16. Iodine

## 16.1 Role of iodine in human metabolic processes

At present, the only physiological role known for iodine in the human body is in the synthesis of thyroid hormones by the thyroid gland. Therefore, the dietary requirement of iodine is determined by normal thyroxine (T_4) production by the thyroid gland without stressing the thyroid iodide trapping mechanism or raising thyroid stimulating hormone (TSH) levels.

Iodine from the diet is absorbed throughout the gastrointestinal tract. Dietary iodine is converted into the iodide ion before it is absorbed. The iodide ion is 100% bioavailable and absorbed totally from food and water. This is, however, not true for iodine within thyroid hormones ingested for therapeutic purposes.

Iodine enters the circulation as plasma inorganic iodide, which is cleared from the circulation by the thyroid and kidney. The iodide is used by the thyroid gland for synthesis of thyroid hormones, and the kidney excretes excess iodine with urine. The excretion of iodine in the urine is a good measure of iodine intake. In a normal population with no evidence of clinical iodine deficiency either in the form of endemic goitre or endemic cretinism, urinary iodine excretion reflects the average daily iodine requirement. Therefore, for determining the iodine requirements and the iodine intake, the important indexes are serum T_4 and TSH levels (exploring thyroid status) and urinary iodine excretion (exploring iodine intake). A simplified diagram of the metabolic circuit of iodine is given in Figure 16.1.

All biological actions of iodide are attributed to the thyroid hormones. The major thyroid hormone secreted by the thyroid gland is T_4. T_4 in circulation is taken up by the cells and is de-iodinated by the enzyme 5′-monodeiodinase in the cytoplasm to convert it into triiodothyronine (T_3), the active form of thyroid hormone. T_3 traverses to the nucleus and binds to the nuclear receptor. All the biological actions of T_3 are mediated through the binding to the nuclear receptor, which controls the transcription of a particular gene to bring about the synthesis of a specific protein.

FIGURE 16.1
Summary of thyroid hormone production and regulation
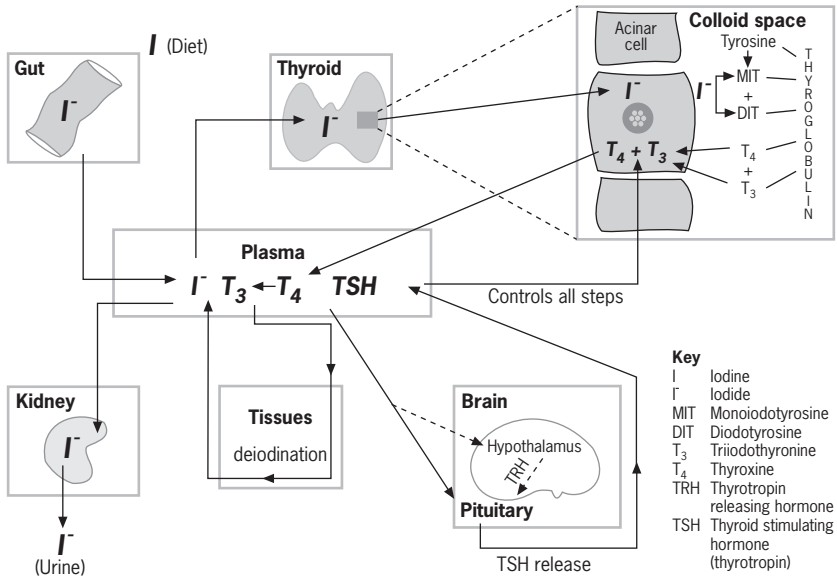
Source: reference (*1*).

The physiological actions of thyroid hormones can be categorized as 1) growth and development and 2) control of metabolic processes in the body. Thyroid hormones play a major role in the growth and development of the brain and central nervous system in humans from the 15th week of gestation to 3 years of age. If iodine deficiency exists during this period and results in thyroid hormone deficiency, the consequence is derangement in the development of the brain and central nervous system. These derangements are irreversible; the most serious form being that of cretinism. The effect of iodine deficiency at different stages of life is given in Table 16.1.

The other physiological role of thyroid hormones is to control several metabolic processes in the body. These include carbohydrate, fat, protein, vitamin, and mineral metabolism. For example, thyroid hormone increases energy production, increases lipolysis, and regulates neoglucogenesis, and glycolysis.

16.2 Populations at risk for iodine deficiency

Iodine deficiency affects all populations at all stages of life, from the intra-uterine stage to old age, as shown in Table 16.1. However, pregnant women, lactating women, women of reproductive age, and children younger than 3

TABLE 16.1
Effects of iodine deficiency, by life stage

Life stage	Effects
Fetus	Abortions
	Stillbirths
	Congenital anomalies
	Increased perinatal mortality
	Increased infant mortality
	Neurological cretinism: mental deficiency, deaf mutism, spastic diplegia, and squint
	Myxedematous cretinism: mental deficiency, hypothyroidism and dwarfism
	Psychomotor defects
Neonate	Neonatal goitre
	Neonatal hypothyroidism
Child and adolescent	Goitre
	Juvenile hypothyroidism
	Impaired mental function
	Retarded physical development
Adult	Goitre with its complications
	Hypothyroidism
	Impaired mental function
	Iodine-induced hyperthyroidism

Sources: adapted from references (*2–4*).

years of age are considered the most important groups in which to diagnose and treat iodine deficiency (*2, 5*), because iodine deficiency occurring during fetal and neonatal growth and development leads to irreversible damage of the brain and central nervous system and, consequently, to irreversible mental retardation.

16.3 Dietary sources of iodine

The iodine content of food depends on the iodine content of the soil in which it is grown. The iodine present in the upper crust of the earth is leached by glaciation and repeated flooding, and is carried to the sea. Seawater is, therefore, a rich source of iodine (*6*). The seaweed located near coral reefs has an inherent biological capacity to concentrate iodine from the sea. The reef fish which thrive on seaweed are also rich in iodine. Thus, a population consuming seaweed and reef fish will have a high intake of iodine, as is the case in Japan. Iodine intakes by the Japanese are typically in the range of 2–3 mg/day (*6*). In several areas of Africa, Asia, Latin America, and parts of Europe, iodine intake varies from 20 to 80 μg/day. In Canada and the United States and some parts of Europe, the intake is around 500 μg/day. The average iodine content

TABLE 16.2
Average iodine content of foods (µg/kg)

Food	Fresh basis		Dry basis	
	Mean	Range	Mean	Range
Fish (fresh water)	30	17–40	116	68–194
Fish (marine)	832	163–3180	3715	471–4591
Shellfish	798	308–1300	3866	1292–4987
Meat	50	27–97	—	—
Milk	47	35–56	—	—
Eggs	93	—	—	—
Cereal grains	47	22–72	65	34–92
Fruits	18	10–29	154	62–277
Legumes	30	23–36	234	223–245
Vegetables	29	12–201	385	204–1636

Source: reference (6).

TABLE 16.3
Iodine content of selected environmental media

Medium	Iodine content
Terrestrial air	1 µg/l
Marine air	100 µg/l
Terrestrial water	5 µg/l
Sea water	50 µg/l
Igneous rocks	500 µg/kg
Soils from igneous rocks	9000 µg/kg
Sedimentary rocks	1500 µg/kg
Soils from sedimentary rocks	4000 µg/kg
Metamorphic rocks	1600 µg/kg
Soils from metamorphic rocks	5000 µg/kg

Source: reference (6).

of foods (fresh and dry basis) as reported by Koutras et al. (6) is given in Table 16.2.

The iodine content of food varies with geographic location because there is a large variation in the iodine content of the various environmental media (Table 16.3) (6). Thus, the average iodine content of foods shown in Table 16.2 cannot be used universally for estimating iodine intake.

16.4 Recommended intakes for iodine

The daily intake of iodine recommended by the Food and Nutrition Board of the United States National Academy of Sciences in 1989 was 40 µg/day for young infants (0–6 months), 50 µg/day for older infants (7–12 months), 60–100 µg/day for children (1–10 years), and 150 µg/day for adolescents and

adults (*7*). These values approximate to 7.5 μg/kg/day for infants aged 0–12 months, 5.4 μg/kg/day for children aged 1–10 years, and 2 μg/kg/day for adolescents and adults. These amounts are proposed to allow normal T_4 production without stressing the thyroid iodide trapping mechanism or raising TSH levels.

16.4.1 Infants

The recommendation of 40 μg/day for infants aged 0–6 months (or 8 μg/kg/day, 7 μg/100 kcal, or 50 μg/l milk) is probably based on the observation reported in the late 1960s that the iodine content of human milk was approximately 50 μg/l and the assumption that nutrition of the human-milk-fed infant growing at a satisfactory rate represents an adequate level of nutrient intake (*8, 9*). However, recent data indicate that the iodine content of human milk varies markedly as a function of the iodine intake of the population (*10*). For example, it ranges from 20 to 330 μg/l in Europe and from 30 to 490 μg/l in the United States (*8, 10, 11*). It is as low as 12 μg/l in populations experiencing severe iodine deficiency (*8, 10*). On this basis, an average human-milk intake of 750 ml/day would give an intake of iodine of about 60 μg/day in Europe and 120 μg/day in the United States. The upper United States value (490 μg/l) would provide 368 μg/day or 68 μg/kg/day for a 5-kg infant.

Positive iodine balance in the young infant, which is required for increasing the iodine stores of the thyroid, is achieved only when the iodine intake is at least 15 μg/kg/day in term infants and 30 μg/kg/day in pre-term infants (*12*). The iodine requirement of pre-term infants is twice that of term infants because of a much lower retention of iodine by pre-term infants (*8, 12*). Based on the assumption of an average body weight of 6 kg for a child of 6 months, 15 μg/kg/day corresponds approximately to an iodine intake and requirement of 90 μg/day. This value is twofold higher than the present United States recommendations.

On the basis of these considerations, The World Health Organization (WHO) in 2001 updated its 1996 recommendations (*13*) and proposed, together with the United Nations Children's Fund (UNICEF) and the International Council for Control of Iodine Deficiency Disorders (ICCIDD), an iodine intake of 90 μg/day from birth onwards (*14*). To reach this objective, and based on an intake of milk of about 150 ml/kg/day, it was further proposed that the iodine content of formula milk be increased from 50 μg/l, the former recommendation, to 100 μg/l for term infants and to 200 μg/l for pre-term infants.

For a urine volume of about 4–6 dl/day, the urinary concentration of iodine indicating iodine repletion should be in the range of 150–220 μg/l

(1.18–1.73 μmol/l) in infants aged 0–3 years. Such values have been observed in iodine-replete infants in Europe (*15*), Canada (*16*), and the United States (*16*). Under conditions of moderate iodine deficiency, as seen in Belgium for example, the average urinary iodine concentration is only 100 μg/l (0.80 μmol/l) in this age group. It reaches a stable normal value of about 200 μg/l (1.57 μmol/l) only from the 30th week of daily iodine supplementation with a physiological dose of 90 μg/day (*17*, *18*) (Figure 16.2).

When the urinary iodine concentration in neonates and young infants is below a threshold of 50–60 μg/l (0.39–0.47 μmol/l), corresponding to an intake of 25–35 μg/day, there is a sudden increase in the prevalence of neonatal serum TSH values in excess of 50 mU/ml, indicating subclinical hypothyroidism, eventually complicated by transient neonatal hypothyroidism (*19*). When the urinary iodine concentration is in the range of 10–20 μg/l (0.08–0.16 μmol/l), as observed in populations with severe endemic goitre, up to 10% of the neonates have overt severe hypothyroidism, with serum TSH levels above 100 mU/ml and serum T_4 values below 30 μg/l (39 nmol/l) (*19*). Left untreated, these infants will develop myxedematous endemic cretinism (*20*).

FIGURE 16.2
Changes over time in the median urinary concentration of iodine in healthy Belgian infants aged 6–36 months and supplemented with iodine at 90 μg/kg/day for 44 weeks (each point represents 32–176 iodine determinations)

$$y = 21.57 - (14.31)(0.867)^x$$
$$n = 589$$
$$p < 0.001$$
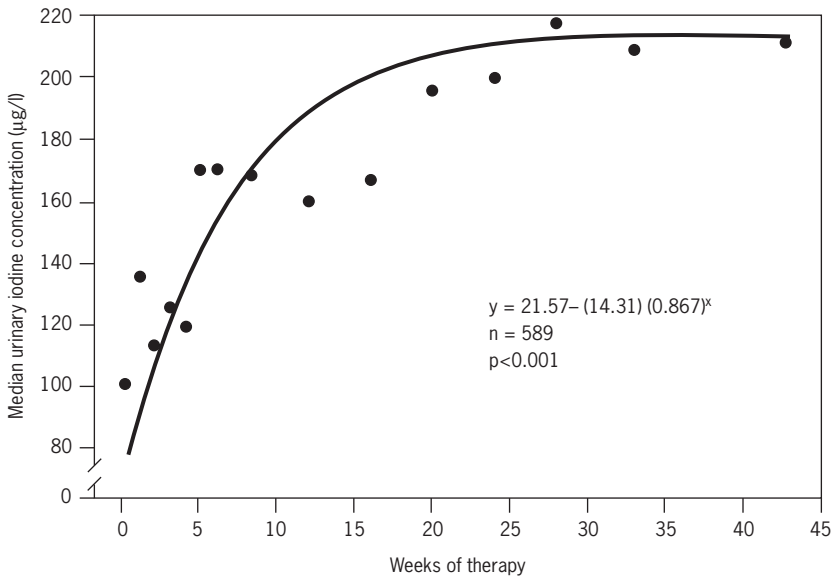
Source: reference (*18*).

Overall, existing data point to an iodine requirement of the young infant of 15 µg/kg/day (30 µg/kg/day in pre-term infants). Hyperthyrotropinaemia (high levels of serum TSH), indicating subclinical hypothyroidism with the risk of brain damage, occurs when the iodine intake is about one third of this value, and dramatic neonatal hypothyroidism, resulting in endemic cretinism, occurs when the intake is about one tenth of this value.

16.4.2 Children

The daily iodine requirement on a body weight basis decreases progressively with age. A study by Tovar and colleagues (*21*) correlating 24-hour thyroid radioiodine uptake and urinary iodine excretion in 9–13-year-old school-children in rural Mexico suggested that an iodine intake in excess of 60 µg/day is associated with a 24-hour thyroidal radioiodine uptake below 30%. Lower excretion values are associated with higher uptake values. An iodine intake of 60 µg/day is equivalent to 3 µg/kg/day in an average size 10-year-old child (approximate body weight of 20 kg). An intake of 60–100 µg/day for a child of 1–10 years thus seems appropriate. These requirements are based on the body weight of Mexican children who participated in this study. The Food and Agriculture Organization of the United Nations calculates the average body weight of a 10-year-old child as being 25 kg. Using the higher average body weight, the iodine requirement for a 1–10-year-old child would be 90–120 µg/day.

16.4.3 Adults

A requirement for iodine of 150 µg/day for adolescents and adults is justified by the fact that it corresponds to the daily urinary excretion of iodine and to the iodine content of food in non-endemic areas (i.e. in areas where iodine intake is adequate) (*22*, *23*). It also provides the iodine intake necessary to maintain the plasma iodide level above the critical limit of 0.10 µg/dl, which is the average level likely to be associated with the onset of goitre (*24*). More-over, this level of iodine intake is required to maintain the iodine stores of the thyroid above the critical threshold of 10 mg, below which an insufficient level of iodination of thyroglobulin leads to disorders in thyroid hormone synthesis (*23*).

Data reflecting either iodine balance or its effect on thyroid physiology can help to define optimal iodine intake. In adults and adolescents who consume adequate amounts of iodine, most dietary iodine eventually appears in the urine; thus, the urinary iodine concentration is a useful measure for assessing iodine intake (*1*, *23*). For this, casual samples are sufficient if enough are col-lected and if they accurately represent a community (*14*, *25*). A urinary iodine

concentration of 100 μg/l corresponds to an intake of about 150 μg/day in the adult. Median urinary iodine concentrations below 100 μg/l in a population are associated with increases in median thyroid size and possibly in increases in serum TSH and thyroglobulin values. Correction of the iodine deficiency will bring all these measures back into the normal range. Recent data from the Thyro-Mobil project in Europe have confirmed these relationships by showing that the largest thyroid sizes are associated with the lowest urinary iodine concentrations (*26*). Once a median urinary iodine excretion of about 100 μg/l is reached, the ratio of thyroid size to body size remains fairly constant. Moulopoulos et al. (*27*) reported that a urinary iodine excretion between 151 and 200 μg/g creatinine (1.18–1.57 μmol/g creatinine), corresponding to a concentration of about 200 μg/l (1.57 μmol/l), correlated with the lowest values for serum TSH in a non-goitrous population. Similarly, recent data from Australia show that the lowest serum TSH and thyroglobulin values were associated with urine containing 200–300 μg iodine/g creatinine (1.57–2.36 μmol iodine/g creatinine) (*28*).

Other investigations followed serum TSH levels in adult subjects without thyroid glands who were given graded doses of T_4 and found that an average daily dose of 100 μg T_4 would require at least 65 μg of iodine to be used with maximal efficiency by the thyroid in order to establish euthyroidism. In practice, such maximal efficiency is never obtained and therefore considerably more iodine is necessary. Data from controlled observations associated a low urinary iodine concentration with a high goitre prevalence, high radioiodine uptake, and low thyroidal organic iodine content (*12*). Each of these measures reached a steady state once the urinary iodine excretion was 100 μg/l (0.78 μmol/l) or greater.

16.4.4 Pregnant women

The iodine requirement during pregnancy is increased to provide for the needs of the fetus and to compensate for the increased loss of iodine in the urine resulting from an increased renal clearance of iodine during pregnancy (*29*). Previously, requirements have been derived from studies of thyroid function during pregnancy and in the neonate under conditions of moderate iodine deficiency. For example, in Belgium, where the iodine intake is estimated to be 50–70 μg/day (*30*), thyroid function during pregnancy is characterized by a progressive decrease in the serum concentrations of free-thyroid hormones and an increase in serum TSH and thyroglobulin. Thyroid volume progressively increases and is above the upper limit of normal in 10% of the women by the end of pregnancy. Serum TSH and thyroglobulin are higher in the neonates than in the mothers (*31*). These abnormalities are prevented only

TABLE 16.4
Daily iodine intake recommendations by the World Health Organization, United Nations Children's Fund, and International Council for Control of Iodine Deficiency Disorders

Group	Iodine intake	
	(µg/day)	(µg/kg/day)
Infants and children, 0–59 months	90	6.0–30.0
Children, 6–12 years	120	4.0
Adolescents and adults, from 13 years of age through adulthood	150	2.0
Pregnant women	200	3.5
Lactating women	200	3.5

Source: reference (*14*).

when the mother receives a daily iodide supplementation of 161 µg/day during pregnancy (derived from 131 µg potassium iodide and 100 µg T_4 given daily) (*32*). T_4 was administered with iodine to the pregnant women to rapidly correct subclinical hypothyroidism, which would not have occurred if iodine had been administered alone. These data indicate that the iodine intake required to prevent the onset of subclinical hypothyroidism of mother and fetus during pregnancy, and thus to prevent the possible risk of brain damage of the fetus, is approximately 200 µg/day.

On the basis of the above considerations for the respective population groups, the Expert Consultation concluded that the WHO/UNICEF/ICCIDD recommendations for daily iodine intakes (*14*) were the best available and saw no grounds for altering them at the present time. The current intake recommendations for iodine are summarized in Table 16.4.

16.5 Upper limits

While a physiological amount of iodine is required for insuring a normal thyroid function, a large excess of iodine can be harmful to the thyroid by inhibiting the process of synthesis and release of thyroid hormones (Wolff-Chaikoff effect) (*33*). The threshold upper limit of iodine intake (the intake beyond which thyroid function is inhibited) is not easy to define because it is affected by the level of iodine intake before exposure to iodine excess. Indeed, long-standing moderate iodine deficiency is accompanied by an accelerated trapping of iodide and by a decrease in the iodine stores within the thyroid (*23*). Under these conditions, the critical ratio between iodide and total iodine within the thyroid, which is the starting point of the Wolff-Chaikoff effect, is more easily reached in conditions of insufficient dietary supply of iodine than under normal conditions. In addition, the neonatal

thyroid is particularly sensitive to the Wolff-Chaikoff effect because the immature thyroid gland is unable to reduce the uptake of iodine from the plasma to compensate for increased iodine ingestion (*34*). Consequently, the upper limit of iodine intake will depend on both basal status of iodine intake and age.

16.5.1 Iodine intake in areas of moderate iodine deficiency

In a study in Belgium, iodine overload of mothers (caused by use of cutaneous povidone iodine for epidural anaesthesia or caesarean section) increased the milk iodine concentration of women and increased urinary iodine excretion in their term newborn infants (mean weight about 3 kg) (*35*). In the absence of iodine overload, the mean iodine content of breast milk was 9 μg/dl (0.63 μmol/l) and the urinary iodine of the infant at 5 days of life was 12 μg/dl (0.94 μmol/l). After the use of povidone iodine in the mother for epidural anaesthesia or for caesarean section, the mean milk iodine concentrations were 18 and 128 μg/dl, and were associated with average infant urinary iodine excretion levels of 280 and 1840 μg/l (2.20–14.48 μmol/l), respectively (*35*). Based on an intake of some 6.5 dl of breast milk per day, the estimated average iodine intakes in the babies of iodine overload mothers were 117 and 832 μg/day, or 39 and 277 μg/kg/day, respectively. The lower dose significantly increased the peak TSH response to exogenous thyroid-releasing hormone but did not increase the (secretory) area under the TSH response curve. The higher dose increased the peak response and secretory area as well as the baseline TSH concentration. Serum T_4 concentrations were not altered, however (*35*). Thus, these infants had a mild and transient, compensated hypothyroid state. More generally, the use of povidone iodine in mothers at the time of delivery increased neonatal TSH and the recall rate at the time of screening for congenital hypothyroidism (*36*). These data indicate that modest iodine overloading of term infants in the neonatal period in an area of relative dietary iodine deficiency (Belgium) can impair thyroid hormone formation.

Similarly, studies in France and Germany indicated that premature infants exposed to cutaneous povidone iodine or fluorescinated alcohol-iodine solutions, and excreting iodine in urine in excess of 100 μg/day, manifested decreased T_4 and increased TSH concentrations in serum (*37*, *38*). The extent of these changes was more marked in premature infants with less than 34 weeks gestation than in those with 35–37 weeks gestation. The term infants were not affected.

These studies suggest that in Europe, the upper limit of iodine intake which predisposes to blockage of thyroid secretion in neonates and especially in pre-

mature infants (i.e. from about 120 μg/day, 40 μg/kg/day) is only 1.5 to 3 times higher than the average intake from normal human milk and roughly equivalent to the upper range of recommended intake.

16.5.2 Iodine intake in areas of iodine sufficiency

Similar studies have not been conducted in the United States, where transient hypothyroidism is eight times lower than in Europe because iodine intake is much higher in the United States (*39*). For example, urinary concentrations of 50 μg/dl and above in neonates, which can correspond to a Wolff-Chaikoff effect in Europe, are frequently seen in healthy neonates in North America (*15*, *16*).

The average iodine intake of infants in the United States in 1978, including infants fed whole cow milk, was estimated by the market-basket approach (*40*) to be 576 μg/day (standard deviation [SD], 196); that of toddlers, 728 μg/day (SD, 315) and that of adults, 952 μg/day (SD, 589). The upper range for infants (968 μg/day) would provide a daily intake of 138 μg/kg for a 7-kg infant, and the upper range for toddlers (1358 μg/day) would provide a daily intake of 90 μg/kg for a 15-kg toddler.

Table 16.5 summarizes the recommended upper limits of dietary intake of iodine by group, which did not appear to impair thyroid function in the group of Delange infants in European studies; in adults in loading studies in the United States; or during ingestion of the highest estimates of dietary intake in the United States (*40*). Except for the value for premature infants who appear hypersensitive to iodine excess, the probable safe upper limits listed in Table 16.5 are 15–20 times higher than the recommended intakes. These data

TABLE 16.5
Recommended dietary intakes of iodine and upper limits, by group

Group	Recommended intake (μg/kg/day)	Upper limit[a] (μg/kg/day)
Infants and children		
Premature	30	100
0–6 months	15	150
7–12 months	15	140
1–6 years	6	50
7–12 years	4	50
Adolescents and adults (13+ years)	2	30
Pregnant women	3.5	40
Lactating women	3.5	40

[a] Probably safe.
Source: adapted from reference (*18*).

refer to all sources of iodine intake. The average iodine content of infant formulas is approximately 5 μg/dl. The upper limit probably should be one that provides a daily iodine intake of no more than 100 μg/kg. For this limit—with the assumption that the total intake is from infant formula—and with a daily milk intake of 150 ml/kg (100 kcal/kg), the upper limit of the iodine content of infant formula would be about 65 μg/dl. The current suggested upper limit of iodine in infant formula of 75 μg/100 kcal (89 μg/500 kJ or 50 μg/dl), therefore, seems reasonable.

16.5.3 Excess iodine intake

Excess iodine intake in healthy adults in iodine-replete areas is difficult to define. Many people are regularly exposed to huge amounts of iodine—in the range 10–200 mg/day—without apparent adverse effects. Common sources are medicines (e.g. amiodarone contains 75 mg iodine per 200-mg capsule), foods (particularly dairy products), kelp (eaten in large amounts in Japan), and iodine-containing dyes (for radiologic procedures). Occasionally, each of these may have significant thyroid effects, but generally, they are tolerated without difficulty. Braverman et al. (*41*) showed that people without evidence of underlying thyroid disease almost always remain euthyroid in the face of large amounts of excess iodine and escape the acute inhibitory effects of excess intrathyroidal iodide on the organification (i.e. attachment of oxidized iodine species to tyrosil residues in the thyroid gland for the synthesis of thyroid hormones) of iodide and on subsequent hormone synthesis (escape from, or adaptation to, the acute Wolff-Chaikoff effect). This adaptation most likely involves a decrease in thyroid iodide trapping, perhaps corresponding to a decrease in the thyroid sodium-iodide transporter recently cloned (*42*).

This tolerance to huge doses of iodine in healthy iodine-replete adults is the reason why WHO stated in 1994 that, "Daily iodine intakes of up to 1 mg, i.e. 1000 μg, appear to be entirely safe" (*43*). This statement, of course, does not include neonates and young infants (due to factors previously discussed). In addition, it has to be considered that iodine excess can induce hypothyroidism in patients affected by thyroiditis (*44*) and can induce hyperthyroidism in cases of a sudden and excessive increment of iodine supply in patients with autonomous thyroid nodules (*3, 4, 45*). Finally, iodine excess can trigger thyroid autoimmunity in genetically susceptible animals and individuals and may modify the pattern of thyroid cancer by increasing the ratio of papillary–follicular thyroid cancers (*46*).

In conclusion, it clearly appears that the benefits of correcting iodine deficiency far outweigh the risks of iodine supplementation (*46, 47*).

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