limits on allowable amounts of perchlorate in food or drinking water. Ensuring adequate iodine intakes is another strategy for mitigating the effects of environmental NIS inhibitor exposures.

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