

# Thyroid volume and urinary iodine in European schoolchildren: standardization of values for assessment of iodine deficiency

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## Abstract

Up to 1992, most European countries used to be moderately to severely iodine deficient. The present study aimed at evaluating possible changes in the status of iodine nutrition in 12 European countries during the past few years. Thyroid volume was measured by ultrasonography in 7599 schoolchildren aged 7–15 years in one to fifteen sites in The Netherlands, Belgium, Luxembourg, France, Germany, Austria, Italy, Poland, the Czech and Slovak Republics, Hungary and Romania. The concentrations of urinary iodine were measured in 5709 of them. A mobile unit (ThyroMobil van) equipped with a sonographic device and facilities for the collection of urine samples visited all sites in the 12 countries. All ultrasounds and all urinary iodine assays were performed by the same investigators. The status of iodine nutrition in schoolchildren has markedly improved in many European countries and is presently normal in The Netherlands, France and Slovakia. It remains unchanged in other countries such as Belgium. There is an inverse relationship between urinary iodine and thyroid volume in schoolchildren in Europe. Goiter occurs as soon as the urinary iodine is below a critical threshold of 10 µg/dl. Its prevalence is up to 10 to 40% in some remote European areas. This work produced updated recommendations for the normal volume of the thyroid measured by ultrasonography as a function of age, sex and body surface area in iodine-replete schoolchildren in Europe. This study proposes a method for a standardized evaluation of iodine nutrition on a continental basis, which could be used in other continents.

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## Introduction

Endemic goiter, occasionally complicated by endemic cretinism, has been reported in Europe up to the turn of the 20th century, especially from remote, isolated, mountainous areas in central parts of the continent including Switzerland, Austria, Northern Italy, Bulgaria and the former Czechoslovakia (1–4). The problem of the disorders induced by iodine deficiency (iodine deficiency disorders or IDD (5)) has been entirely eradicated in Switzerland thanks to the implementation and monitoring of a program of salt iodization (6). Probably because of the impact on the medical world of this remarkable program, IDD seems to have been considered no longer as a significant public health problem in Europe during the last five decades. However, re-evaluation of the problem in the late

1980s under the sponsorship of the European Thyroid Association clearly indicated that except for most of the Scandinavian countries, Austria and Switzerland, most of the European countries or at least certain areas of these countries were still affected, especially in the Southern part of the continent (7). Shortly thereafter, it was shown that changes in the iodine supplies in the adult populations were accompanied by parallel changes in the iodine content of breast milk and of the urine of neonates (8). These surveys also revealed a lack of information on IDD in countries of the Eastern part of the continent.

Based on this information and thanks to changes in the political situation in Europe, the status of iodine nutrition was re-evaluated in 1992 in all European countries, including the Eastern part of the continent (9). Iodine deficiency was under control in only five

countries, namely Austria, Finland, Norway, Sweden and Switzerland. It was marginal in Belgium, the Czech and Slovak Republics, Denmark, France, Hungary, Ireland, Portugal and the United Kingdom and had recurred after transitory resolution in Croatia, The Netherlands, and possibly in some Eastern European countries. Finally, iodine deficiency persisted and ranged from moderate to severe in all the other European countries.

Based on these results, the European office of the World Health Organization (WHO) recommended all European governments to establish, support and fund a national committee in charge of the problem of iodine deficiency, with representatives from medicine, nutrition, legislation, public health, industry and the media, with high level access to governments, the salt industry and research institutions. Initiation of adequate legislation was also recommended to ensure availability of iodized salt and, in between, to monitor specifically the iodine intake of pregnant and lactating women and young infants in order to prevent neonatal hypothyroidism and subsequent brain damage in the growing infant, the most serious public health consequence of iodine deficiency.

The present study aimed at evaluating the impact of these recommendations on the status of iodine nutrition in different European countries. The study has been conducted by a core group of 11 endocrinologists representing each of the 12 countries involved in the study, namely The Netherlands, Belgium, Luxemburg, France, Germany, Austria, Italy, Poland, the Czech and Slovak Republics, Hungary and Romania.

On the basis of the recommendations of WHO, UNICEF and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) (10), it was decided to investigate schoolchildren aged 6–15 years, to measure thyroid volume by ultrasonography and the urinary concentration of iodine. According to these organizations, iodine deficiency is indicated by prevalence of more than 5% of clinically detectable goiter or of thyroid volume determined by ultrasonography above the 97th percentile for a population of children with a normal iodine intake, and by a median urinary iodine below 10  $\mu\text{g}/\text{dl}$ .

One of the interesting characteristics of the project has been that, in order to ensure homogeneity in the methods used and to decrease the inter-observer variability, the ultrasounds were performed in all children by the same trained investigator (J P, Bratislava, Slovakia) and all iodine assays were performed in the same laboratory, namely the Department of Clinical Chemistry of the University Hospital Saint-Pierre in Brussels, Belgium (F V and her colleagues).

## Patients and methods

### Global organization of the project

The countries were selected on the basis of the existence of marked differences in the past in the iodine intake in

the 12 countries and on the possibility of recent changes in the status of iodine nutrition in some of them. Each of the countries involved in the project was represented by a national investigator, who selected a minimum of three sites to be investigated per country. The sites corresponded either to places investigated in the past in order to appreciate possible changes in the iodine supply or to places which had never been investigated.

Groups of at least 100 schoolchildren of both sexes and aged 6–15 years were investigated at each site.

A mobile unit ('ThyroMobil' van, Fig. 1) equipped with a sonographic device, a computer for processing the thyroid measurements on the spot and facilities for the collection and storage of urine samples, visited the schools in all sites of the 12 countries under investigation. It covered a total of about 30 000 km within a 12-month interval.

The ThyroMobil was located on the school yard of the sites under investigation. The children were sonographed class by class. The urine samples were collected just before or after sonography. Height and weight were measured, allowing the calculation of body surface area (BSA). The results of the sonography were transferred immediately into the computer. In cases of abnormality in the clinical or echographic examination of the thyroid, the parents of the children received a written note directed to the home physician describing the abnormal results of the examination.

In order to increase awareness of the public to iodine nutrition, the national investigators, the principal investigator of the ThyroMobil project (F D) as well as representatives of the academic bodies and of the UNICEF national committees took part in a press conference in each country during the visit of the ThyroMobil van.

The investigation was approved by the ethical committee of the University of Brussels, the national Ministries of Health and Education and by representatives of the parents of the schoolchildren in the 12 countries.



**Figure 1** The ThyroMobil van and schoolchildren under investigation.

## Patients

The investigation included 7599 schoolchildren, 3758 boys and 3841 girls, from 57 sites in the 12 countries. The number of sites per country varied from one (Luxemburg) to 15 (France). The age of the children varied from 6 to 17 years. Most were aged 6–15 years. The mean age was 10.4 (s.d. 2.4) years for boys and 10.5 (s.d. 2.5) years for girls. Thyroid ultrasound was performed in all children. Urine samples were collected in 5709 of them from 49 sites.

## Methods

**Thyroid volume.** Thyroid volume was estimated using real-time sonography according to Brunn *et al.* (11) with a Siemens Sonoline SI-400, using a 7.5 MHz linear array transducer. Longitudinal and transverse scans were performed allowing the measurement of the depth (d), the width (w) and the length (l) of each lobe. The volume of the lobe was calculated by the formula:  $V \text{ (ml)} = 0.479 \times d \times w \times l \text{ (cm)}$ . The thyroid volume was the sum of the volumes of both lobes. The volume of the isthmus was not included.

During the early phase of the study, the criteria used for defining the upper limit of normal for thyroid volume (percentile 97; P97) in children with a normal iodine intake were those proposed by Gutekunst & Martin-Teichert (12).

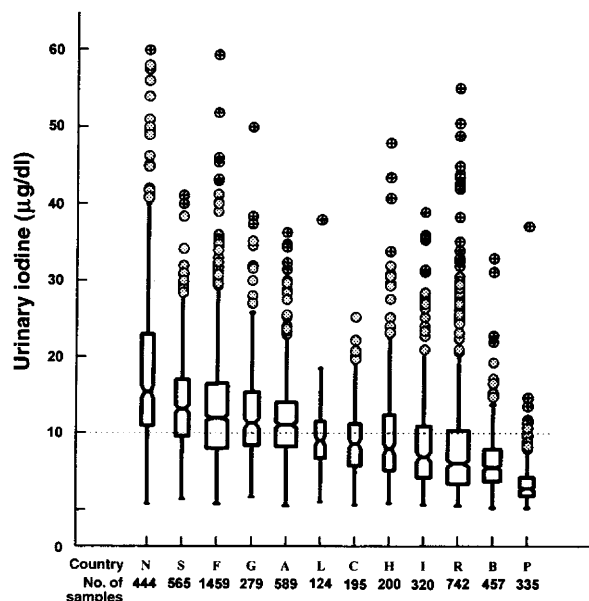
**Urinary iodine.** The urinary iodine concentrations were measured by the colorimetric ceric ion arsenious acid wet ash method based on the Sandell–Kolthoff reaction (13) using a Technicon auto-analyzer (14).

**Body surface area.** The body surface area (BSA  $\text{m}^2$ ) was calculated by using the formula:  $\text{BSA} = W^{0.425} \times H^{0.725} \times 71.84 \times 10^{-4}$  where W is the weight in kg and H the height in cm.

**Statistical methods.** Usual statistics (proportions, mean, standard deviation, median, range) have been used to describe the data (15).

The frequency distributions of both thyroid volume and urinary iodine were most usually asymmetrical and skewed towards high values.

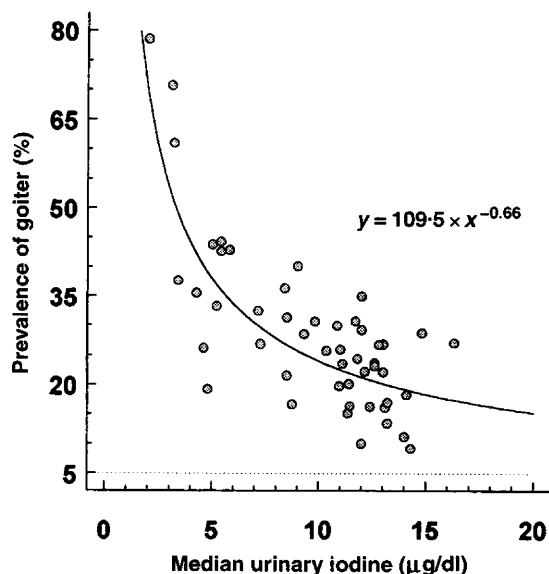
For thyroid volume, a logarithmic transformation was used to normalize the distribution. The Kolmogorov–Smirnov test was applied to check normality of the transformed variable in each age group and BSA group, separately for girls and boys. Moreover, normal probability–probability (P–P) plots were established in each group allowing a visual check of normality. All the Kolmogorov–Smirnov tests were non-significant and normal P–P plots proved to be very satisfying. Means and standard deviations of the logarithm of the thyroid volume were thus used as parameters to fit a normal distribution to the data of



**Figure 2** Notched box-plot presentation of urinary iodine concentrations in schoolchildren in The Netherlands (N), Slovakia (S), France (F), Germany (G), Austria (A), Luxemburg (L), the Czech Republic (C), Hungary (H), Italy (I), Romania (R), Belgium (B) and Poland (P). The number of samples is indicated.

each group. On the basis of these normal distributions, P97 values were computed from the P97 of the standard normal distribution.

P50 and P97 obtained for both sexes as a function of age or BSA were then smoothed using regression.



**Figure 3** Inverse relationship in schoolchildren between the median urinary iodine concentrations and the prevalence of goiter estimated on the basis of the ultrasonographic criteria proposed by Gutekunst & Martin-Teichert (12). The dotted line for a prevalence of goiter of 5% represents the upper limit of normal according to the WHO–UNICEF–ICCIDD criteria used in this study (10).

**Table 1** Range of the median urinary concentrations of iodine found in school children in all sites investigated. Values above the lower limit of normal ( $10 \mu\text{g/dl}$ ) in all sites were found in only three countries.

Country	No. of sites	Range of median urinary iodine ( $\mu\text{g/dl}$ )
The Netherlands	3	14.1–16.3
Slovak Republic	4	13.0–14.3
Germany	2	10.3–12.6
Austria	4	9.8–12.0
France	15	8.5–13.1
Luxemburg	1	9.0
Czech Republic	2	8.5–8.7
Italy	2	5.4–8.4
Hungary	3	5.2–11.5
Belgium	3	5.0–5.8
Romania	7	3.4–14.0
Poland	3	2.0–3.2

Quadratic regression proved to lead to a very satisfying fit; square of the multiple correlation coefficient was used as a measure of the adequacy of the fit.

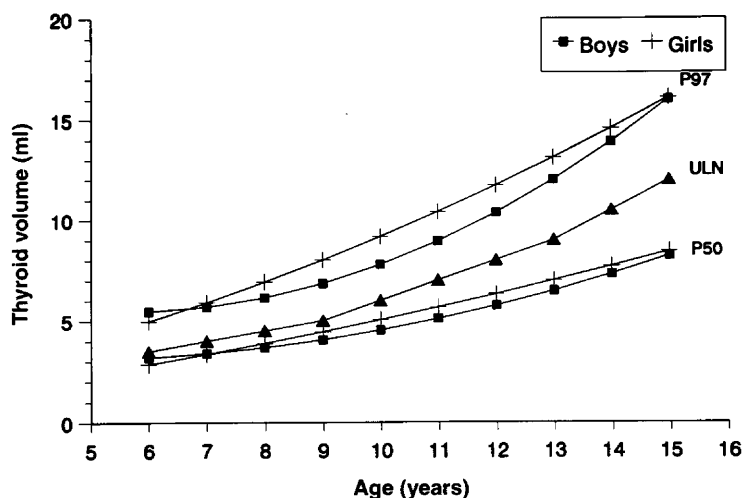
For urinary iodine, the distributions were represented by means of box-plots (16) which give the median, the upper (P75) and the lower (P25) quartiles (Fig. 2). The ends of the 'whiskers' (vertical bars) are the adjacent values defined from the interquartile range (IQR). The upper adjacent value is the largest observation equal to or lower than the top of the box (P75) + 1.5 IQR whilst the lower adjacent value is the smallest observation equal to or higher than the bottom of the box (P75) – 1.5 IQR. The individual values falling outside the range of the two adjacent values are also represented. The notches provide an approximate test ( $\alpha = 0.05$ ) of the nul hypothesis that true medians are equal. If two notches overlap, this nul hypothesis was not rejected.

## Results

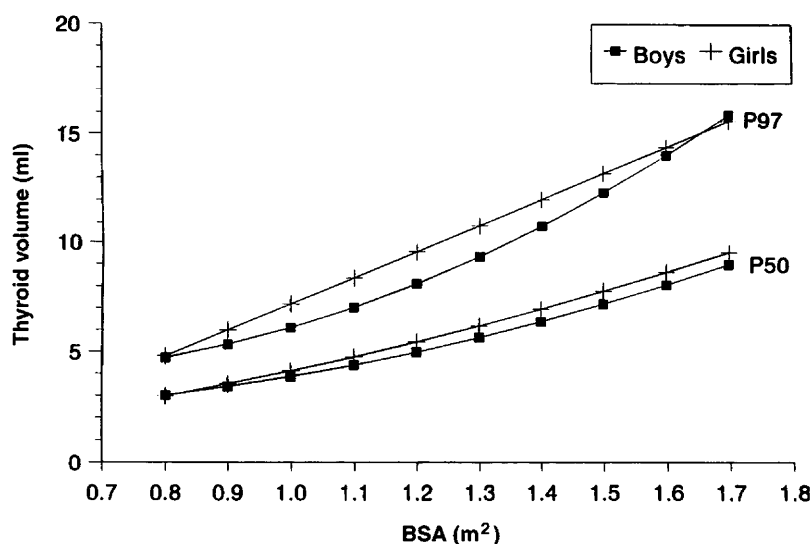
Figure 2 shows the notched box-plot presentation of urinary iodine concentrations in all countries investigated. The countries are listed by decreasing values of the medians. The medians stayed within the normal range in The Netherlands, the Slovak Republic, France, Germany and Austria. They were borderline in Luxemburg and distinctly below the normal in the other countries, namely the Czech Republic, Hungary, Italy, Romania, Belgium and Poland.

Table 1 shows for each country the range of the medians obtained in the different sites investigated. They were above  $10 \mu\text{g/dl}$  in all sites in The Netherlands, the Slovak Republic, Germany and in the vast majority of the sites in Austria and France. Most sites in Hungary and especially in Romania had low values but some others were markedly elevated. The medians were homogeneous and moderately low in Belgium and quite low in the sites investigated in Poland.

Figure 3 shows the relationship in the 49 sites under investigation between the median urinary iodine and the prevalence of goiter based on the ultrasonographic criteria defined by Gutekunst & Martin-Teichert (12). As could be expected, there was an inverse relationship between the two variables. However, an unexpected observation was that, when using these criteria of goiter, the prevalence of goiter was definitely above normal, i.e. above 5%, in all sites, including the sites with a normal iodine intake. For example, the prevalence of goiter was 14% in Slovakia where the median urinary iodine was  $14 \mu\text{g/dl}$ ; it was almost 25% in Germany and 29% in Austria respectively. The prevalence was about 40% in Belgium and as high as 50–80% in Poland. These figures appear extremely surprising, considering that in Belgium, for example, almost no child had a visible goiter.



**Figure 4** Changes as a function of age and sex of thyroid volume measured by ultrasonography in iodine-replete areas in Europe. P50 corresponds to the median and P97 to the upper limit of normal. The curve ULN represents the upper limit of normal proposed by Gutekunst & Martin-Teichert (12) for girls and boys and which was used in the early phase of the present study.



**Figure 5** Changes as a function of age and BSA of thyroid volume measured by ultrasonography in iodine-replete areas in Europe.

Therefore, after having controlled the adequacy of our own measurements of thyroid volume and urinary iodine, we questioned the criteria proposed by Gutekunst & Martin-Teichert (12) and we re-evaluated thyroid volume in normal children from our own data by selecting a cluster of children originating from sites where the median urinary iodine was at least 10 µg/dl in groups of at least 50 children. Such conditions were gathered in 23 sites located in The Netherlands, the Slovak Republic, Austria and France. We showed that there was no difference in thyroid volume as a function of the duration of correction of iodine deficiency, for example between Austria with its long history of salt iodization and France with a more recent correction of iodine deficiency. The cluster was made up of 3265 children, about 50% boys and girls. In this cluster, there was no difference in urinary iodine concentrations as a function of age and sex between 6 and 14 years.

Figure 4 shows the results obtained in the cluster for the median (P50) and for the upper limit of normal (P97) for thyroid volume as a function of age and sex. The latter was distinctly above the upper limit of normal proposed earlier by Gutekunst & Martin-Teichert (12) (ULN on Fig. 4). There was no difference for thyroid volume between girls and boys until the beginning of puberty. The volume was higher in girls, especially for the upper limit of normal, from the age of 9 years onwards but this difference disappeared at the age of 15 years.

Figure 5 shows the results obtained for thyroid volume in the same cluster of iodine-replete children as a function of BSA, irrespective of age. This presentation of the results was used in order to take into account the differences in body development between children of the same age in different countries.

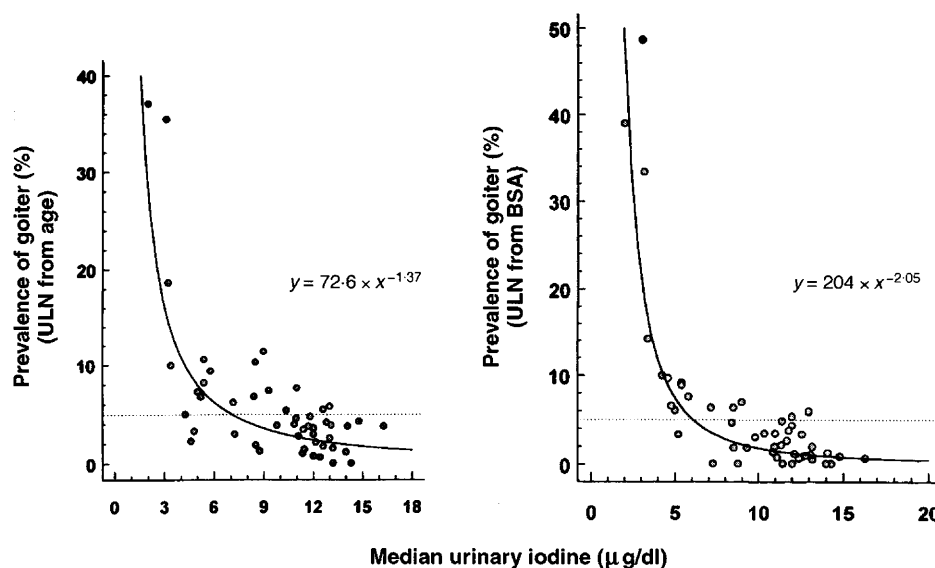
Table 2 shows the values proposed by the authors of this report for the upper limit of normal for thyroid

volume measured by ultrasonography in iodine-replete boys and girls in Europe as a function of age and BSA.

Figure 6 shows the relationship observed on all sites investigated between the urinary concentrations of iodine and the prevalence of goiter determined by using these new criteria. The inverse relationship between urinary iodine and prevalence of goiter was confirmed but, contrasting with Fig. 3, the prevalence was almost systematically below 5% as long as the urinary iodine was above 10 µg/dl. This relationship

**Table 2** Upper limit of normal thyroid volume (ml) measured by ultrasonography in iodine-replete boys and girls in Europe as a function of age and BSA.

Age (years)	Thyroid volume upper limit of normal (ml)	
	Boys	Girls
6	5.4	5.0
7	5.7	5.9
8	6.1	6.9
9	6.8	8.0
10	7.8	9.2
11	9.0	10.4
12	10.4	11.7
13	12.0	13.1
14	13.9	14.6
15	16.0	16.1
BSA (m²)		
0.8	4.7	4.8
0.9	5.3	5.9
1.0	6.0	7.1
1.1	7.0	8.3
1.2	8.0	9.5
1.3	9.3	10.7
1.4	10.7	11.9
1.5	12.2	13.1
1.6	14.0	14.3
1.7	15.8	15.6



**Figure 6** Inverse relationship in schoolchildren between the median urinary iodine concentrations and the prevalence of goiter estimated on the basis of the ultrasonographic criteria defined in the present study. ULN, upper limit of normal.

with a cut-off of 10 µg/dl was more accurate when using the upper limit of normal based on BSA rather than based on age. The possible explanation is that the BSA may vary from one country to another for children of the same age. For example, BSA is almost systematically 30% lower in schoolchildren in Romania than in The Netherlands. This observation underlines the importance of considering not only age but also weight and height in the evaluation of the thyroid volume and thus the prevalence of goiter in schoolchildren.

## Discussion

This study constituted an attempt to re-evaluate the status of iodine nutrition in European countries by using standardized methods to determine the two main variables defining the degree of iodine deficiency, i.e. thyroid volume measured by ultrasonography and urinary iodine concentration in schoolchildren.

Although our survey included a substantial number of countries, it does not give a picture of Europe as a whole, as all European countries could not be involved because of lack of resources. Similarly, the studies in each country were by no means nationwide and, consequently, not necessarily representative of the country as a whole, as they were limited to a few sites which were occasionally selected on the basis of different criteria. For example, the two sites in Germany which appeared to have a normal iodine intake are not representative for the country which, generally speaking, is still moderately iodine deficient (17, 18). Conversely, the three sites investigated in Poland were selected as being isolated in a former severely endemic goiter area. These three sites are still

severely iodine deficient. This corresponds to the results of a nationwide survey in Poland which evidenced differences in severity between different parts of the country (19). A similar situation has been observed in Romania. By contrast, the three sites investigated in Belgium, which were situated respectively in the Western, central and Eastern parts of the country, showed a uniform degree of iodine deficiency and are probably representative of the whole country. The results obtained in the central part (Brussels area) are unchanged as compared with the results obtained in this area up to 15 years ago (20).

In spite of these limitations, the study gives a fairly good image of the changing pattern of iodine nutrition in Europe, especially considering that the use of the ThyroMobil van and the centralization of the samples for iodine analysis ensured the standardization of the methods used and avoided inter-observer variability, frequently encountered in former collaborative international studies.

The status of iodine nutrition has markedly improved in many European countries as compared with the situation reported in 1992 (9) and is presently entirely normal in schoolchildren in The Netherlands, Slovakia and France. The changes are most probably due to the implementation of programs of salt iodization. In other countries where such programs are not implemented nationwide, the changes could be due to improvement of food habits as a result of nutritional education or to changes in the dairy industry by the use of iodophors.

However, iodine deficiency remains unchanged in some countries such as Belgium where, in spite of the sustained efforts of the IDD National Committee, no legal measures have yet been taken on a national basis.

Moreover, iodine deficiency has not yet been entirely corrected in other European countries in spite of the existence of national programs.

The values reported in this study for thyroid volume measured by echography in iodine-replete schoolchildren are close to the ones reported by Vitti *et al.* (21) in an iodine-replete area in Italy, at least for prepubertal children. However, they are distinctly higher than the ones reported by Gutekunst *et al.* (22) in Stockholm and by Ivarsson *et al.* (23) in Malmo, Sweden, where the iodine intake has been thought to be adequate for a long time. It could be argued that our higher values for thyroid volume in 'normal children' could be explained by the fact that the correction of iodine deficiency is too recent in our iodine-replete sites to allow complete normalization of thyroid volume in children who were possibly moderately iodine deficient during early infancy and childhood (24, 25). However, our values are similar to the ones reported some 10 years ago by Klima *et al.* (26) in children aged 7–11 years in Austria and by Takalo *et al.* (27) in iodine-replete children aged 13 years in Finland where the iodine intake has been optimal for decades. They are also similar, or even lower, than the ones reported in children in Japan (28), where the iodine intake has been elevated for several generations. Further studies of thyroid volume measured by ultrasonography are certainly needed in the USA and in Japan. In the meantime, the 'normal values' proposed by this study are consistent with the view that the prevalence of goiter in schoolchildren is below 5% as long as the urinary iodine is above 10 µg/dl (10). They have been adopted as a reference by the WHO.

In conclusion, this work shows that, in spite of a definite improvement, Europe has not yet succeeded in eradicating IDD. Substantial progress must be made in the implementation of nationwide prophylactic programs. This implies the active commitment of national authorities, which is not always easy to obtain. In the meantime, there remains room in some European countries for the therapeutic supplementation of iodine in the target groups, namely pregnant and lactating women (29) and young infants (30).

This work produced updated recommendations for the normal volume of the thyroid as a function of age, sex and BSA and set the criteria for defining goiter based on ultrasonographic investigation in iodine-replete schoolchildren in Europe.

Finally, this study allowed the proposal of a method for standardized evaluation of iodine nutrition on a continental basis. This method is quite simple and could be expanded on a national basis in all countries under investigation. It could also be easily introduced in other countries in Europe or even in other continents. The last 5 years have been characterized by the massive implementation of programs of salt iodization not only in Europe but also in Asia, Africa

and South America (31). Many of these programs have been remarkably successful but close clinical and biological monitoring is required (32) in order to guarantee the sustainable elimination of IDD without unfavorable side-effects (33, 34).

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