Chapter 12
Iodine

Summary of the human metabolic processes requiring iodine

At present, the only physiologic 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 bio-available and absorbed totally from food and water. This is not true for iodine within thyroid hormones ingested for therapeutic purposes. Iodine enters the circulation as plasma inorganic iodide, which is cleared from circulation by the thyroid and kidney. The iodide is used by the thyroid gland for synthesis of thyroid hormones, and the kidney excretes 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, the important indexes are serum T_4 and TSH levels (indicating normal thyroid status) and urinary iodine excretion. The simplified diagram of metabolic circuit of iodine is given in ***Figure 20*** (*1*).

Overview of significant scientific information

All biologic actions of iodide are attributed to the thyroid hormones. The major thyroid hormone secreted by the thyroid gland is T_4 (tetra-iodo-thyronine). T_4 in circulation is taken up by the cells and is de-iodinated by the enzyme 5' prime-mono-de-iodinase in the cytoplasm to convert it into tri-iodo-thyronine (T_3), the active form of thyroid hormone. T_3 traverses to the nucleus and binds to the nuclear receptor. All the biologic 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.

The physiologic actions of thyroid hormones can be categorised 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 brain and central nervous systems in humans from the 15th week of gestation to age 3 years. If iodine deficiency exists during this period and results in thyroid hormone deficiency, the consequence is derangement in the development of 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 34*** (*2*).

The other physiologic role of thyroid hormone 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.

Figure 20

Simplified diagram of the metabolic circuit of iodine

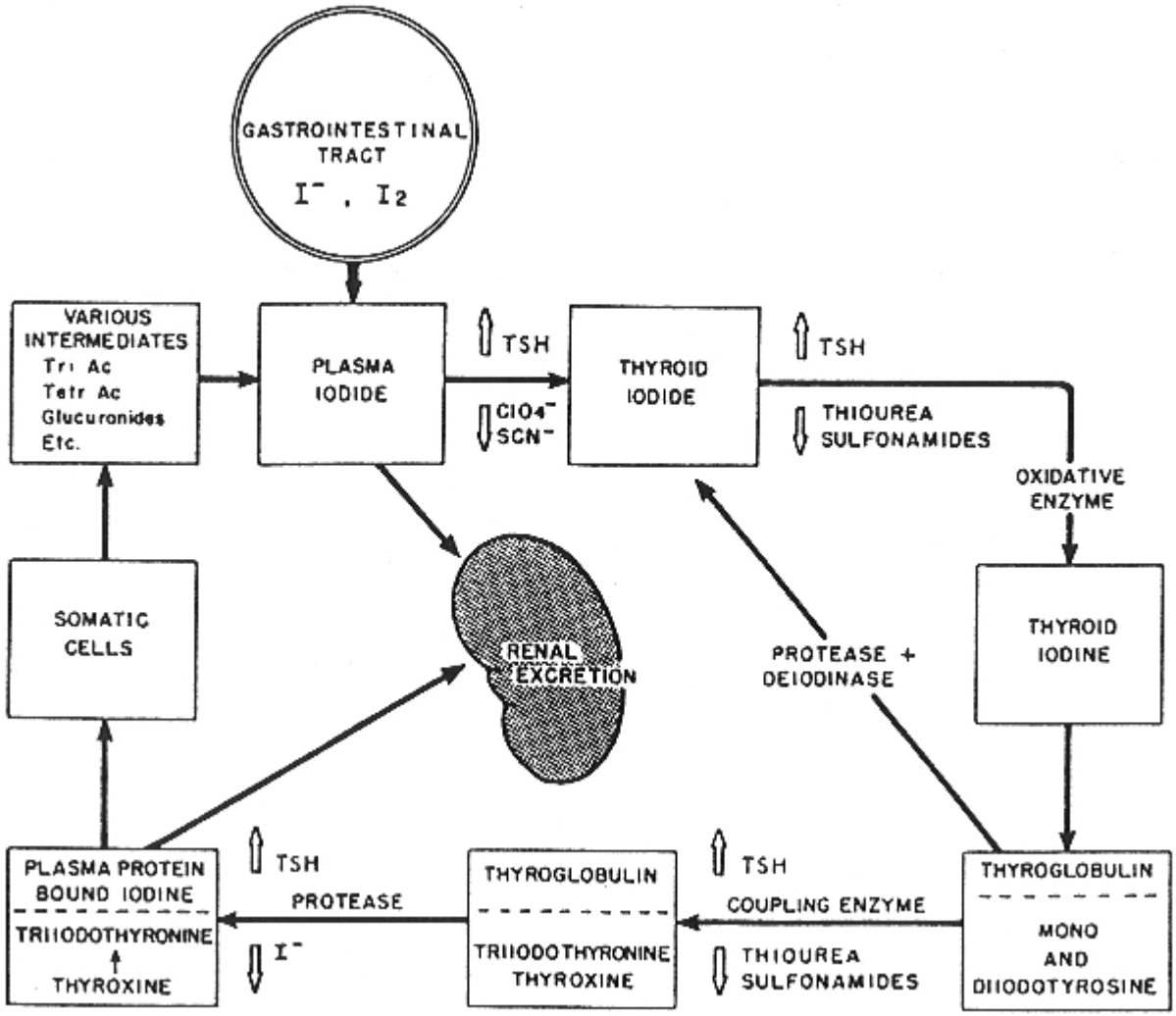


Table 34

The spectrum of iodine deficiency disorders

Life stage	Effects
Foetus	Abortions Stillbirths Congenital anomalies Increased perinatal mortality Increased infant mortality Neurological cretinism: mental deficiency, deaf mutism, spastic diplegia, and squint Myxedematous cretinism: mental deficiency 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

Population at risk

Iodine deficiency affects all stages of human life, from the intra-uterine stage to old age, as shown in ***Table 34***. However, pregnant women, lactating women, women of reproductive age, and children younger than 3 years are considered to be at high risk (*3*). During foetal and neonatal growth and development, iodine deficiency leads to irreversible damage to the brain and central nervous system.

Dietary sources

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 earth is leached by glaciation and repeated flooding and is carried to the sea. Sea water is, therefore, a rich source of iodine (*4*). The seaweed located near coral reefs has an inherent biologic capacity to concentrate iodine from the sea. The reef fish which thrive on seaweed are rich in iodine. Thus, a population consuming seaweed and reef fish has a high intake of iodine, as the case in Japan. The amount of iodine intake by the Japanese is in the range of 2–3 mg/day (*4*). In several areas of Asia, Africa, Latin America, and parts of Europe, iodine intake varies from 20 to 80 μg/day. In the United States and Canada and some parts of Europe, the intake is around 500 μg/day. The average iodine content of foods (fresh and dry basis) as reported by Koutras *et al.* (*4*) is given in ***Table 35.***

Table 35

Average iodine content of foods (in µg/g)

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

The iodine content of food varies with geographic location because there is a large variation in the iodine content of the inorganic world (***Table 36***) (*4*). Thus, the average iodine content of foods shown in ***Table 35*** can not be used universally for estimating iodine intake.

Recommended intake

The daily intake of iodine recommended by the National Research Council of the US National Academy of Sciences in 1989 was 40 µg/day for young infants (0–6 months), 50 µg/day for older infants (6–12 months), 60–100 µg/day for children (1–10 years), and 150 µg/day for adolescents and adults (*5*). These values approximate 7.5 µg/kg/day for age 0–12 months, 5.4 µg/kg/day for age 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.

Iodine requirements in infancy

The US 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 derived from the observation that until the late 1960s the iodine content of human milk was approximately 50 µg/l and from the concept that nutrition of the human-milk-fed infant growing at a satisfactory rate has been the standard against which nutrition requirements have been set (6, 7). However, more recent data indicate that the iodine content of human milk varies markedly as a function of the iodine intake of the population. For example, it ranges from 20 to 330 µg/l in Europe and from 30 to 490 µg/l in the United States (6, 8). It is as low as 12 µg/l under conditions of severe iodine deficiency (6, 8). 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 US 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 the increasing iodine stores of the thyroid, is achieved only when the iodine intake is at least 15 µg/kg/day in full-term infants and 30 µg/kg/day in pre-term infants (9). The iodine requirement of pre-term infants is twice that of term infants because of a 50 percent lower retention of iodine by pre-term infants. This corresponds approximately to an iodine intake of 90 µg/day. (This is probably based on the assumption of average body weight of 6 kg for a child of 6 months, the mid-age of an infant.) This value is twofold higher than the US recommendations.

On the basis of these considerations, a revision is proposed for the earlier World Health Organization (WHO), United Nations Children's Fund (UNICEF), and International Council for the Control of Iodine Deficiency Disorders (ICCIDD) recommendations (10): an iodine intake of 90 µg/day from birth onwards is suggested. To reach this objective, and based on an intake of milk of about 150 ml/kg/day, the iodine content of formula milk should be increased from 50 to 100 µg/l for full-term infants and to 200 µg/l for pre-term infants.

For a urine volume of about 4–6 dl/day from 0 to 3 years, the urinary concentration of iodine indicating iodine repletion should be in the range of 150–220 µg/l (1.18-1.73µmol/l) in infants aged 0–36 months. Such values have been observed in iodine-replete infants in Europe (11), Canada (12), and the United States (12). Under conditions of moderate iodine deficiency, as seen in Belgium, the average urinary iodine concentration is only 50–100 µg/l (0.39-0.79µmol/l) in this age group. It reaches a stable normal value of 180–220 µg/l (1.41-1.73µmol/l) only after several months of daily iodine supplementation with a physiologic dose of 90 µg/day (***Figure 21***).

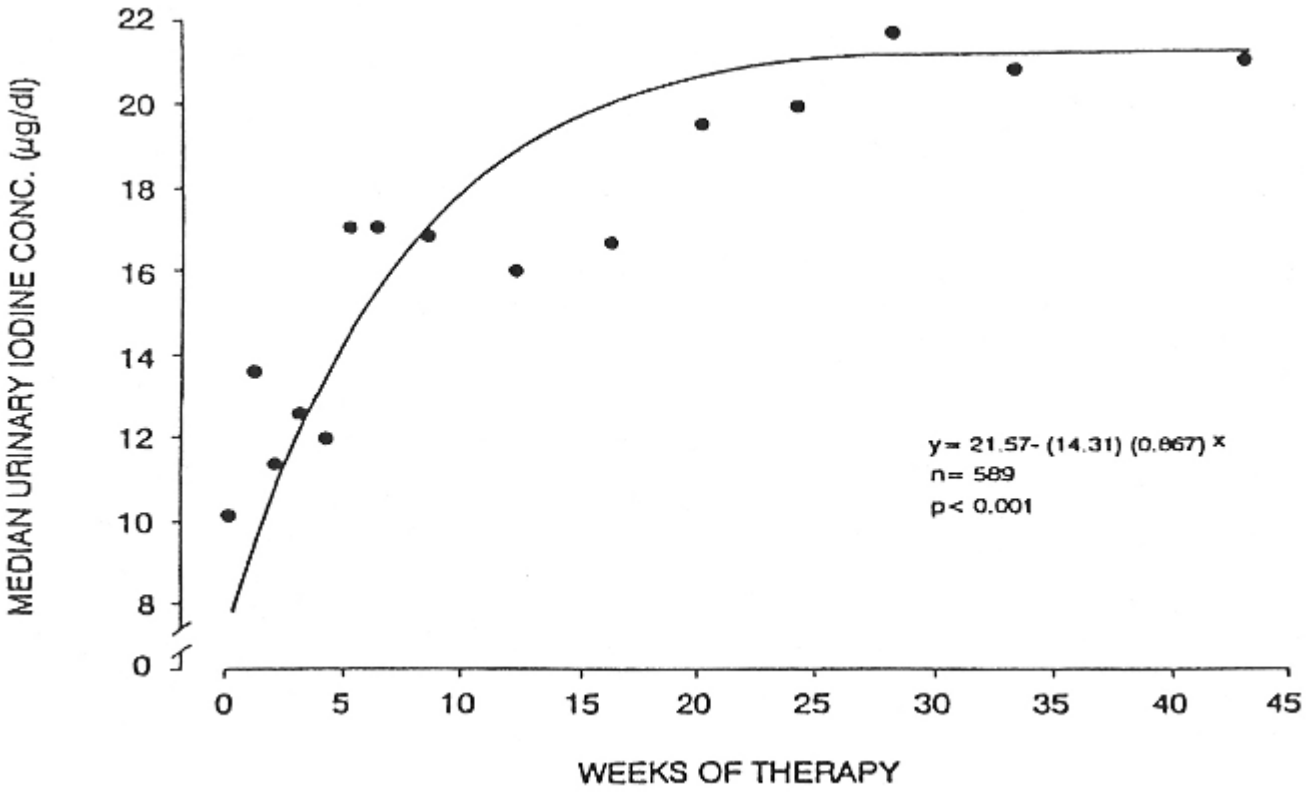
Table 36

Iodine content of the inorganic world

Location	Iodine content
Terrestrial air	1.0 µg/l
Marine air	100.0 µg/l
Terrestrial water	5.0 µg/l
Sea water	50.0 µg/l
Igneous rocks	500.0 µg/kg
Soils from igneous rocks	9000.0 µg/kg
Sedimentary rocks	1500.0 µg/kg
Soils from sedimentary rocks	4000.0 µg/kg
Metamorphic rocks	1600.0 µg/kg
Soils from the metamorphic rocks	5000.0 µg/kg

Figure 21

Changes over time for 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 (13).

When the urinary iodine concentration in neonates and young infants is below a threshold of 50-60 µg/l (0.39-0.47µmol/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 sub-clinical hypothyroidism and eventually complicated by transient neonatal hypothyroidism (14). When the urinary iodine concentration is in the range of 10–20 µg/l (0.08-0.16µmol/l), as observed in severe endemic goitre regions, up to 10 percent of the neonates have overt severe hypothyroidism, with serum TSH levels above 100 mU/mL and serum T_3 values below 30 µg/l (39 nmol/L) (14). Untreated, these infants progress to myxedematous endemic cretinism (15).

Thus, the iodine requirement of the young infant approximates 15 µg/kg/day (30 µg/kg/day in pre-term infants). Hyperthyrotropinemia (high levels of serum TSH), indicating sub-clinical 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.

Iodine requirements in children

The daily iodine need on a body weight basis decreases progressively with age. A study by Tovar and colleagues (16) correlating 24-hour thyroid radioiodine uptake and urinary iodine excretion in 9–13-year-old schoolchildren 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 percent. Lower excretion values are associated with higher uptake values. This would approximate 3 μg/kg/day in an average size 10-year-old child (approximate body weight of 20 kg), so that an intake of 60–100 μg/day for child of 1–10 years seems appropriate. These requirements are based on the body weight of Mexican children who participated in this study. The average body weight of a 10-year-old child, as per the Food and Agriculture Organization references, is 25 kg. Thus, the iodine requirement for a 1–10-year-old child would be 90–120 μg/day.

Iodine requirements in adults

Iodine at 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 (areas where iodine intake is adequate) (5). 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 (17). Moreover, 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 iodisation of thyroglobulin leads to disorders in thyroid hormone synthesis (18).

Data reflecting either iodine balance or its effect on thyroid physiology can help to define optimal iodine intake. In adults and adolescents in equilibrium with their nutritional environment, most dietary iodine eventually appears in the urine, so the urinary iodine concentration is a useful measure for assessing iodine intake. For this, casual samples are sufficient if enough are collected and if they accurately represent a community (19). 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 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 relations by showing that the largest thyroid sizes are associated with the lowest urinary iodine concentrations (20). 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.* (21) 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), gave the lowest values for serum TSH in a non-goitrous population. Similar recent data from Australia show that the lowest serum TSH and thyroglobulin values were associated with urine containing 200–300 μg iodine/g creatinine (1.57-2.36μmol/g creatinine) (22).

Other investigations followed serum TSH levels in subjects without thyroid glands who were given graded doses of T_4 and found that euthyroidism established in adults with an average daily dose of 100 μg T_4 would require at least 65 μg of iodine with maximal efficiency of iodine use by the thyroid. 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 (23). Each of these measures reached a steady state once the urinary iodine excretion was 100 μg/l (0.78 μmol/l)or greater.

Iodine requirements in pregnancy

The iodine requirement during pregnancy is increased to provide for the needs of the foetus and to compensate for the increased loss of iodine in the urine resulting from an increased renal clearance of iodine during pregnancy (24). These 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 (25), thyroid function during pregnancy is characterised by a progressive decrease of the serum concentrations of thyroid hormones and an increase in serum TSH and thyroglobulin. Thyroid volume progressively increases and is above the upper limit of normal in 10 percent of the women by the end of pregnancy. Serum TSH and thyroglobulin are still higher in the neonates than in the mothers (26). These abnormalities are prevented only 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) (27). T_4 with iodine was probably administered to the pregnant women to rapidly correct sub-clinical 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 sub-clinical hypothyroidism of mother and foetus during pregnancy, and thus to prevent the possible risk of brain damage of the foetus, is approximately 200 µg/day.

On the basis of the considerations reviewed above for the respective population groups to meet the daily iodine requirements, revisions of the current recommendations for daily iodine intake by WHO, UNICEF, and ICCIDD (10) are proposed; these proposed revisions are presented in ***Table 37***.

Table 37

Proposed revision for daily iodine intake recommendations of 1996 by the World Health Organization, United Nations Children's Fund, and International Council for the Control of Iodine Deficiency Disorders

Population sub-groups	Total iodine intake µg/day	Iodine µg/kg/day
Infants (first 12 months)	90[a]	15.0
Children (1–6 years)	90	6.0
Schoolchildren (7–12 years)	120	4.0
Adults (12+ years)	150	2.0
Pregnant and lactating women	200	3.5

[a] Revised to 90 µg from the earlier recommendation of 50 µg.

Upper limit of iodine intake for different age groups

An iodine excess also can be harmful to the thyroid of infants by inhibiting the process of synthesis and release of thyroid hormones (Wolff-Chaikoff effect) (28). 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 (18). 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 during iodine depletion

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 (29). For these reasons transient neonatal hypothyroidism or transient hyperTSHemia after iodine overload of the mother, especially after the use of povidone iodine, has been reported more frequently in European countries such as in Belgium, France, and Germany, which have prevailing moderate iodine deficiency (30-33).

Iodine intake in areas of moderate iodine deficiency

In a study in Belgium, iodine overload of mothers (cutaneous povidone iodine) increased the milk iodine concentration and increased iodine excretion in the term newborns (mean weight about 3 kg). Mean milk iodine concentrations of 18 and 128 µg/dl were associated with average infant urinary iodine excretion levels of 280 and 1840 µg/l (2.20-14.48 µmol/l), respectively (30). Estimated average iodine intakes would be 112 and 736 µg/day, or 37 and 245 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 larger dose increased both the peak response and secretory area as well as the baseline TSH concentration. Serum T_4 concentrations were not altered, however. Thus, these infants had a mild and transient, compensated hypothyroid state. Non-contaminated mothers secreted milk containing 9.5 µg iodine/dl, and the mean urinary iodine concentration of their infants was 144 µg/l (1.13 µmol/l). These data indicate that modest iodine overloading of term infants in the neonatal period in an area of relative dietary iodine deficiency (Belgium) also can impair thyroid hormone formation.

Similarly, studies in France 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 (32). 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 full-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 premature infants (about 200 µg/day) is 2 to 3 times the average intake from human milk and about equivalent to the upper range of intake.

Iodine intake in areas of iodine sufficiency

Similar studies have not been conducted in the United States, where transient hypothyroidism is rarely seen perhaps because iodine intake is much higher. 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 (11, 12).

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 (34) to be 576 µg/day (standard deviation [SD] 196); that of toddlers was 728 µg/day (SD 315) and of adults was 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 38 summarises the recommended dietary intake of iodine for age and approximate level of intake which appear not to impair thyroid function in the European studies of Delange in infants, in the loading studies of adults in the United States, or during ingestion of the highest estimates of dietary intake (just reviewed) in the United States (34). Except for the values for premature infants, these probably safe limits are 15–20 times more than the recommended intakes. These data 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 and with the assumption that the total intake is from infant formula, with a daily 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 formulas of 75 µg/100 kcal (89µg/500 kJ or 50 µg/dl), therefore, seems reasonable.

Table 38

Recommended dietary intakes of iodine and probable safe upper limits

Group	Recommended µg/kg/day	Upper limit[a] µg/kg/day
Premature infants	30	100
Infants 0–6 months	15	150
Infants 7–12 months	15	140
Children 1–6 years	6	50
School children 7–12 years	4	50
Adolescents and adults (12+ years)	2	30
Pregnancy and lactation	3.5	40

[a] Probably safe.

Excess iodine intake

Excess iodine intake is more difficult to define. Many people regularly ingest 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). Excess consumption of salt has never been documented to be responsible for excess iodine intake. Occasionally each of these may have significant thyroid effects, but generally they are tolerated without difficulty. Braverman *et al*. (35) 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 intra-thyroidal iodide on the organification (i.e., attachment of `oxidized iodine' species to throsyl 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 (36). Some people, especially those with long-standing nodular goitre who live in iodine-deficient regions and are generally ages 40 years or older, may develop iodine-induced hyperthyroidism after ingestion of excess iodine in a short period of time.

Iodine fortification

Iodine deficiency is present in almost all parts of the developed and developing world, and environmental iodine deficiency is the main cause of iodine deficiency disorders. Iodine is irregularly distributed over the earth's crust, resulting in acute deficiencies in areas such as mountainous regions and flood plains. The problem is aggravated by accelerated deforestation

and soil erosion. Thus, the food grown in iodine-deficient regions can never provide enough iodine for the people and livestock living there. The iodine deficiency results from geologic rather than social and economic conditions. It cannot be eliminated by changing dietary habits or by eating specific kinds of foods but must be corrected by supplying iodine from external sources. It has, therefore, been a common practice to use common salt as a vehicle for iodine fortification for the past 75 years. Salt is consumed at approximately the same level throughout the year by the entire population of a region. Universal salt iodisation is now a widely accepted strategy for preventing and correcting iodine deficiency disorders.

There are areas where consumption of goitrogens in the staple diet (e.g., cassava) affects the proper utilisation of iodine by the thyroid gland. For example, in Congo, Africa, as a result of cassava diets there is an overload of thiocyanate (37). To overcome this problem, appropriate increases in salt iodisation are required to ensure the recommended dietary intake. The iodisation of salt is done either by spraying potassium iodate or potassium iodide in amounts that ensure a minimum of 150 μg iodine/day. Both of these forms of iodine are absorbed as iodide ions and are completely bio-available. Other methods of iodine prophylaxis are also used: iodised oil (capsule and injections), iodised water, iodised bread, iodised soya sauce, iodoform compounds used in dairy and poultry, and certain food additives (38).

Iodine loss occurs as a result of improper packaging, Humidity and moisture, and transport in open trucks and railway wagons exposed to sunlight. To compensate for these losses, higher levels of iodine are used during the production of iodised salt. Losses during the cooking process vary from 20 percent to 40 percent depending on the type of cooking used (39).

To ensure the consumption of recommended levels of iodine, the iodine content of salt at the production level should be monitored with proper quality assurance programmes. Regular evaluation of the urinary iodine excretion pattern in the population consuming iodised salt or exposed to other iodine prophylactic measures would help the adjusting of iodine intake (40).

Recommendations

Recommendations for future research:

- elaborate the role of T_4 in brain development at the molecular level;
- investigate the relation between selenium and iodine deficiency, which has been reported in certain areas of Africa; and
- investigate the possible interference of infections and other systemic illnesses with iodine or thyroid hormone use (such interference has not been reported on a population basis).

Recommendations for future actions:

- establish quality assurance procedures at iodised salt production sites;
- track the progress of iodine deficiency disease elimination through the implementation of cyclic monitoring, which involves division of the country into five zones and carrying out the assessment in one zone each year; and
- develop and validate quantitative testing kits for iodised salt.

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