Environmental Iodine Intake Affects the Type of Nonmalignant Thyroid Disease

P. Laurberg,1 I. Bülow Pedersen,1 N. Knudsen,2,3 L. Ovesen,4 and S. Andersen1

The relationship between the iodine intake level of a population and the occurrence of thyroid diseases is U-shaped with an increase in risk from both low and high iodine intakes. Developmental brain disorders and endemic goiter caused by severe iodine deficiency may seriously deteriorate overall health status and economic performance of a population. Severe iodine deficiency with a median 24-hour urinary iodine excretion of the population below 25 μg needs immediate attention and correction. Less severe iodine deficiency with median urinary iodine excretion below 120 μg per 24 hours is associated with multinodular autonomous growth and function of the thyroid gland leading to goiter and hyperthyroidism in middle aged and elderly subjects. The lower the iodine intake, the earlier and more prominent are the abnormalities. At the other end of the spectrum, severely excessive iodine intake starting at median urinary iodine excretion levels around 800 μg per 24 hours is associated with a higher prevalence of thyroid hypofunction and goiter in children. A number of studies indicate that moderate and mild iodine excess (median urinary iodine >220 μg per 24 hours) are associated with a more frequent occurrence of hypothyroidism, especially in elderly subjects. The exact mechanism leading to this has not been clarified, and more studies are needed to define the limits of excessive iodine intake precisely. Due to the frequent occurrence of thyroid disorders, proper monitoring and control of the population iodine intake level is a cost-effective alternative to diagnosing, therapy and control of the many individual cases of thyroid diseases that might have been prevented.

Introduction

Reduction of the risk of disease is important in health care for any population. To plan and achieve risk reduction it is necessary to have a basic knowledge of the relationship between exposure to a risk factor and the corresponding risk of disease. Such a relationship may take many shapes, some of which are illustrated in Figure 1 (1,2).

U-shaped curves as shown for the relation between the iodine intake level and the risk of thyroid disease are common in nutrition. An example is the relation between total energy intake and disease where both low and high intakes are associated with an increase in risk.

In the case of iodine intake it is well documented and accepted that a low iodine intake is associated with a high risk of disease, the most prominent abnormalities being developmental brain damage and endemic goiter (3,4). Because the iodine intake from natural sources is low in many areas of the world, much effort has been devoted to increasing the iodine intake of populations. The importance of this activity for prevention of disease, guided by international organizations (The International Council for Control of Iodine Deficiency Disorders, The World Health Organization, UNICEF) cannot be overestimated. Currently, two-thirds of the world population are more or less covered by public iodine supplementation programs (5).

Comparatively less focus has been on the other end of the risk/iodine intake curve, i.e., the increase in risk from a high iodine intake. Few populations have a high iodine intake from natural sources. The most common causes are regular intake of seaweed or soup made from seaweed; e.g., Japan is a classic example (6), and a high iodine content of drinking water; certain parts of China are prominent examples (7,8). In Iceland, fish products have traditionally been used for animal feeding causing high iodine content in meat and dairy products (9). However, a relatively high iodine intake of a population may have other causes. Uncontrolled iodine supplementation may lead to high iodine intake (10). Another artificial source of iodine important for population iodine intake is iodine containing chemicals used for prepa-

1Department of Endocrinology and Medicine, Aalborg Hospital, Aalborg, Denmark.
2Centre for Preventive Medicine, Glostrup University Hospital, Copenhagen, Denmark.
3Department of Internal Medicine I, Bispebjerg University Hospital, Copenhagen, Denmark.
4Danish Veterinary and Food Administration, Copenhagen, Denmark.
ration of food. In the United States, iodine-containing conditioners used by bakers in the past were a major cause for the high iodine intake that was periodically observed (11). Iodine supplements to domestic animals leading to high iodine contents of dairy products and meat have commonly been involved in unexpected and unplanned increases in a population’s iodine intake. The history behind the increase in iodine intake in the United Kingdom caused by such a mechanism has been published recently (12).

Many studies have been performed in patients with various thyroid abnormalities to evaluate the effect of an increase in iodine intake. It has been shown that moderate doses of iodine are not well tolerated by most patients with past or present thyroid abnormalities (13). On the other hand, when similar studies have been performed in small groups of healthy subjects, little adverse effect has been observed (14). It is beyond the scope of this article to discuss these studies, which are important for elucidating mechanisms and for the guidance of an individual patient seeking advice. Because a considerable proportion of any population will have past or present thyroid abnormalities, it is to be expected that the population iodine intake will be important for the manifestations of thyroid diseases. This should, however, be evaluated from epidemiological studies where the risk/exposure relationship between the iodine intake level and the incidence and prevalence of various thyroid diseases has been analyzed.

**High Population Iodine Intake and Thyroid Disease**

The classic example of a high prevalence of disease caused by a high iodine intake is the endemic coast goiter in Hokkaido, Japan (15). The usual diet of the inhabitants was high in iodine rich seaweeds and urinary iodine excretion in patients with goiter was approximately 20,000 μg per 24 hours. In some areas, 14% of the population had goiter, which could be very large. Restriction of dietary iodine intake was followed by goiter regression in some patients, and most goiters responded to administration of thyroid preparations (15). Thyrotropin (TSH) assays were not available, but presumably an increase in serum TSH was involved in generation of goiter.

Goiter associated with high iodine intake is, however, not restricted to intakes of many milligrams per day. In China, Mu et al. (7) examined thyroid status in children from two villages, where the iodine concentrations in drinking water were 54 and 462 μg/L, respectively. The mean urinary iodine excretions were 428 and 1235 μg/g creatinine, respectively. These values indicate an iodine intake considerably higher than the recommended intake of 150 μg per 24 hours for adults (16), but much less than in the Hokkaido study (15). The area with the most excessive iodine intake was clearly an endemic goiter area (Fig. 2) and thyroid volume measured by ultrasound was correspondingly high (7). There were no signs of neurological deficits or impairment of cognitive function, but abnormally elevated TSH was common. Mean serum TSH (7.8 mU/L) was above the normal range in this area, whereas mean serum TSH was high-normal (3.9 mU/L) in children from the area with less excessive iodine intake. This well-conducted study demonstrates the high prevalence of thyroid abnormalities in children associated with a high iodine intake.

**Shift from Low to Sufficient or High Iodine Intake**

Many populations have been exposed to a change from low to high iodine intake. Where this has been intentional some kind of disease monitoring has often followed. It is now well established that iodine supplementation to an iodine-deficient population may be accompanied by a several
to manifold increase in the incidence of hyperthyroidism, depending on the severity of the iodine deficiency and the magnitude of the increase in iodine intake (10). The main cause seems to be an increase of thyroid hormone synthesis in autonomous thyroid nodules, which have developed during the period of low iodine intake. This increase in disease incidence is transient, because the more sufficient iodine intake reduces the risk of future development of autonomous thyroid nodules (10).

The major effect of an increase in iodine intake on the incidence of hyperthyroidism is observed within the first few years, but the surge may last longer. In Tasmania it took more than 10 years before hyperthyroidism incidence figures approached preiodine supplementation values (10,17). However, previous iodine deficiency may influence the pattern of thyroid diseases in a population for even longer periods. In the United Kingdom it was recorded that the type of hyperthyroidism in different towns to a large extent reflected the degree of iodine deficiency present before iodine intake started to increase 20 years earlier (18).

Epidemiology of Hypothyroidism and Hyperthyroidism in Moderately Low and High Iodine Intake Areas

After a change in a population’s iodine intake there is a prolonged delay before a new steady state is reached in the occurrence of thyroid disease. This hampers interpretation of epidemiological studies. It is necessary to take into consideration not only the present iodine intake level, but also the history of iodine intake of the population under study.

There are several other problems encountered when trying to obtain an overview of the pattern of the many studies performed. Some studies are based on subjects who are attending clinics or living in institutions rather than on population cohorts. Diseases and medications may not be reported. Ethnicity and age composition of cohorts vary. The quality of diagnostic methods is different. Up until the late 1980s few TSH assays could measure serum TSH below the range for healthy subjects. Hence, information on subclinical hyperthyroidism was not obtained. Widely differing cut-offs for abnormal serum TSH have been used. In population studies there is a continuum from frank normal to severely abnormal values, and even small differences in cutoff levels between normal and abnormal may severely bias comparison between studies. In some populations the fraction of subjects receiving thyroid hormone is high and this may heavily influence the prevalence of high and low serum TSH.

The interpretation problems can be illustrated by a recent epidemiological study performed in the United States (19). The study was population based and comprised 279 ambulatory white women over age 65. The normal range for the TSH assay was 0.5 to 5.5 mU/L. Abnormal values were, however, reported for TSH 0.1 mU/L or less (low) and greater than 5.5 mU/L (high), presumably leaving some participants with below normal TSH unreported. TSH was high in 6.8% and low in 3.6% of participants. Considering the TSH range mentioned above the immediate conclusion would be that there was not much difference in the prevalence of some degree of thyroid hyperfunction (with low TSH) and thyroid hypofunction (with high TSH) in this population. Accordingly the study would not support the conclusion to be given below, that thyroid hypofunction is very common, and much more so than thyroid hyperfunction, in the elderly in populations with a relatively high iodine intake such as the population participating in this study.

However, from the data given it can be calculated that 11% to 12% of these elderly women took thyroid hormones, and 90% of cases of low serum TSH were associated with thyroid hormone intake. The reason for the intake of thyroid hormone is not given. Likely reasons are substitution for autoimmune hypothyroidism or hypothyroidism after surgery or radioiodine therapy. Another possibility is attempted suppression of goiter and thyroid nodules. If it is hypothesized that the medication was predominantly taken for previously diagnosed thyroid hypofunction, the prevalence of thyroid hypofunction (treated plus untreated) in this population may be as high as 18%, whereas the prevalence of thyroid hyperfunction with TSH 0.1 mU/L or less from nonmedication...
may be as low as 0.4%. The calculation illustrates that it is possible to reach different conclusions depending on how data are selected and analyzed. More importantly, it shows how easily even major trends may be overlooked.

We have performed epidemiological studies specifically designed to evaluate differences in the incidence and prevalence of hyperthyroidism and hypothyroidism in areas with moderately low iodine intake (Jutland, Denmark) and moderately high iodine intake (Iceland). From what we know, these different levels of iodine intake have been present for the lifetime of the inhabitants. The relatively high iodine intake in Iceland with urinary iodine excretion around 300 μg per 24 hours in young subjects (9), is mainly due to a relatively high consumption of fish, and the traditional use of fish meal for animal feeding. In Jutland, the iodine intake is low, approximately 40 to 70 μg/d (20). The two areas have a similar genetic background (21) and similar levels of economic development and health care.

Figure 3 shows the incidence of hyperthyroidism in various age groups in the two populations (22). In Iceland, hyperthyroidism was two to three times more common than in Jutland in young and middle-aged subjects. On the other hand, hyperthyroidism was much more common in the elderly in Jutland. This means that a comparison of total incidences would depend on the age composition of the populations studied. As the populations included relatively many young subjects (Fig. 4) the total incidences of hyperthyroidism were not very different, but significantly higher in Jutland (Fig. 5). When the average age of the populations becomes higher, the incidence of hyperthyroidism will increase considerably in the low iodine intake area. The calculated lifetime risk for developing hyperthyroidism up to the age of 90 years was 2.3 times higher in Jutland than in Iceland.

The incidence of the common types of hyperthyroidism is depicted in Figure 5. Nearly all cases of hyperthyroidism in Iceland were Graves’ disease and occurred in young and middle-aged subjects. The few cases of nodular thyroid disease were mainly seen in the elderly.

In Jutland, young subjects with hyperthyroidism had mostly Graves’ disease, but there were relatively more cases of Graves’ disease in the elderly compared to Iceland. The discrepancy in age distribution is the cause for the large difference in incidence of hyperthyroidism in the young (Fig. 3) versus the relatively modest difference in total incidence of Graves’ disease (Fig. 5). The lifetime risk of Graves’ disease was not different between areas.

A major difference between populations was that multinodular toxic goiter was the most common cause of hyperthyroidism in Jutland, but relatively rare in Iceland. In Jutland, both multinodular toxic goiter and solitary toxic adenoma were predominantly diagnosed in elderly subjects, but solitary toxic adenomas at a somewhat younger age than multinodular toxic goiter (23).

The incidence of hypothyroidism in Jutland, which was studied simultaneously (24), is shown in Figure 6. Hypothyroidism was less common than hyperthyroidism at all ages except newborns. The majority of patients (79%) had spontaneous autoimmune hypothyroidism (16% of these had goiter, Hashimoto’s disease). There are few other studies of incidences of hyperthyroidism and hypothyroidism in the same population. In the Whickham follow-up study, hypothyroidism was much more common than hyperthyroidism (25). The population studied in Whickham had a higher age because only adults were studied at the first investigation 20 years previously (26). This might explain some of the difference in overall incidence of thyroid disease. In the two studies of the population in Whickham, urinary iodine and creatinine concentrations were measured in a sub-

FIG. 3. Incidences of overt hyperthyroidism in various age groups in Iceland (with high iodine intake) and in East Jutland, Denmark (with low iodine intake) in a comparative study (JUICE 1). The number of subjects in each age group are depicted in Figure 4. The population-years observed were 1,264,450. **p < 0.001 between areas in age group. *p < 0.01. Data from Laurberg et al. (22).
set of the subjects. Values corresponding to a 24-hour urinary output of 100 to 120 $\mu$g of iodine were found (25,26). At the time of the first study, iodine analyses of food suggested a daily intake of 250 $\mu$g of iodine in the United Kingdom (27). The reason for this discrepancy is not clear, but major circannual variations in iodine intake in the U.K. population have been reported (27,28). Without doubt the iodine intake of the Whickam population was considerably higher than the Jutland population, and this is the most likely cause for the difference in disease pattern.

**Prevalence of Thyroid Hypofunction and Hyperfunction in Populations with Different Iodine Intake Levels**

As discussed previously it is difficult to compare results of epidemiological studies evaluating the prevalence of thyroid hypofunction and hyperfunction. Any comparison of studies is open to criticism. Figure 7 illustrates prevalences of hypothyroidism with high TSH (combination of clinical and subclinical disease) and hyperthyroidism with low serum TSH in a number of studies.

Iceland (1988) and Jutland, Denmark (1988) were part of the same epidemiological study, with similar age groups (approximately 68 years), identical set up, and mixing of samples from the two areas in all assays (29). They gave different disease patterns with a high prevalence of hyperthyroidism in Jutland and a low prevalence in Iceland. For hypothyroidism the pattern was quite the opposite: high prevalence in Iceland and low prevalence in Jutland. The other studies shown in Figure 7 have all used a TSH assay with the capacity to measure subnormal values. They are selected, but they are more or less typical for many other studies. Colorado (1995) (30) comprised 25,862 participants in a statewide health fair. Medium age of participants was 56 years; 55% were females. A serum TSH above the normal range (>5.1 mU/L) was found in 9.5% of the participants, whereas a low serum TSH (<0.3 mU/L) was present in 2.2%.

**FIG. 4.** Age distribution of the population cohorts observed for measuring incidences of overt hyperthyroidism in Iceland and in East Jutland, Denmark (JUICE 1). Because disease incidences vary widely between age groups, it is important to know the age distribution when evaluating total incidences (Fig. 5). Data from Laurberg et al. (22).

**FIG. 5.** Total incidences and incidences of the four most common types of hyperthyroidism in the Jutland/Iceland comparative study (JUICE 1). Data from Laurberg et al. (22).
Thyroid medication (type not given) was taken by 5.9%, and 58% of subjects with low TSH were taking thyroid medication. Because of the high frequency of intake of thyroid medication exact figures for the prevalence of thyroid hyperfunction and hypofunction cannot be given. Among subjects not taking thyroid medication 8.9% had an elevated and 1.0% a low serum TSH.

Until approximately 1960, the natural iodine deficiency of many areas of the United States was partly ameliorated by intake of iodized salt (31). Subsequently iodate was intro-
duced in the baking industry as a bread stabilizer (11) and the iodine content of dairy products became high (32). This introduced a period of excessive population iodine intake with median intakes ranging from 500 μg to 1000 μg/d in various surveys (32–34). More recently the iodine content of food has decreased again, providing a median iodine intake of approximately 200 μg/d, but with a very skewed distribution (mean value approximately twice as high as median value) (34).

Hence, the participants of the Colorado study investigated in 1995 (Fig. 7) had been exposed to a high iodine intake for most of their lives, similar to the Icelandic population investigated in 1988. On the other hand, the population cohort (age, 60–87 years) examined in Framingham, MA, USA, in 1979 (35,36) may have been exposed to a relatively low iodine intake during the early part of their life. Phillips et al. (18) reported that previous low iodine intake gave a relatively high incidence of nonautoimmune hyperthyroidism even 20 years after an increase in iodine intake. The relatively high prevalence of low serum TSH (not caused by thyroid hormone intake) in the Framingham cohort (Fig. 7) may be due to such a mechanism, whereas the high prevalence of high TSH may be due to relatively high iodine intake at the time of the study. A similar variation from low to relatively high iodine intake occurred in the United Kingdom (12) (Birmingham, 1988; [37]), Fig. 7.

The studies depicted in Figure 7 from Denmark (29), Italy (38), and Germany (39–41) have all been performed in populations with long-standing mild to moderate iodine deficiency. They uniformly show a pattern of high prevalence of thyroid hyperfunction with low serum TSH and low prevalence of thyroid hypofunction with elevated serum TSH.

The pattern of many cases of thyroid hyperfunction in mild or moderate iodine deficiency and many cases of thyroid hypofunction with high iodine intake has been found in many other studies (42–55).

Mechanisms Behind the High Prevalence of Low Serum TSH in Mild to Moderate Iodine Deficiency

Thyroid nodules are common in all populations. Some are neoplastic (mostly benign) with autonomous hormone synthesis and secretion (hot nodules), or more commonly loss of the capacity to trap iodine and synthesize hormones (cold nodules). Other nodules are part of the heterogeneous abnormality of multinodular or simple goiter (see Laurberg [56] for review). The mechanisms leading to this abnormality with multifocal polyclonal autonomous thyroid growth and function are only partly known. The abnormality is associated with and may be driven by a low organic iodine content of the thyroid gland (56,57). Some of the hyperfunctioning areas are monoclonal neoplasias harboring the same TSH-receptor activating point mutations as solitary toxic thyroid nodules (58–60).

The progression of autonomous thyroid hormone secretion in patients with multinodular goiter may vary as illustrated in Figure 8. Over a period of years some patients progress to overt hyperthyroidism and some remain euthyroid. Some patients stabilize with a below normal serum TSH, indicating that thyroid hormone secretion has more or less been taken over by autonomous tissue. A load of iodine may induce transient hyperthyroidism, presumably by the increase in substrate availability for thyroid hormone synthesis.

The reason for the difference in progression between patients is not known. One possible cause may be differences in the responsiveness to TSH of differently mutated TSH receptors found in some of the hyperactive nodules. Figure 9 illustrates the difference in TSH induced cyclic adenosine monophosphate (cAMP) generation in cells with various mutated TSH-receptors found in toxic thyroid nodules. In general the mutated receptors are more responsive to TSH than the wild-type TSH-receptor, but the dose response curves vary (61,62). Some mutated receptors respond to a tenfold decrease in TSH with a normalization of cAMP production, whereas other mutations lead to much more TSH responsive and active receptors. Further studies are needed to clarify the importance of this mechanism.

The increase in frequency of multinodularity in the thyroid gland with advancing age in low-iodine intake areas such as Denmark (63) is associated with a decrease in serum TSH of the female population with age. This is more promi-

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**FIG. 8.** Illustration of various types of progression of autonomous thyroid hormone secretion in patients with multinodular goiter. Autonomoue hormone secretion may cover part (patient 1) or about all (patient 2) of physiological needs. When autonomous hormone secretion exceeds the needs, the patient becomes hyperthyroid (patient 4). Such a development may transiently be induced by a load of iodine (patient 3). Adapted from Laurberg (56).
deficiency is linked to the development of multifocal autonomous function of the gland. It is the same disease that leads to the high prevalence of goiter (56).

**Mechanisms Behind the High Prevalence of Elevated Serum TSH in Populations with High Iodine Intake**

Two types of mechanisms are likely to be involved in the increase in the prevalence of hypothyroidism in a population when the iodine intake level becomes high. One mechanism is induction of thyroid hypofunction due to autoimmune thyroiditis, the other is the inhibitory effect of iodine on many thyroidal processes involved in thyroid hormone synthesis and secretion.

It has been demonstrated in a number of animal models prone to developing autoimmune thyroiditis that a variation from low to normal to high iodine intake is associated with a progressive increase in thyroiditis (13, 66, 67). Moreover, several studies of human thyroid specimens removed during surgery have shown an increase in the prevalence of histological thyroiditis after an increase in iodine intake of the population (68–71). It has, however, been suggested that part of this alteration in histological picture may be caused by a relative increase in normal thyroid tissue not affected by nodularity (72).

Iodine inhibits a range of processes in the thyroid gland from iodine uptake to the release of thyroid hormones from the follicular cells. This is part of an autoregulatory process, presumably protecting against thyroid hormone hypersecretion after a sudden high iodine intake. However, the autoregulation is far from perfect and often tends to induce thyroid hypofunction. In areas with a high iodine intake, such as Japan, a considerable proportion of patients with newly diagnosed overt hypothyroidism will become euthyroid if they normalize their iodine intake (73–76).

At present it is not clear which is the major mechanism: enhancement of thyroid autoimmunity by a high iodine intake or induction of thyroid hypofunction by inhibition of

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**FIG. 9.** Cyclic adenosine monophosphate (cAMP) production by COS cells transiently expressing wild-type human thyrotropin (TSH) receptor or various mutated TSH receptors identified in toxic thyroid nodules. Cells were incubated with increasing doses of bovine TSH. Note the different cAMP levels and TSH responsiveness of the various mutated receptors. Data from Paschke et al. (61).

**FIG. 10.** Mean serum thyrotropin (TSH) after logarithmic transformation and 95% confidence intervals for the mean in 4,356 participants of the Danthyroid population study. The calculation is based on participants who had not been treated for thyroid disorders. The Copenhagen area had mild (median urinary iodine excretion in subjects not taking iodine supplement 61 μg/L) and the Aalborg area moderate (45 μg/L) iodine deficiency. In each area the study included four groups of females and one male group within the age intervals indicated (years). Data from Knudsen et al. (64).
hormone synthesis and secretion from a gland susceptible to develop hypofunction when exposed to iodine.

Similar mechanisms may be involved in the association between a high iodine intake and goiter (7,8,15). Goiter may be due to accumulation of lymphatic tissue in Hashimoto’s disease or somehow related to the iodine inhibition of colloid intake and degradation by the thyroidal follicular cells. The major relation may be that a high iodine intake often leads to a high serum TSH, which may induce thyroid hyperplasia.

Optimal Iodine Intake Level for Risk Reduction

It is difficult to depict precisely the shape of the exposure-risk curve for iodine intake/thyroid disease (Fig. 1). This may vary with age, gender, exposure to goitrogenic substances, etc. The tendency to develop thyroid disease when exposed to a risk factor may be genetically determined (77). However, much information on iodine intake and thyroid disease has been gathered from epidemiological studies and recent studies published as abstracts have added to the understanding (78–82). In Denmark, comparative epidemiological studies of population cohorts with median urinary iodine concentrations of 45 and 61 μg/L (subjects not taking supplements) have indicated that small increases in iodine intake may lead to a considerable decrease in the prevalence (64) and incidence (78) of hyperthyroidism and goiter (63). This indicates that the risk-exposure curve is relatively steeply falling with an increase in iodine intake in a population with mild or moderate iodine deficiency. On the other hand, the prevalence of some degree of thyroid hypofunction (64) and the incidence of overt hypothyroidism (78) was slightly higher in the population with urinary iodine concentration of 61 μg/L, suggesting that the increase in thyroid hypofunction takes place over the whole range of iodine intake levels from mild iodine deficiency to severe iodine excess.

In keeping with this, a large comparative prevalence study from China indicated that an increase of population iodine intake from a level around 150 μg/d to around 500 μg/d had little measurable effects, except for a threefold increase in the prevalence of thyroid hypofunction (79–82).

Intervals of Iodine Intake and Risk

Table 1 suggests some iodine intake intervals associated with an increase in the risk of thyroid disease. As discussed previously, this may be modified depending on intake of goitrogenics. The intake level is defined from the median 24-hour iodine excretion of the adult population under evaluation. Urinary iodine excretion is the most convenient way of studying the iodine intake of a population. To avoid 24-hour urinary collections, estimates may be based on measurements of iodine and creatinine in nonfasting daytime (83) spot urinary samples and knowledge of the average 24-hour urinary creatinine excretion in the population/subpopulation under study (84–86). If a median 24-hour urinary volume of 1.5 liter is assumed, rough estimates may be based on spot urinary iodine concentrations by multiplying measured values by 1.5.

In Table 1 optimal iodine intake is defined as a relatively narrow interval of 120 to 220 μg per 24 hours. This includes the officially recommended intake of 150 μg/d (16) (urinary iodine excretion is approximately 90% of intake). The grouping of iodine deficiency is nearly identical to standard classification (3,4) where the most recent values are given as urinary iodine concentrations (4). It is stressed that developmental defects are seen in severe iodine deficiency, whereas the main effects of moderate and mild iodine deficiency are goiter and hyperthyroidism caused by multinodular autonomous thyroid growth and function. Some studies have suggested a higher than control prevalence of minor neuropsychointellectual deficits in children from moderately iodine deficient areas (4). Such studies are diffi-

<table>
<thead>
<tr>
<th>Median 24-hour urinary iodine excretion of population or subpopulation</th>
<th>Risk associated with iodine intake level</th>
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<tr>
<td>Severe iodine deficiency</td>
<td>&lt;25 μg</td>
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<td></td>
<td>Developmental brain damage</td>
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<td>Reproductive impairment</td>
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<td>Decreased child survival</td>
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<td>Endemic goiter in young and elderly subjects</td>
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<td>Hypothyroidism</td>
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<td></td>
<td>Hyperthyroidism</td>
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<td>Moderate iodine deficiency</td>
<td>25–60 μg</td>
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<td></td>
<td>Hyperthyroidism and goiter in the middle aged and elderly</td>
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<tr>
<td>Mild iodine deficiency</td>
<td>60–120 μg</td>
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<td></td>
<td>Hyperthyroidism and goiter in the elderly</td>
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<td>(less severe)</td>
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<tr>
<td>Optimal iodine intake</td>
<td>120–220 μg</td>
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<td>Mild iodine excess</td>
<td>220–400 μg</td>
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<td>Hypothyroidism in the elderly (less severe)</td>
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<td></td>
<td>Hypothyroidism in the middle aged and elderly</td>
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<td>Severe iodine excess</td>
<td>&gt;800 μg</td>
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<td>Endemic goiter</td>
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If the 24-hour urine volume is around 1.5 liter, optimal iodine intake gives a median nonfasting spot urine concentration of ~80–150 μg/L. Values are for populations of adults. Intake should be ~50 μg per 24 hours higher in pregnant and lactating women (4).
cult to perform and the association is not firmly established. However, this adds to the conclusion that iodine deficiency should be corrected. The upper limit of mild iodine deficiency has been set at 120 μg per 24 hours. This is based on studies from Copenhagen demonstrating that nodular thyroid disease with hyperthyroidism is prevalent even when the median urinary iodine excretion approaches 100 μg per 24 hours (63,64,78,87).

Table 1 in addition attempts to define excess iodine intake levels and the associated risk. This is important for planning of iodine supplementation programs (88). As reviewed, the incidence of hypothyroidism apparently starts to increase slowly with increasing iodine intake already below the optimal iodine intake level, and this becomes worse with higher iodine intake. Therefore, the upper limit of optimal iodine intake has been set relatively low at 220 μg/d.

The progression in risk is indicated by the somewhat arbitrary grouping into mild and moderate iodine excess, paralleling mild and moderate iodine deficiency. Severe iodine excess has been set at greater than 800 μg per 24 hours, because studies from China (7,8,89–92) indicate that thyroid hypofunction and endemic goiter in children may develop above this intake level. In the Ten-state Nutrition Survey in the United States (93) higher prevalence of goiter was found in states with high frequencies of iodine intake above such a level. More studies in different populations will probably modify the iodine excretion values proposed in Table 1, especially the values of iodine excess. In some populations iodine intakes are so heterogeneous that identification of subpopulations with different dietary habits and iodine intake levels may be needed. This may identify subpopulations with deficient or excessive iodine intake, even if the median urinary iodine excretion of the entire population is within the optimal level.

Clearly it is not possible to plan and direct the iodine intake of every individual to be within the optimal interval. It is, however, important to know what to head for when planning for populations. The main purpose of Table 1 is to focus on the importance of surveillance of population iodine intake levels, of monitoring of the iodine supplementation and fortification programs now involving a majority of world inhabitants, and of proper public control of the use of iodine containing chemicals and supplements in farming and the food industry.

Avoidance of severe iodine deficiency is a must for any official health care system. But also, the excess morbidity associated with mild iodine deficiency and iodine excess should be avoided.

Thyroid diseases are common in all populations, and proper targeting of the iodine intake level will prevent many new cases of disease. Surveillance and control of iodine intake is highly cost effective as compared with diagnosing, therapy, and control of the many individual cases of thyroid disease that might have been prevented.

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Address reprint requests to:
Peter Laurberg, M.D.
Department of Endocrinology and Medicine
Aalborg Hospital
DK-9000 Aalborg
Denmark

E-mail: Laurberg@aas.nja.dk
This article has been cited by:


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