

# High thyroid volume in children with excess dietary iodine intakes<sup>1–3</sup>

Michael B Zimmermann, Yoshiya Ito, Sonja Y Hess, Kenji Fujieda, and Luciano Molinari

## ABSTRACT

**Background:** There are few data on the adverse effects of chronic exposure to high iodine intakes, particularly in children.

**Objective:** The objective of the study was to ascertain whether high dietary intakes of iodine in children result in high thyroid volume (Tvol), a high risk of goiter, or both.

**Design:** In an international sample of 6–12-y-old children ( $n = 3319$ ) from 5 continents with iodine intakes ranging from adequate to excessive, Tvol was measured by ultrasound, and the urinary iodine (UI) concentration was measured. Regressions were done on Tvol and goiter including age, body surface area, sex, and UI concentration as covariates.

**Results:** The median UI concentration ranged from 115  $\mu\text{g/L}$  in central Switzerland to 728  $\mu\text{g/L}$  in coastal Hokkaido, Japan. In the entire sample, 31% of children had UI concentrations  $>300 \mu\text{g/L}$ , and 11% had UI concentrations  $>500 \mu\text{g/L}$ ; in coastal Hokkaido, 59% had UI concentrations  $>500 \mu\text{g/L}$ , and 39% had UI concentrations  $>1000 \mu\text{g/L}$ . In coastal Hokkaido, the mean age- and body surface area-adjusted Tvol was  $\approx 2$ -fold the mean Tvol from the other sites combined ( $P < 0.0001$ ), and there was a positive correlation between  $\log(\text{UI concentration})$  and  $\log(\text{Tvol})$  ( $r = 0.24$ ,  $P < 0.0001$ ). In the combined sample, after adjustment for age, sex, and body surface area,  $\log(\text{Tvol})$  began to rise at a  $\log(\text{UI concentration}) > 2.7$ , which, when transformed back to the linear scale, corresponded to a UI concentration of  $\approx 500 \mu\text{g/L}$ .

**Conclusions:** Chronic iodine intakes approximately twice those recommended—indicated by UI concentrations in the range of 300–500  $\mu\text{g/L}$ —do not increase Tvol in children. However, UI concentrations  $\geq 500 \mu\text{g/L}$  are associated with increasing Tvol, which reflects the adverse effects of chronic iodine excess. *Am J Clin Nutr* 2005;81:840–4.

**KEY WORDS** Thyroid volume, goiter, children, urinary iodine, excess iodine

## INTRODUCTION

More than two-thirds of the 5 billion people living in countries affected by iodine deficiency now have access to iodized salt (1, 2). Iodine excess is occurring more frequently, particularly when salt iodine concentrations are too high or are poorly monitored (2). For example, in Brazil, Algeria, Côte d'Ivoire, Zimbabwe, and Uganda, the median urinary iodine (UI) concentration is  $>300 \mu\text{g/L}$ , whereas that in Chile and Congo is  $>500 \mu\text{g/L}$  (3, 4). High dietary iodine can also come from natural sources, such as seaweed in coastal Japan (5, 6), iodine-rich drinking water in China (7, 8), and iodine-rich meat and milk

in Iceland from animals fed fish products (9). As a result of both the use of iodine-containing agents in dairy farming and food preparation (10, 11) and the consumption of iodine from fortified salt, the mean UI concentration in school-age children in the US is  $\approx 300 \mu\text{g/L}$  (12).

The World Health Organization/International Council for Control of Iodine Deficiency Disorders (WHO/ICCIDD) cautioned that a median UI concentration  $>300 \mu\text{g/L}$  in 6–12-y-old children is excessive (1). By extrapolating from studies in adults, the Institute of Medicine has set the tolerable upper intake level (UL) for iodine in 4–8-y-old and 9–13-y-old children at 300 and 600  $\mu\text{g/d}$ , respectively (13). Experts have highlighted the need for more research on the safety in children of iodine intakes between 200–1000  $\mu\text{g/d}$  (13, 14).

Excess dietary iodine may increase the risk of thyroiditis, hyperthyroidism, hypothyroidism, and goiter (14). In healthy adults, short-term iodine intakes of 500–1500  $\mu\text{g/d}$  have mild inhibitory effects on thyroid function (15–17). The consequences of prolonged exposure to high intakes of iodine, particularly in children, are less clear. Endemic goiter in children has been described in coastal Japan, where iodine intake from seaweed was  $>10\,000 \mu\text{g/d}$  (5). Lower intakes, in the range of 400–1300  $\mu\text{g/d}$ , from iodine-rich drinking water, were associated with increased serum thyrotropin (TSH) and thyroid volume (Tvol) in a small sample of Chinese children (7).

In this study, we analyzed a broad range of UI concentration and Tvol data from a recent international study of school-age children (18), and we included new data from Hokkaido, one of the islands of Japan, on which there traditionally is a high iodine intake. Our aim was to determine whether chronic high iodine intakes are associated with greater thyroid size in school-age children.

<sup>1</sup> From the Human Nutrition Laboratory, Swiss Federal Institute of Technology, Zürich, Switzerland (MBZ and SYH); the Department of Pediatrics, Asahikawa Medical College, Asahikawa, Japan (YI and KF); and the Department for Growth and Development, University Children's Hospital, Zürich, Switzerland (LM).

<sup>2</sup> Supported by the Swiss Federal Institute of Technology and the Swiss Foundation for Nutrition Research, the Japanese Growth Science Foundation, Merck KGaA (Darmstadt, Germany), the Medical Research Council (Cape Town, South Africa), and the World Health Organization.

<sup>3</sup> Reprints not available. Address correspondence to M Zimmermann, Human Nutrition Laboratory, Swiss Federal Institute of Technology Zürich, Seestrasse 72/Postfach 474, CH-8803 Rüschlikon, Switzerland. E-mail: michael.zimmermann@ilw.agrl.ethz.ch.

Received September 21, 2004.

Accepted for publication December 7, 2004.

**TABLE 1**  
Characteristics of an international sample of 6–12-y-old children (*n* = 3319)<sup>1</sup>

Location and sample size	Sex ratio (M/F)	Age	BSA	Age- and BSA-adjusted log thyroid volume <sup>2</sup>	Age- and BSA-adjusted thyroid volume (mL) <sup>2</sup>
		<i>y</i>	<i>m</i> <sup>2</sup>		
Jona, Switzerland ( <i>n</i> = 534)	1.04	9.6 ± 1.9 <sup>3</sup>	1.10 ± 0.18	0.414 ± 0.0049	2.59 (2.57–2.62) <sup>4</sup>
Manama, Bahrain ( <i>n</i> = 526)	1.03	9.3 ± 1.8	1.08 ± 0.23	0.335 ± 0.0055	2.16 (2.14–2.19)
Cape Town, South Africa ( <i>n</i> = 591)	0.99	9.5 ± 2.0	1.12 ± 0.22	0.378 ± 0.0055	2.39 (2.36–2.41)
Lima, Peru ( <i>n</i> = 524)	1.47	9.5 ± 1.6	1.17 ± 0.20	0.384 ± 0.0050	2.42 (2.40–2.44)
Chelsea, MA ( <i>n</i> = 562)	1.16	8.6 ± 1.3	1.10 ± 0.19	0.344 ± 0.0064	2.21 (2.18–2.24)
Central Hokkaido, Japan ( <i>n</i> = 302)	1.16	9.1 ± 1.7	1.05 ± 0.20	0.456 ± 0.0085	2.86 (2.81–2.91)
Coastal Hokkaido, Japan ( <i>n</i> = 280)	1.01	9.4 ± 1.7	1.09 ± 0.19	0.691 ± 0.011	4.91 (4.81–5.01)
All sites ( <i>n</i> = 3319)	1.12	9.3 ± 1.8	1.11 ± 0.21	0.405 ± 0.0028	2.54 (2.53–2.56)

<sup>1</sup> BSA, body surface area.

<sup>2</sup> Significant difference between any 2 of the sites, *P* < 0.0001 (ANOVA with multiple comparisons using the Tukey method), except for comparisons of Bahrain and the United States and of Peru and South Africa, where the differences were not significant.

<sup>3</sup>  $\bar{x}$  ± SD (all such values).

<sup>4</sup> Median; range in parentheses (all such values).

**SUBJECTS AND METHODS**

**Subjects**

The multiethnic sample included children living in North and South America, Central Europe, the Eastern Mediterranean, Africa, and the Western Pacific (Table 1). The sample was recruited from primary schools whose pupils were of middle to low socioeconomic status (18).

Written informed consent was obtained from the parents of participating students. Ethical approval for the study was given by the Swiss Federal Institute of Technology Zürich as well as by each local institution involved in the study.

**Methods**

Height and weight were measured by using standard anthropometric technique (19). Heights were recorded to the nearest millimeter and weights to the nearest 100 g. Tvol was measured by using an Aloka SSD-500 echocamera (Aloka, Mure, Japan) equipped with 7.5-MHz linear transducers. Measurements were performed while subjects sat upright in a straight-backed chair with the neck extended. For each thyroid lobe, the maximum perpendicular anteroposterior and mediolateral dimensions were measured on a transverse image of the largest diameter, without including the isthmus. The maximum craniocaudal diameter of each lobe was then measured on a longitudinal image. The thyroid capsule was not included. The ultrasound measurements were done by one of us (MZ or SH). Intraobserver variability, as defined by limits of agreement (20) for repeat measurements done in ≈4% of the sample by one of us (MZ or SH), were –0.087, 0.134 and –0.114, 0.165. For interobserver variability, the limits of agreement for duplicate measurements done in ≈6% of the sample were –0.202, 0.246.

Spot urine samples were collected, and aliquots were stored at –20 °C until they were analyzed. Measurement of UI concentrations was done in Zürich by using the Pino modification of the Sandell-Kolthoff reaction (21), which was validated against the results of inductively coupled plasma mass spectrometry (22). External control was provided by the Ensuring the Quality of Urinary Iodine Procedures (EQUIP) round-robin program of the Centers for Disease Control and Prevention. The intraassay CV of the Sandell-Kolthoff method in our laboratory was 9.1% at

45.7 ± 4.5 µg/L, 2.8% at 100.1 ± 2.8 µg/L, and 1.2% at 584 ± 6.8 µg/L.

**Data and statistical analyses**

Data processing and statistical analyses were done by using S-PLUS-2000 (version 2000; Insightful Corporation, Seattle, WA) and EXCEL (XP Edition; Microsoft, Seattle, WA) software. Body surface area (BSA) was calculated as

$$BSA = \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 71.84 \times 10^{-4} \quad (1)$$

Tvol was calculated by using the equation of Brunn et al (23):

$$\text{Volume of each lobe (mL)} = \text{AP diameter (cm)} \times \text{ML diameter (cm)} \times \text{CC diameter (cm)} \times 0.479 \quad (2)$$

Then the lobe volumes are summed. Median daily iodine intake was estimated from median UI concentration by the method of the Institute of Medicine (13), which assumes that 92% of dietary iodine is excreted in the urine and calculates 24-h urine volume in children by using body weight– and age-specific median urine volumes for 7–15-y-old children (24). To normalize their distributions, UI concentration and Tvol were log<sub>10</sub> transformed, and analysis of variance was used for comparisons among sites. Multiple regression was done to look for associations of UI concentrations and Tvol with adjustment for age, sex, and BSA. Log<sub>10</sub>(Tvol) was plotted against log<sub>10</sub>(UI concentration) and a Lowess smoothed line was calculated by using S-PLUS-2000 software (25). Goiter was defined by using sex- and BSA-specific reference criteria for Tvol (18), and, in the coastal areas of Hokkaido, logistic regression of goiter with covariates of sex and UI concentration was done.

**RESULTS**

The sample size and subject characteristics and the age- and BSA-adjusted Tvol (Tvol<sub>adj</sub>) by site and combined are shown in Table 1. The mean Tvol<sub>adj</sub> in coastal Hokkaido was approximately twice the combined mean Tvol<sub>adj</sub> at the other 6 sites (*P* < 0.0001). The United States and Bahrain had significantly smaller

**TABLE 2**

Urinary iodine (UI) concentration and estimated iodine intake and classification of intakes, by study site and combined, in an international sample of 6–12-y-old children ( $n = 3319$ )

Location	UI concentration	Log (UI concentration) <sup>1</sup>	Distribution of UI concentrations (>300/>500/>1000 $\mu\text{g/L}$ )	Iodine intake <sup>2</sup>	Estimated iodine intake <sup>3</sup>
	$\mu\text{g/L}$		%		$\mu\text{g/d}$
Jona, Switzerland	116 (2–450) <sup>4</sup>	$2.04 \pm 0.26^5$	1/0/0	Adequate	120
Manama, Bahrain	185 (1–678)	$2.22 \pm 0.36$	22/5/0	Adequate	183
Cape Town, South Africa	189 (4–704)	$2.24 \pm 0.28$	17/2/0	Adequate	205
Lima, Peru	253 (32–931)	$2.37 \pm 0.23$	32/4/0	More than adequate	300
Chelsea, MA	292 (23–1890)	$2.45 \pm 0.24$	48/11/1	More than adequate	314
Central Hokkaido, Japan	296 (53–13700)	$2.57 \pm 0.44$	50/26/15	More than adequate	292
Coastal Hokkaido, Japan	728 (38–11100)	$2.82 \pm 0.48$	77/59/39	Excessive	741
All sites	218 (1–13700)	$2.34 \pm 0.38$	31/11/5	More than adequate	241

<sup>1</sup> Significant difference between any 2 of the sites,  $P < 0.0001$  (ANOVA with multiple comparisons using the Tukey method, except for comparisons of Bahrain and South Africa and of the United States and Peru, where the differences were not significant).

<sup>2</sup> According to criteria of the World Health Organization for median UI concentrations (1).

<sup>3</sup> Median (all such values).

<sup>4</sup> Median; range in parentheses (all such values).

<sup>5</sup>  $\bar{x} \pm \text{SD}$  (all such values).

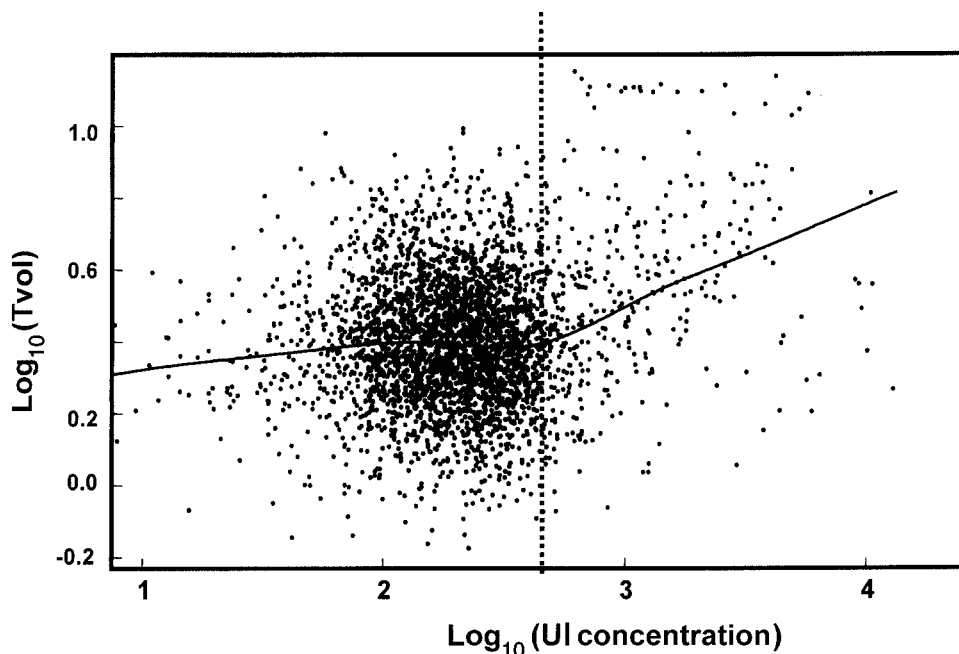
$\text{Tvol}_{\text{adj}}$  than did the other sites ( $P < 0.0001$ ). The UI concentrations and the corresponding estimated iodine intakes (13) by site and combined are shown in **Table 2**. According to the WHO/ICCIDD criteria for assessing iodine nutrition by using median UI concentrations (1), iodine intakes were adequate in Switzerland, South Africa, and Bahrain; more than adequate in Peru, the United States, and central Hokkaido; and excessive in coastal Hokkaido.

Compared with the children at the other the sites, the children in coastal Hokkaido had significantly greater  $\text{Tvol}_{\text{adj}}$  over the entire range of UI concentrations. With the exception of coastal Hokkaido, there was no significant correlation between UI concentrations and  $\text{Tvol}_{\text{adj}}$  in any of the individual sites. In coastal Hokkaido, higher concentrations predicted significantly higher  $\text{Tvol}_{\text{adj}}$  in both boys ( $r = 0.19$ ,  $P = 0.03$ ) and

girls ( $r = 0.28$ ,  $P < 0.001$ ); the odds ratio for goiter was 1.75 (95% CI: 1.1, 2.9;  $P = 0.03$ ) for a 10-fold increase in UI concentration. The plot of  $\log(\text{Tvol})$  and  $\log(\text{UI concentration})$  for all sites combined is shown in **Figure 1**.  $\log(\text{Tvol})$  begins to increase at  $\log(\text{UI concentrations}) > 2.7$ , which, transformed back to the linear scale, corresponds to a UI concentration of  $\approx 500 \mu\text{g/L}$ .

## DISCUSSION

Most data on the effects of high iodine intake come from short-term studies in adults. The administration of pharmacologic quantities of iodine (10–1000 mg/d for several weeks) to euthyroid adults decreases serum thyroxine and triiodothyronine



**FIGURE 1.** Plot of  $\log_{10}$ [thyroid volume (Tvol)] and  $\log_{10}$ [urinary iodine (UI) concentration] showing a Lowess smoothed line calculated for an international sample of 6–12-y-old children ( $n = 3319$ ), with sexes and sites combined.

concentrations and produces a compensatory increase in basal and thyrotropin-releasing hormone-stimulated serum TSH concentrations (26, 27). Smaller doses of oral iodine (500–1500  $\mu\text{g}/\text{d}$ ) may also have a mild inhibitory effect on thyroid hormone secretion in euthyroid adults (15–17). Paul et al (15) gave healthy adults 250, 500, and 1500  $\mu\text{g}$  iodine/d for 14 d. At doses of 250 and 500  $\mu\text{g}/\text{d}$ , there were no detectable effects, but the 1500  $\mu\text{g}/\text{d}$  dose produced mild abnormalities in the pituitary-thyroid axis. Gardner et al (16) assigned 30 men to receive either 500, 1500, or 4500  $\mu\text{g}$  iodide/d for 2 wk. Mean UI concentrations in the 3 groups increased to 638, 1498, and 5035  $\mu\text{g}/\text{L}$ , respectively. The 500- $\mu\text{g}/\text{d}$  dose significantly increased serum TSH response to thyrotropin-releasing hormone, and the 2 larger doses increased both basal and thyrotropin-releasing hormone-stimulated serum TSH concentrations. Mean thyroxine and free thyroxine index decreased significantly at the 2 higher iodine doses. These studies indicate that iodine intakes of  $\geq 500$   $\mu\text{g}/\text{d}$  over several weeks induce subtle, reversible changes in pituitary-thyroid function in adults (with values remaining within the normal range), probably by inhibiting thyroid hormone release (15–17).

Several studies have reported that excess iodine has a goitrogenic effect in adults. In Peace Corps volunteers, ingestion for up to 32 mo of  $\geq 50$  mg iodine/d from iodine-resin water filters increased mean ( $\pm$ SD) UI concentrations to  $11.1 \pm 19.1$  mg/L (28). Goiter by palpation was found in 44% of the subjects; 30  $\pm$  11 wk after removal of excess iodine, the goiter prevalence decreased to 30% (29). LeMar et al (30) reported a reversible, TSH-dependent thyroid enlargement in response to iodine excess from tetraglycine hydroperiodide water-purification tablets. A dose of 32 mg iodine/d for 3 mo given to 8 healthy adults increased mean UI concentrations from 0.28 to 40 mg/d. Mean Tvol, determined by ultrasound, increased by 37% after 3 mo in those subjects but returned to baseline an average of 7.1 mo afterward. Namba et al (31) gave 10 healthy men 27 mg iodine/d for 28 d. Mean Tvol increased significantly (16%) after 4 wk and returned to baseline 4 wk after iodine withdrawal.

In children, excess dietary iodine has been associated with goiter and thyroid dysfunction. In a report of what the authors called “endemic coastal goiter” in Hokkaido, Japan (5), the traditional local diet was high in iodine-rich seaweed. UI excretion in children consuming the local diet was  $\approx 23\,000$   $\mu\text{g}/\text{d}$ . The overall prevalence of visible goiter in children was 3–9%, but, in several villages,  $\approx 25\%$  of the children had visible goiter. Most of the goiters responded to the administration of thyroid hormone, restriction of dietary iodine intake, or both. TSH assays were not available, but it was suggested that an increase in serum TSH was involved in the generation of goiter. No cases of clinical hypothyroidism or hyperthyroidism were reported.

Goiter in children may also be precipitated by iodine intake well below the high amount in the studies from Hokkaido. Li et al (7) examined thyroid status in 171 Chinese children from 2 villages where the iodine concentrations in drinking water were 462 and 54  $\mu\text{g}/\text{L}$ , and the children’s mean UI concentrations were 1235 and 428  $\mu\text{g}/\text{g}$  creatinine, respectively. The mean serum TSH concentration (7.8 mU/L) was high in the first village and high-normal (3.9 mU/L) in the second village. In the first village, the goiter rate was  $>60\%$  and mean ( $\pm$ SD) Tvol was  $13.3 \pm 2.7$ , whereas the goiter rate was 15–20% and mean ( $\pm$ SD) Tvol was  $5.9 \pm 1.8$  in the second village. There were no signs of neurologic deficits in the children. In other reports from China, drinking water with iodine concentrations  $>300$   $\mu\text{g}/\text{L}$  resulted in

UI concentrations  $>900$   $\mu\text{g}/\text{L}$  and a goiter rate of  $>10\%$  (8). Although the mechanism remains unclear, increased thyroid size associated with high iodine intake may be due to autoimmune-mediated lymphoid infiltration of the thyroid (32, 33), inhibition of thyroid hormone release that increases serum TSH and thyroid stimulation (7, 27), or both. Taken together, the Chinese studies suggest that goiter and thyroid dysfunction may occur in children at iodine intakes in the range of 400–1300  $\mu\text{g}/\text{d}$ .

Our data support previous findings of thyroid sensitivity to high iodine intakes and suggest that chronic iodine intakes  $\geq 500$   $\mu\text{g}/\text{d}$  in children increase thyroid size. However, this possibility is based mainly on the data from coastal Hokkaido; in central Hokkaido and in the United States—the 2 other sites with a high prevalence of UI concentrations  $>500$   $\mu\text{g}/\text{L}$ —there was no significant increase in Tvol at higher UI concentrations. This difference could be due to dietary or environmental factors (or both) in coastal Hokkaido that potentiate the effects of high iodine intake. A limitation of our study was that thyroid function tests and antithyroid antibodies were not measured in the sample. It is possible that children with high iodine intakes could have subtle changes in pituitary-thyroid function that were not reflected by increases in thyroid size. However, in previous studies of iodine excess in adults and children that measured Tvol by ultrasound (most of which reported iodine intakes much higher than those in our sample), nearly all detected an increase in Tvol (5, 7, 8, 28–31). This suggests that an increased Tvol is a reasonable marker of thyroid dysfunction in response to iodine excess. Although our findings support the contention that moderately high dietary intakes of iodine—in the range of 300–500  $\mu\text{g}/\text{d}$ —are well tolerated by healthy children, iodine intakes in this range are of no benefit and may have adverse effects not detected in this study.



For assistance in data collection and analysis, we thank Y Shishiba and M Irie (Tokyo); O Ueda, Y Sasaki, and M Fujine (Asahikawa, Japan); T Mukai (Nakashibetsu, Japan); B de Benoist (Geneva); F Delange (Brussels); L Braverman and E Pearce (Boston, MA); P Jooste (Cape Town, South Africa); K Moosa (Manama, Bahrain); E Pretell (Lima, Peru); S Renggli, M Balsat, and F Rohner (Zürich, Switzerland); M Haldimann (Bern, Switzerland); and K Bagchi (Cairo, Egypt), as well as the teachers and children in the participating schools.

The data were collected by MZ, YI, and SH; the statistical analyses were done by MZ and LM; the first draft of the manuscript was written by MZ; and each of the authors made substantial contributions to the study design, data analyses, and editing of the manuscript. None of the authors had a personal or financial conflict of interest.

## REFERENCES

1. World Health Organization/United Nations Children’s Fund/International Council for the Control of Iodine Deficiency Disorders. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers. Geneva: World Health Organization, 2001 (WHO/NHD/01.1).
2. Delange F, de Benoist B, Pretell E, Dunn JT. Iodine deficiency in the world: where do we stand at the turn of the century? *Thyroid* 2001;11:437–47.
3. International Council for the Control of Iodine Deficiency Disorders. Current IDD status database. Internet: <http://www.iccid.org> (accessed 20 September 2004).
4. World Health Organization. WHO global database on iodine deficiency. Internet: <http://www3.who.int/whosis/micronutrient/> (accessed 20 September 2004).
5. Suzuki H, Higuchi T, Sawa K, Ohtaki S, Horiuchi Y. “Endemic coast goiter” in Hokkaido, Japan. *Acta Endocrinol (Copenh)* 1965;50:161–76.
6. Katamine S, Mamiya Y, Sekimoto K, et al. Iodine content of various

- meals currently consumed by urban Japanese. *J Nutr Sci Vitaminol (Tokyo)* 1986;32:487–95.
7. Li M, Liu DR, Qu CY, et al. Endemic goiter in Central China caused by excessive iodine intake. *Lancet* 1987;1:257–9.
  8. Zhao I, Chen Z, Maberly G. Iodine-rich drinking water of natural origin in China. *Lancet* 1998;352:2024.
  9. Sigurdsson G, Franzson L. Urine excretion of iodine in an Icelandic population. *Icelandic Med J* 1988;74:179–81.
  10. London WT, Vought RL, Brown FA. Bread—dietary source of large quantities of iodine. *N Engl J Med* 1965;273:381.
  11. Pearce EN, Pino S, He X, Bazrafshan HR, Lee SL, Braverman LE. Sources of dietary iodine: bread, cows' milk, and infant formula in the Boston area. *J Clin Endocrinol Metab* 2004;89:3421–4.
  12. Hollowell JG, Staehling NW, Hannon WH, et al. Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971–1974 and 1988–1994). *J Clin Endocrinol Metab* 1998;83:3401–8.
  13. Institute of Medicine. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy Press, 2001:290–393.
  14. Pennington JAT. Iodine toxicity. Springfield, VA: National Technical Information Service, US Department of Commerce, 1989.
  15. Paul T, Meyers B, Witorsch RJ, et al. The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. *Metabolism* 1988;37:121–4.
  16. Gardner DF, Centor RM, Utiger RD. Effects of low dose oral iodide supplementation on thyroid function in normal men. *Clin Endocrinol (Oxf)* 1988;28:283–8.
  17. Chow CC, Phillips DI, Lazarus JH, Parkes AB. Effect of low dose iodide supplementation on thyroid function in potentially susceptible subjects: are dietary iodide levels in Britain acceptable? *Clin Endocrinol (Oxf)* 1991;34:413–6.
  18. Zimmermann MB, Hess SY, Molinari L, et al. New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a WHO/NHD Iodine Deficiency Study Group Report. *Am J Clin Nutr* 2004;79:231–7.
  19. World Health Organization. Physical status: the use and interpretation of anthropometry. *World Health Organ Tech Rep Ser* 1995;854:1–462.
  20. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurements. *Lancet* 1986;1:307–10.
  21. Pino S, Fang SL, Braverman LE. Ammonium persulfate: a safe alternative oxidizing reagent for measuring urinary iodine. *Clin Chem* 1996;42:239–43.
  22. Haldimann M, Zimmerli B, Als C, Gerber H. Direct determination of urinary iodine by inductively coupled plasma mass spectrometry using isotope dilution with iodine-129. *Clin Chem* 1998;44:817–24.
  23. Brunn J, Block U, Ruf G, Bos I, Kunze WP, Scriba PC. Volumetrie der Schilddrüsenlappen mittels Real-time-Sonographie. [Volume measurement of the thyroid using real-time sonography.] *Dtsch Med Wochenschr* 1981;106:1338–40 (in German).
  24. Mattsson S, Lindstrom S. Diuresis and voiding pattern in healthy schoolchildren. *Br J Urol* 1995;76:783–9.
  25. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc* 1979;74:829–36.
  26. Wolff J. Iodine goiter and the pharmacological effects of excess iodide. *Am J Med* 1969;47:101–24.
  27. Braverman LE. Iodine and the thyroid: 33 years of study. *Thyroid* 1994;4:351–6.
  28. Khan LK, Li R, Gootnick D. Thyroid abnormalities related to iodine excess from water purification units. Peace Corps Thyroid Investigation Group. *Lancet* 1998;352:1519.
  29. Pearce EN, Gerber AR, Gootnick DB, et al. Effects of chronic iodine excess in a cohort of long-term American workers in West Africa. *J Clin Endocrinol Metab* 2002;87:5499–502.
  30. LeMar HJ, Georgitis WJ, McDermott MT. Thyroid adaptation to chronic tetraglycine hydroperiodide water purification tablet use. *J Clin Endocrinol Metab* 1995;80:220–3.
  31. Namba H, Yamashita S, Kimura H, et al. Evidence of thyroid volume increase in normal subjects receiving excess iodide. *J Clin Endocrinol Metab* 1993;76:605–8.
  32. Mizukami Y, Michigishi T, Nonomura A, et al. Iodine-induced hypothyroidism: a clinical and histological study of 28 patients. *J Clin Endocrinol Metab* 1993;76:466–71.
  33. Boyages SC, Bloot AM, Maberly GF, et al. Thyroid autoimmunity in endemic goitre caused by excessive iodine intake. *Clin Endocrinol (Oxf)* 1989;31:453–65.