Iodine deficiency has multiple adverse effects on growth and development because of inadequate thyroid hormone production. Four methods are generally recommended for assessment of iodine nutrition: urinary iodine concentration, thyroid size, and blood concentrations of thyroid-stimulating hormone and thyroglobulin. Iodine intakes ≤1 mg/d are well tolerated by most adults, because the thyroid is able to adjust to a wide range of intakes. A daily dose of 1 μg iodine/kg body weight is recommended for infants and children receiving parenteral nutrition (PN), but this is far below their requirement. Daily iodine requirements in adults receiving enteral nutrition or PN are estimated to be 70–150 μg, but most PN formulations do not contain iodine. Despite this, deficiency is unlikely because absorption from iodine-containing skin disinfectants and other adventitious sources can provide sufficient iodine. However, if chlorhexidine replaces iodine-containing disinfectants for catheter care, iodine deficiency may occur during long-term PN, and periodic testing of thyroid functions may be prudent. Infants may be particularly vulnerable because of their small thyroidal iodine store, but available data do not yet support routine supplementation of preterm infants with iodine. Adults may be less vulnerable because thyroidal iodine stores may be able to support thyroid hormone production for several months. More studies to clarify this issue would be valuable.

Iodine (atomic weight 126.9 g/atom) is an essential component of the hormones produced by the thyroid gland. Thyroid hormones and, therefore, iodine are essential for mammalian life.1,4 Iodine (as iodide) is widely but unevenly distributed in the Earth’s environment. In many regions, leaching from glaciations, flooding, and erosion have depleted surface soils of iodide, and most iodide is found in the oceans. Iodine-deficient soils are common in mountainous areas (eg, the Alps, Andes, Atlas, and Himalaya ranges) and areas of frequent flooding, especially in South and Southeast Asia (eg, the Ganges River plain of northeastern India).1 Many inland areas, including the Midwestern region of North America, central Asia and Africa, and central and eastern Europe, are iodine deficient. Iodine deficiency in populations residing in these areas will persist until iodine enters the food chain through the addition of iodine to foods (eg, iodization of salt) or dietary diversification introduces foods produced outside the iodine-deficient area.

The native iodine content of most foods and beverages is low, and most commonly consumed foods provide 3–80 μg/serving.3–7 Major dietary sources of iodine in the United States and Europe are bread and milk.3–4 Boiling, baking, and canning of foods containing iodated salt cause only small losses (≤10%) of iodine content.9 Iodine content in foods is also influenced by iodine-containing compounds used in irrigation, fertilizers, livestock feed, dairy industry disinfectants, and bakery dough conditioners.9 Recommendations for iodine intake by age and population group are shown in Table 1.2,5

Iodide is rapidly and nearly completely absorbed (>90%) in the duodenum; the sodium/iodide symporter on the apical membrane of enterocytes mediates active iodine uptake.10 Iodate, widely used in salt iodization, is reduced in the gut and absorbed as iodide. Thyroid clearance of circulating iodine varies with iodine intake; in conditions of adequate iodine supply, ≥10% of absorbed iodine is taken up by the thyroid. In chronic iodine deficiency, this fraction can exceed 80%.11 Under normal circumstances, plasma iodine has a half-life of approximately 10 hours, but this is reduced in iodine deficiency. The body of a healthy adult contains 15–20 mg iodine, of which 70%–80% is in the thyroid. In chronic iodine deficiency, the iodine content of the thyroid may fall to <20 μg. In iodine-sufficient areas, the adult thyroid traps approximately 60 μg iodine/d to balance losses and maintain thyroid hormone synthesis; the sodium/iodide symporter transfers iodide into the thyroid at a concentration gradient 20–50 times that of plasma.12 Iodine comprises 65% and 59% of the weights of thyroxine (T4) and triiodothyronine (T3), respectively.1 Turnover is relatively slow; the half-life of T4 is approximately 5 days and for T3 it is 1.5–3 days. The released iodine enters the plasma iodine pool and can be taken up again by the thyroid or excreted by the kidney. Greater than 90% of ingested iodine is ultimately excreted in the urine.

**Table 1.** Recommendations for iodine intake by age and population group

<table>
<thead>
<tr>
<th>Age/Population</th>
<th>Iodine Intake (μg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (0–5 months)</td>
<td>100</td>
</tr>
<tr>
<td>Children (6–12 months)</td>
<td>200</td>
</tr>
<tr>
<td>Children (1–3 years)</td>
<td>250</td>
</tr>
<tr>
<td>Children (4–8 years)</td>
<td>300</td>
</tr>
<tr>
<td>Children (9–13 years)</td>
<td>350</td>
</tr>
<tr>
<td>Adolescents (14+)</td>
<td>400</td>
</tr>
<tr>
<td>Adults (both sexes)</td>
<td>150</td>
</tr>
</tbody>
</table>

**Abbreviations used in this paper:** PN, parenteral nutrition; T3, triiodothyronine; T4, thyroxine; Tg, thyroglobulin; TPN, total parenteral nutrition; TSH, thyroid-stimulating hormone; Tvol, thyroid volume; UI, urinary iodine concentration.

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Table 1. Recommendations for Iodine Intake (μg/d) by Age or Population Group

<table>
<thead>
<tr>
<th>Age or population group</th>
<th>Iodine intake, μg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Institute of Medicine(^a)</td>
<td></td>
</tr>
<tr>
<td>Infants aged 0–12 mo(^b)</td>
<td>110–130</td>
</tr>
<tr>
<td>Children aged 1–8 y</td>
<td>90</td>
</tr>
<tr>
<td>Children aged 9–13 y</td>
<td>120</td>
</tr>
<tr>
<td>Adults ≥14 y</td>
<td>150</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>220</td>
</tr>
<tr>
<td>Lactation</td>
<td>290</td>
</tr>
<tr>
<td>World Health Organization(^2)</td>
<td></td>
</tr>
<tr>
<td>Children aged 0–5 y</td>
<td>90</td>
</tr>
<tr>
<td>Children aged 6–12 y</td>
<td>120</td>
</tr>
<tr>
<td>Adults &gt;12 y</td>
<td>150</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>250</td>
</tr>
<tr>
<td>Lactation</td>
<td>250</td>
</tr>
</tbody>
</table>

\(^a\)Recommended Daily Allowance.\(^5\)
\(^b\)Adequate intake.
\(^2\)Recommended nutrient intake.\(^2\)

**Assessment**

Four methods are generally recommended for assessment of iodine nutrition: urinary iodine concentration (UI), the goiter rate, serum thyroid-stimulating hormone (TSH), and serum thyroglobulin (Tg).\(^13\) These indicators are complementary, in that UI is a sensitive indicator of recent iodine intake (days), Tg shows an intermediate response (weeks to months), whereas changes in the indicator of recent iodine intake (days), Tg shows an intermediate response (weeks to months), whereas changes in the goiter rate reflect long-term iodine nutrition (months to years).

**Thyroid Size**

Two methods are available for measuring goiter: (1) neck inspection and palpation and (2) thyroid ultrasonography. By palpation, a thyroid is considered goitrous when each lateral lobe has a volume greater than the terminal phalanx of the thumbs of the subject being examined.\(^2\) However, palpation of goiter in mild iodine deficiency has poor sensitivity and specificity, and measurement of thyroid volume (Tvol) by ultrasonography is preferable.\(^14\) Thyroid ultrasonography is noninvasive, quickly done (2–3 minutes per subject), and feasible even in remote areas with the use of portable equipment. However, interpretation of Tvol data requires valid reference criteria, and age- and sex-specific references are available for 6- to 12-year-old children,\(^15\) but there are no established reference values for adults. Mean (±SD) Tvol measured by ultrasonography in 50 healthy Dutch adults (age, 20–70 years) was 10.7 ± 4.6 mL (range, 2.7–20.4 mL), with the mean value in men (12.7 ± 4.4 mL) significantly greater than in women (8.7 ± 3.9 mL).\(^16\) In healthy Spanish adults (n = 268) the mean Tvol in men was 9.19 mL (95% CI, 9.09–10.65 mL) and in women was 6.19 mL (95% CI, 6.22–9.92 mL).\(^17\) Goiter can be classified by thyroid ultrasonography only if Tvol is determined by a standard method.\(^15\) Thyroid ultrasonography is subjective; differences in technique can produce interobserver errors in Tvol as high as 26%.\(^18\)

**Urinary Iodine Concentration**

Because >90% of ingested iodine is excreted in the urine, UI is an excellent indicator of recent iodine intake. UI can be expressed as a concentration (μg/L), in relation to creatinine excretion (μg iodine/g creatinine), or as 24-hour excretion (μg/d). For populations, because it is impractical to collect 24-hour samples in field studies, UI can be measured in spot urine specimens from a representative sample of the target group and expressed as the median, in μg/L (Table 2).\(^2\) However, because individual iodine intakes, and, therefore, spot UIs are highly variable from day to day,\(^19\) a common mistake is to assume that subjects with a spot UI < 100 μg/L are iodine deficient. To estimate iodine intakes in persons, 24-hour collections are preferable. The mean UI measured in three 24-hour urine samples collected over a week during which the habitual diet is consumed can provide an estimate of usual iodine intake in a person. An alternative is to use the age- and sex-adjusted iodine/creatinine ratio

### Table 2. Epidemiologic Criteria for Assessing Iodine Nutrition in a Population Based on Median or Range of Urinary Iodine Concentrations

<table>
<thead>
<tr>
<th>Median urinary iodine</th>
<th>Iodine intake</th>
<th>Iodine nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 μg/L</td>
<td>Insufficient</td>
<td>Severe iodine deficiency</td>
</tr>
<tr>
<td>20–49 μg/L</td>
<td>Insufficient</td>
<td>Moderate iodine deficiency</td>
</tr>
<tr>
<td>50–99 μg/L</td>
<td>Insufficient</td>
<td>Mild iodine deficiency</td>
</tr>
<tr>
<td>100–199 μg/L</td>
<td>Adequate</td>
<td>Optimal</td>
</tr>
<tr>
<td>200–299 μg/L</td>
<td>More than adequate</td>
<td>Risk of iodine-induced hyperthyroidism in susceptible groups</td>
</tr>
<tr>
<td>&gt;300 μg/L</td>
<td>Excessive</td>
<td>Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)</td>
</tr>
</tbody>
</table>

**School-aged children**

- <150 μg/L Insufficient
- 150–249 μg/L Adequate
- 250–499 μg/L More than adequate
- ≥500 μg/L Excessive\(^a\)

**Pregnant women**

- <100 μg/L Insufficient
- ≥100 μg/L Adequate

**Lactating women\(^b\)**

- <100 μg/L Insufficient
- ≥100 μg/L Adequate

**Children younger than 2 y**

- <100 μg/L Insufficient
- ≥100 μg/L Adequate

Adapted from reference 2.

\(^a\)Excessive means in excess of the amount required to prevent and control iodine deficiency.

\(^b\)In lactating women, the values for median urinary iodine are lower than the iodine requirements because of the iodine excreted in breast milk.
in adults, but this also has limitations. Creatinine may be unreliable for estimating daily iodine excretion from spot samples, especially in malnourished subjects in whom creatinine concentration is low. For persons, daily iodine intake can be estimated from the UI in 24-hour urine samples, assuming an average iodine bioavailability of 92%; that is, urinary iodine (\( \mu g/24\ h \))/0.92 = daily iodine intake. By using this formula, a mean UI of 100 \( \mu g/L \) in 24-hour urine samples from a person would suggest an average dietary iodine intake of approximately 110 \( \mu g/d \). For populations, daily iodine intake can be extrapolated from the median UI in spot urine samples by using estimates of mean 24-hour urine volume and assuming an average iodine bioavailability of 92% with the use of the following formula: urinary iodine (\( \mu g/L \)) × 0.0235 × body weight (kg) = daily iodine intake.

To using this formula, a median UI of 100 \( \mu g/L \) in spot urine samples corresponds roughly to an average daily intake of 150 \( \mu g \).

**Thyroid-Stimulating Hormone**

Because serum TSH is determined mainly by the concentration of circulating thyroid hormone, which in turn reflects iodine intake, TSH can be used as an indicator of iodine nutrition. However, in older children and adults, although serum TSH may be slightly increased by iodine deficiency, values often remain within the normal range. TSH is therefore a relatively insensitive indicator of iodine nutrition in adults. In contrast, TSH is a sensitive indicator of iodine status in the newborn period. Compared with the adult, the newborn thyroid contains less iodine but has higher rates of iodine turnover. Particularly when iodine supply is low, maintaining high iodine turnover requires increased TSH stimulation. Serum TSH concentrations are therefore increased in iodine-deficient infants for the first few weeks of life, a condition termed transient newborn hypothyroidism. In areas of iodine deficiency, an increase in transient newborn hypothyroidism, indicated by >3% of newborn TSH values above the threshold of 5 mU/L whole blood collected 3–4 days after birth, suggests iodine deficiency in the population. Newborn TSH is an important measure because it reflects iodine status during a period when the developing brain is particularly sensitive to iodine deficiency.

**Thyroglobulin**

Tg is synthesized only in the thyroid and is the most abundant intrathyroidal protein. In iodine sufficiency, small amounts of Tg are secreted into the circulation, and serum Tg is normally <10 \( \mu g/L \). In iodine deficiency, serum Tg increases because of greater thyroid cell mass and TSH stimulation. Serum Tg is well correlated with the severity of iodine deficiency as measured by UI. Tg falls rapidly with iodine repletion, and Tg is a more sensitive indicator of iodine repletion than is TSH or \( T_4 \).

A new assay for Tg has been developed for dried blood spots taken by a finger prick, simplifying collection and transport. In prospective studies, dried blood spot Tg has been shown to be a sensitive measure of iodine status and reflects improved thyroid function within several months after iodine repletion. However, several questions need to be resolved before Tg can be widely adopted as an indicator of iodine status. One question is the need for concurrent measurement of anti-Tg antibodies to avoid potential underestimation of Tg; it is unclear how prevalent anti-Tg antibodies are in iodine deficiency, or whether they are precipitated by iodine prophylaxis. Another limitation is large interassay variability and poor reproducibility, even with the use of standardization.

This has made it difficult to establish normal ranges and/or cutoffs to distinguish severity of iodine deficiency. However, an international reference range and a reference standard for dried blood spot Tg in iodine-sufficient school children (4–40 \( \mu g/L \)) has been made available.

**Thyroid Hormone Concentrations**

Thyroid hormone concentrations (\( T_4 \) and \( T_3 \)) are poor indicators of iodine intake. In iodine-deficient persons, serum \( T_3 \) increases or remains unchanged, and serum \( T_4 \) usually decreases. However, these changes are often within the normal range and make thyroid hormone concentrations an insensitive measure of iodine nutrition.2

**Effects of Deficiency**

Iodine deficiency has multiple adverse effects on growth and development in animals and human beings. These are collectively termed the iodine deficiency disorders (Table 3) and result from inadequate thyroid hormone production because of a lack of sufficient iodine.

**Goiter**

Thyroid enlargement (goiter) is the classic sign of iodine deficiency and can occur at any age, even in the newborn. It is a physiologic adaptation to chronic iodine deficiency. As iodine intake falls, secretion of TSH increases in an effort to maximize uptake of available iodine, and TSH stimulates thyroid hypertrophy and hyperplasia. Initially, goiters are characterized by diffuse, homogeneous enlargement, but, over time, nodules often develop. Many thyroid nodules that develop in persons with iodine deficiency derive from a somatic mutation and are of monoclonal origin; the mutations appear to be more likely to result in nodules under the influence of a growth promoter, such as iodine deficiency. Iodine deficiency is associated with a high occurrence of multinodular toxic goiter, mainly seen in women older than 50 years.
Table 3. The Iodine Deficiency Disorders, by Age Group

<table>
<thead>
<tr>
<th>Physiologic groups</th>
<th>Health consequences of iodine deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>Goiter, including toxic nodular goiter</td>
</tr>
<tr>
<td></td>
<td>Increased occurrence of hypothyroidism in</td>
</tr>
<tr>
<td></td>
<td>moderate-to-severe iodine deficiency;</td>
</tr>
<tr>
<td></td>
<td>decreased occurrence of hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>in mild-to-moderate iodine deficiency;</td>
</tr>
<tr>
<td></td>
<td>Increased susceptibility of the thyroid</td>
</tr>
<tr>
<td></td>
<td>gland to nuclear radiation</td>
</tr>
<tr>
<td>Fetus</td>
<td>Abortion</td>
</tr>
<tr>
<td></td>
<td>Stillbirth</td>
</tr>
<tr>
<td></td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td></td>
<td>Perinatal mortality</td>
</tr>
<tr>
<td>Neonate</td>
<td>Infant mortality</td>
</tr>
<tr>
<td></td>
<td>Endemic cretinism</td>
</tr>
<tr>
<td>Child and adolescent</td>
<td>Impaired mental function</td>
</tr>
<tr>
<td>Adults</td>
<td>Delayed physical development</td>
</tr>
<tr>
<td></td>
<td>Impaired mental function</td>
</tr>
<tr>
<td></td>
<td>Iodine-induced hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>Overall, moderate-to-severe iodine</td>
</tr>
<tr>
<td></td>
<td>deficiency causes subtle but widespread</td>
</tr>
<tr>
<td></td>
<td>adverse effects in a population secondary</td>
</tr>
<tr>
<td></td>
<td>to hypothyroidism, including decreased</td>
</tr>
<tr>
<td></td>
<td>educability, apathy, and reduced work</td>
</tr>
<tr>
<td></td>
<td>productivity, resulting in impaired social</td>
</tr>
<tr>
<td></td>
<td>and economic development</td>
</tr>
</tbody>
</table>

Severe Iodine Deficiency in Pregnancy: Cretinism and Increased Fetal and Perinatal Mortality

The most serious adverse effect of iodine deficiency is damage to the fetus. Maternal $T_4$ crosses the placenta before onset of fetal thyroid function at 10–12 weeks and represents up to 20%–40% of $T_4$ measured in cord blood at birth. Normal concentrations of thyroid hormones are required for neuronal migration and myelination of the fetal brain, and lack of iodine irreversibly impairs brain development. Severe iodine deficiency during pregnancy increases the risk of stillbirths, abortions, and congenital abnormalities. Iodine treatment of pregnant women in areas of severe deficiency reduces fetal and perinatal mortality and improves motor and cognitive performance of the offspring. Severe iodine deficiency in utero causes a condition characterized by gross mental retardation along with various degrees of short stature, deaf mutism, and spasticity that is termed cretinism.

Mild-to-Moderate Deficiency in Pregnancy

The potential adverse effects of mild-to-moderate iodine deficiency during pregnancy are unclear. Maternal subclinical hypothyroidism (an increased TSH hormone in the second trimester) and maternal hypothyroxinemia (a free $T_4$ concentration < 10 percentile at 12-week gestation) are associated with impaired mental and psychomotor development of the offspring. However, in these studies, the maternal thyroid abnormalities were unlikely due to iodine deficiency. In Europe, several randomized controlled trials of iodine supplementation in mild-to-moderately iodine-deficient pregnant women have been done. Iodine reduced maternal and newborn thyroid size and, in some, decreased maternal TSH. However, none of the trials showed an effect on maternal and newborn total or free thyroid hormone concentrations, the most important outcome, and none measured long-term clinical outcomes, such as maternal goiter, thyroid autoimmunity, or child development.

Growth and Cognition in Childhood

Although iodine deficiency in utero impairs fetal growth and brain development, its postnatal effects on growth and cognition are less clear. Cross-sectional studies of moderate-to-severely iodine-deficient children have generally reported impaired intellectual function and fine motor skills; 2 meta-analyses estimated that populations with chronic iodine deficiency experience a reduction in IQ of 12.5–13.5 points. However, observational studies are often confounded by other factors that affect child development, and these studies could not distinguish between the persistent effects of in utero iodine deficiency and the effects of current iodine status. In a controlled trial in 10- to 12-year-old moderately iodine-deficient children who received 400 mg iodine as oral iodized oil or placebo, iodine treatment significantly improved information processing, fine motor skills, and visual problem solving compared with placebo. Thus, in children born and raised in areas of iodine deficiency, cognitive impairment is at least partially reversible by iodine repletion.

Data from cross-sectional studies on iodine intake and child growth are mixed, with most studies finding modest positive correlations. In 5 Asian countries, household access to iodized salt was correlated with increased weight-for-age and mid-upper-arm circumference in infancy. Several controlled intervention studies of iodized oil alone and iodine given with other micronutrients did not find effects on child growth. However, in iodine-deficient children, impaired thyroid function and goiter are inversely correlated with concentrations of insulin-like growth factor-1 and insulin-like growth factor binding protein-3. Recent controlled trials found iodine repletion increased insulin-like growth factor-1 and insulin-like growth factor binding protein-3 and improved somatic growth in children.

Treatment and Prevention

Fortification

In nearly all regions affected by iodine deficiency, the most effective way to control iodine deficiency is through salt iodization. Bread can also be an effective vehicle for iodine by including baker’s salt enriched with iodine. Although iodizing drinking water or irrigation water can also be effective, the higher cost and the
complexity of monitoring are disadvantages. Iodine-containing milk is a major adventitious source in countries such as Switzerland and the United States, because of the use of iodophors in the dairy industry, rather than the deliberate addition of iodine. In iodine-deficient regions, whenever possible, iodine should be routinely added to complement foods for infants to provide approximately 90 μg iodine/d.53

**Iodine Supplementation**

In some regions, iodization of salt may not be practical for control of iodine deficiency, and iodized oil supplements can be used. Iodized oil is prepared by esterification of the unsaturated fatty acids in seed or vegetable oils and the addition of iodine to the double bonds.54 It can be given orally or by intramuscular injection. The intramuscular route has a longer duration of action, but oral administration is more common because it is simpler. Usual doses are 200–400 mg iodine/y, and it is often targeted to women of childbearing age, pregnant women, and children (Table 4). Iodine can also be given as potassium iodide or potassium iodate as drops or tablets. Single oral doses of potassium iodide monthly (30 mg) or biweekly (8 mg) can provide adequate iodine for school-age children. In countries or regions where a salt iodization program covers ≥90% of households and has been sustained for ≥2 years, and the median UI indicates iodine sufficiency, pregnant and lactating women do not need iodine supplementation. In iodine-deficient countries or regions that have weak iodized salt distribution, supplements should be given to pregnant women, lactating women, and infants, according to the strategy shown in Table 4.5

**Iodine in Enteral and Parenteral Nutrition**

**Preterm Infants**

Balance studies in healthy preterm infants have suggested iodine intakes of ≥30 μg/kg body weight/d are required to maintain positive balance, and experts generally recommend iodine intakes of 30–60 μg/kg/d for this group. Formula milks for preterm infants contain 20–170 μg iodine/L, and, depending on the dietary iodine intake of the mother, breast milk generally contains 50–150 μg/L. Thus, particularly during the first postnatal weeks when feed volumes are often low, enteraly fed preterm infants may not achieve the recommended intake of iodine.59

Oral absorption of iodine is efficient; in adults, oral iodine bioavailability is typically 90%–95%. This suggests iodine dosages by the enteral or parenteral route should be nearly equivalent. However, commercially available parenteral nutrition (PN) solutions contain much less iodine than breast milk or preterm formula milks. Clinical nutrition societies in the United States and Europe recommend parenteral iodine intakes of 1 μg/kg body weight/d,64,65 far below fetal accretion rates (Table 5). This conservative recommendation assumes parenterally fed preterm infants will absorb iodine through the skin from topical iodinated disinfectants and will also receive small amounts of adventitious iodine in other infusions. This assumption is supported by the study of Moukarzel et al, who found in 18 infants receiving long-term total PN (TPN) without iodine supplementation that thyroid function test results were normal and that serum iodide concentrations were significantly higher than in control children. The investigators estimated adventitious iodine in TPN solutions and fat emulsions accounted for approximately 50% of the iodine intake, and they assumed that skin absorption of topical iodinated disinfectant accounted for the remaining intake. They concluded it was unnecessary to supplement iodine even in children receiving long-term TPN without added iodine. Moreover, frequent use of iodinated anti-

| Table 4. Recommendations for Iodine Supplementation in Pregnancy and Infancy in Areas Where <90% of Households Are Using Iodized Salt and the Median UI Is <100 μg/L in School Children |
|---------------------------------|---------------------------------|
| **Women of childbearing age**   | A single annual oral dose of 400 mg iodine as iodized oil or A daily oral dose of iodine as potassium iodide so that the total iodine intake meets the RNI of 150 μg iodine/d |
| **Women who are pregnant or lactating** | A single annual oral dose of 400 mg iodine as iodized oil or A daily oral dose of iodine as potassium iodide so that the total iodine intake meets the RNI of 250 μg iodine/d |
| **Children aged 0–6 mo**       | A single oral dose of 100 mg iodine as iodized oil or A daily oral dose of iodine as potassium iodide so that the total iodine intake meets the RNI of 90 μg iodine/d |
| **Children aged 7–24 mo**      | A single annual oral dose of 200 mg iodine as iodized oil as soon as possible after reaching 7 months of age or A daily oral dose of iodine as potassium iodide so that the total iodine intake meets the RNI of 90 μg iodine/d |

Adapted from reference 2. RNI, Recommended Nutrient Intake. aIodine supplements should not be given to a woman who has already been given iodized oil during her current pregnancy or ≤3 months before her current pregnancy started. bShould be given iodine supplements only if the mother was not supplemented during pregnancy or if the child is not being breastfed.
septics in infants can result in transcutaneous absorption of ≥100 μg iodine/d, iodine excess, and neonatal hypothyroidism.67

Because of concerns over possible iodine excess, and the potential advantages of chlorhexidine-based antisepsics,69 the use of iodinated antisepsics in infants may be decreasing, putting infants at risk of iodine deficiency. If parenterally fed preterm infants are not exposed to adventitious sources of iodine, they may receive only 1–3 μg iodine/kg body weight/d and be in negative iodine balance during the first few postnatal weeks.59,60 In the study of Ibrahim et al.60 preterm infants (n = 13) had a mean iodine intake of 3 μg/kg body weight/d at PN rates of 150 mL/kg/d. All 13 infants had negative iodine balances on day 1, 12 remained in negative balance at day 6, but only 3 infants remained in negative balance on day 28.

Several investigators have argued that iodine deficiency should be avoided during this period because it may transiently lower thyroid hormone concentrations in the first weeks of life.59,60 Transient hypothyroxinemia in preterm infants has been linked to impaired neurodevelopment,70–72 but the potential role of iodine in this phenomenon was investigated in only one randomized controlled trial.73 Infants born before 33 weeks’ gestation (n = 121) were randomly assigned to receive either iodine-supplemented formula milk (272 μg iodine/L) or the same formula without iodine supplementation (68 μg iodine/L) until 40 weeks’ postconceptional age. These formulas provided daily iodine intakes of approximately 40–50 μg/kg body weight and 12–16 μg/kg body weight, respectively, in the treatment and control groups. There was no statistically significant effect on thyroid function or in the incidence of lung disease (a frequent complication in preterm infants).73

However, the study had several limitations. Although transient hypothyroxinemia is most closely associated with adverse outcomes in extremely preterm infants,70–72 only 14% of subjects had a birth weight <1000 g. Second, the intervention began only after the infants had established enteral feeding, usually 2 weeks after birth, but in preterm infants iodine balance is often negative, and transient hypothyroxinemia is established in the first 1–2 postnatal weeks. Finally, the trial was probably underpowered to assess a potential effect on neurodevelopment. A recent review concluded the available data are insufficient to support supplementation of preterm infants with iodine.74 Moreover, although subgroup analyses in a single controlled trial suggested T4 replacement may prevent neurodevelopmental morbidity in extremely preterm infants,75 the overall data are insufficient to recommend prophylactic thyroid hormone treatment in preterm infants.76

### Childhood

A daily dose of 1 μg iodine/kg body weight is also recommended for children receiving PN.64,65 A recent study assessed the iodine and thyroid status of children aged 1–17 years (n = 15; mean age, 76 months) on long-term PN.77 Nine children had short bowel syndrome and 6 had other intestinal diseases. Ten were on TPN and 5 on partial PN for 14–84 weeks. There was a significant inverse correlation between duration of PN and UI, and after 12 weeks all children had a UI <100 μg/L, with 8 <50 μg/L (moderate deficiency) and 7 <20 μg/L (severe deficiency). However, despite apparently low iodine intakes there was no significant increase in thyroid size or signs of thyroid dysfunction in the children.

If needed, parenteral trace element additives containing iodine are available for pediatric use. An example is Peditrace solution (Fresenius Kabi, Bad Homburg, Germany), which contains potassium iodide (1.3 μg potassium iodide/mL equivalent to 1 μg iodide/mL). The manufacturer’s recommended dosage for infants and children weighing ≤15 kg and 2 days old or older is 1 mL/kg body weight/day78; the recommended daily dose is 15 mL for children weighing >15 kg.

### Adults

Commercially available products for enteral nutrition generally provide 75–110 μg iodine/serving.79 Daily iodine requirements in adult patients receiving total enteral nutrition or TPN are estimated to be 70–150 μg.80 A recent technical review of PN by the American Gastroenterological Association recommended iodine intakes of 70–140 μg/d (Table 5).81 Although most PN formulations do not contain iodine, deficiency is not likely to occur because of cutaneous absorption from iodine-containing disinfectants and other adventitious sources of iodine;88 PN solutions may contain as much as 15–25 μg iodine as contaminant.82 There are no reported stability or incompatibility problems when iodine additions are made to PN mixtures. Iodine deficiency symptoms have not been reported with in-hospital intravenous nutrition support.83 It has been suggested that

### Table 5. Recommendations for Daily Iodine Intake During Parenteral Nutrition by Age Group

<table>
<thead>
<tr>
<th>Age group</th>
<th>ASCN, ESPGHAN/ESPEN, AGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>1 μg/kg body weight</td>
</tr>
<tr>
<td>Children</td>
<td>1 μg/kg body weight</td>
</tr>
<tr>
<td>Adults</td>
<td>70–140 μg</td>
</tr>
</tbody>
</table>

6Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition (ASCN).64

7European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN).86

8American Gastroenterological Association (AGA).81

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thyroidal iodine stores are often adequate to meet the needs of patients requiring TPN for <3 months, in iodine-sufficient adults, thyroidal iodine content is 15–20 mg. In addition, many persons on long-term PN are able to eat and drink limited amounts and have a functioning duodenum and thus may absorb dietary iodine. For these reasons, many experts do not recommend supplemental iodine routinely for subjects receiving TPN. Iodine status and thyroid hormone concentrations were adequate in Brazilian adults with intestinal malabsorption secondary to short gut syndrome who were receiving long-term TPN without iodine.

If needed, intravenous sodium iodide solutions are available. For example, Iodopen (APP Pharmaceuticals, Schaumberg, IL) contains 100 μg iodine/mL. According to the manufacturer’s specifications, the usual adult dosage for prophylaxis or treatment of iodine deficiency is 1–2 μg iodine/kg body weight/d. For children and pregnant or lactating women, the recommended dosage is 2–3 μg iodine/kg body weight/d.

**Excess and Toxicity**

Most people who are iodine sufficient are remarkably tolerant to high dietary intakes of iodine. Iodine intakes ≤1 mg/d are well tolerated by most adults, because the thyroid is able to adjust to a wide range of intakes and to regulate the synthesis and release of thyroid hormones. Some persons with excess iodine intakes, particularly those who were previously iodine deficient, develop hyperthyroidism (the Jod–Basedow phenomenon). However, excessive intakes may inhibit iodine uptake by the thyroid and impair thyroid hormone synthesis (the Wolff–Chaikoff effect). Thus, excess iodine may cause both hyperthyroidism and hypothyroidism. In children, chronic intakes of ≥500 μg/d are associated with increased Tvol, an early sign of thyroid dysfunction.

Potential adverse acute reactions to parenteral injection of iodine include hypersensitivity reactions (angioneurotic edema, cutaneous and mucosal hemorrhages, fever, arthralgia, lymphadenopathy, eosinophilia). Symptoms of chronic iodide poisoning include a metallic taste in the mouth, increased salivation, gastrointestinal tract irritation, headache, pulmonary edema, and aceneform skin lesions. Thyroid function should be monitored in patients exposed to frequent large amounts of radiographic contrast dyes or the drug amiodarone (both contain large amounts of iodine). When iodine and selenium deficiency occur simultaneously in persons, correction of only iodine deficiency may lead to thyroid damage; thus, both deficiencies should be treated.

European and US expert committees have recommended tolerable upper intake levels for iodine (Table 6) but caution that persons with chronic iodine deficiency may respond adversely to intakes lower than these. For monitoring of populations by using the median UI, recommendations for more than adequate and excess iodine intake are shown in Table 2.

### Future Research Needs

Randomized controlled trials of iodine supplementation are needed in extremely preterm and extremely low birthweight infants, the group at greatest risk of transient hypothyroxinemia, with clinically important outcomes, including respiratory morbidity and neurodevelopment. Iodine requirements for persons on long-term PN should be better defined, particularly when chlorhexidine-based antiseptics are used in place of iodinated antiseptics. If it is shown that there is increased risk of iodine deficiency in such patients, the possible need for revision of current PN iodine guidelines should be considered.

The potential of dried blood spot or serum Tg as an indicator of iodine nutrition should be further investigated.

### Question and Answer Session

**DR BUCHMAN:** Michael, do we know what, if any, contamination of iodine there is in PN solutions?

**DR ZIMMERMANN:** I do not have any personal experience on this issue, but, based on reports from the late 1980s and early 1990s, most of the researchers attributed at least half of the iodine intake as coming from PN formulations.

**DR BUCHMAN:** Is it present in lipids?

**DR ZIMMERMANN:** I do not know. I did not find any reports measuring iodine contamination or actual concentrations of iodine in solutions, but maybe other people are aware of data.

**DR BUCHMAN:** As a follow-up to that, most of what you talked about was cretinism and iodine deficiency in neonates and infants. In the adult population, say the patient with short bowel syndrome who ends up on PN, how long would it take to develop iodine deficiency and...
what manifestations might we look for before seeing a clinically enlarged thyroid?

**DR ZIMMERMANN:** The duration over which you might see disturbances in thyroid function would depend on the iodine status of the person. If the person is an adult in the United States where iodine intakes are sufficient, as I suggested, you might not see any disturbances in thyroid function maybe for 2–3 months. Probably the first sign you would see in a subject that is beginning to develop marginal thyroid dysfunction because of low iodine intakes would be a small increase in thyroid size and perhaps within the normal range an increase in TSH. The problem with using thyroid functions in adults is that even in persons with clear iodine deficiency, usually TSH only rises within the normal range, and T₄ may fall within the normal range, whereas T₃ actually rises somewhat as the system compensates and tries to produce more T₃. So it is very difficult to use thyroid functions in adults unless they are clearly iodine deficient.

**DR BUCHMAN:** Do you have radiolabeled studies of iodine absorption and do we know what percentage of iodine is absorbed, and does absorption change with iodine sufficiency or deficiency? I am asking this so we can translate oral and enteral recommendations into the context of parenteral recommendations.

**DR ZIMMERMANN:** Many studies have shown that from inorganic sources iodine absorption is predictably >90%. If you give thyroid hormone or organic sources of iodine, absorption of iodine is variable. I think recommendations for enteral and PN should be comparable.

**ANONYMOUS:** Are there data about how long neonatal stores of iodine last? Stores last approximately 100 days for an adult, but what about neonates?

**DR ZIMMERMANN:** A newborn is typically born with iodine stores of only approximately 300 µg. The neonate requirement, we do not know exactly, but it is something like 30 µg/kg bodyweight/d, so there are very small stores in a newborn. That is why they are so vulnerable to low iodine intakes even over periods of several days.

**ANONYMOUS:** Following up on that question, could one use TSH concentrations longitudinally for monitoring thyroid status? I am thinking again about the preterm infant who is on PN long term.

**DR ZIMMERMANN:** Once the newborn is past the birth surge in TSH, you could use TSH longitudinally to determine whether the infant is getting adequate iodine. TSH is not always useful in children or adults but is probably quite sensitive in infants.

**DR SHIKE:** From the practical point of view, the role of iodine from what I understand is solely in regard to thyroid hormone synthesis, right? Iodine has no other nont thyroid functions. So if we measure thyroid function periodically, let us not discuss the interval length but periodically, as long as the thyroid functions remain within the normal range, can we use that as a guide to supplementation of iodine?

**DR ZIMMERMANN:** I think you are absolutely right. The whole point of an adequate iodine supply is to obtain euthyroidism in a person. If thyroid functions are normal, but iodine intakes are low, you have to be careful over the long term that you do not end up in negative iodine balance. In that situation thyroid hormone concentrations slowly drop. But if thyroid hormone concentrations remain normal, that is an indication that the person is healthy even with low iodine intakes.

**DR SHIKE:** You pointed out that follow-up of thyroid function has to be more intense in infants. In adults and children, who are starting with a normal thyroid function, how often do you need to assess thyroid function in order not to miss a clinically significant decline?

**DR ZIMMERMANN:** In regard to children, maybe clinicians working in this area have more practical recommendations; I would suggest monthly intervals would be adequate.

**DR SHIKE:** And longer in the adults?

**DR ZIMMERMANN:** Yes.

**DR SHIKE:** Thank you.

**DR HOWARD:** Dr. Zimmermann, you spoke about the iodine content in breast milk. Are the pediatric formulas, especially the more unusual ones, adequately supplemented with iodine?

**DR ZIMMERMANN:** They range enormously. The range that I found reported in the literature was between 20 and 170 µg/L. Breast milk is also extremely variable, depending on the iodine intake of the mother. Reported values from iodine-sufficient countries are 50–200 µg/L of breast milk.

**DR SHENKIN:** I am wondering if there is any specific risk of excess iodine provision in the adults? You mentioned the concern in preterm neonates. In Europe it is standard practice to use a trace element cocktail that provides approximately 130 µg iodine/d for adults on PN. As far as I am aware there are no published reports of any problems with this dose. I am wondering, if in contrast to some of the other elements that we have talked about today, whether there is some advantage in having a standard iodine dose given as part of the multielement cocktail unlike some of the other trace elements whereby we might want to tailor it more specifically to the person. Do you have a view as to whether there is a risk attached to slight excess iodine provision in adults?

**DR ZIMMERMANN:** The iodine thyroid system has a lot of flexibility built into it, and the thyroid will only clear as much iodine as it needs. Depending on the person's iodine status, the thyroid will clear between 10% and 80% of the circulating iodine, and the rest will be excreted by the kidney. There is flexibility built into this system, and in healthy adults you do not see any signs of disturbed thyroid function with daily doses up to...
600–800 μg/d. At approximately 1 mg/d you start to see elevations in TSH.

**DR SHENKIN:** So would you recommend a standard dose be given to adult patients receiving PN as part of a multielement cocktail?

**DR ZIMMERMANN:** I think that would be safe.

**DR JEEJEEBHOOY:** PN is used a lot in patients who have a short bowel, and most of these patients are also taking oral rehydration solutions with a substantial salt content. In Western countries most of the salt is iodized, so I think in general people with short bowels are receiving a lot of oral iodine irrespective of PN. In these circumstances adults receiving PN, particularly, would be unlikely to experience iodine deficiency.

**DR PIRONI:** In regard to this last question, there are some patients on long-term PN who are unable to sustain an oral intake because of intestinal obstruction. I have never seen iodine deficiency in such patients, so it does not seem there is a real need to supply iodine in long-term PN.

**DR ZALOGA (Baxter, Deerfield, IL):** My question relates to the monitoring of patients by following thyroid function tests. Particularly, patients with low T₄, T₃ syndrome, most of whom will have some inflammatory insult or chronic illness. The thyroid axis is extremely sensitive to these insults, and, although the patients may look relatively normal, with an inflammatory insult the patient will drop first T₃, then T₄, and then TSH. How would you assess iodine deficiency in these patients? Would Tg concentrations be useful?

**DR ZIMMERMANN:** If the TSH has dropped because of illness, Tg may not be elevated because Tg typically rises under TSH stimulation. So in the sick thyroid syndrome in which TSH is dropping, Tg may not be of much value. It is extremely difficult to interpret thyroid functions in that setting and to decide if iodine deficiency is present. Collection of 24-hour urinary iodine may be helpful. If urinary iodine is low, providing extra iodine and watching for movement in thyroid function tests may be helpful. But as you pointed out, it is extremely hard to interpret thyroid functions and use them to diagnose iodine deficiency in chronically ill patients.

**DR ZALOGA:** My second point would be on the opposite side of this equation. Patients receiving radiocontrast dyes or other iodinated material that would contribute huge amounts of iodine would also have a distortion in their thyroid function tests, making it difficult to monitor their thyroid status.

**DR ZIMMERMANN:** Certainly patients who receive iodinated contrast material or amiodarone may have distorted thyroid function tests, but they may have adequate iodine stores for a long time afterward.

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Conflicts of interest
The author discloses no conflicts.