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Iodine Deficiency in Europe anno 2002

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Prof. François Delange is one of the most prominent physicians of his time in the fight against iodine deficiency in the world. As a professor of Pediatrics he became involved in its deleterious effects, especially in children, since the 1960's. His most important and groundbreaking work started in Zaïre (Congo), that he traveled more than 30 times (!) and where he and his collaborators described for the first time the myxedematous type of cretinism. This condition was not recognized before as a separate entity and appeared to be caused by iodine deficiency in combination with a damaged thyroid gland. His group performed numerous field studies that enriched the knowledge about iodine deficiency tremendously. He authored more than 300 peer reviewed publications and edited or contributed to 10 books and chapters. He is a frequently invited speaker and a long-term member of the European Thyroid Association. He has been a board member of the International Council for Control of Iodine Deficiency Disorders (ICCIDD) for many years, being the Regional Coordinator for Europe between 1986–2001 and its Executive Director between 1995–2001. He also was or still is a consultant to many international bodies, including the WHO, UNICEF, IAEA, and other prestigious institutions. He has visited most iodine deficient countries in the world once or more times. His present position in the ICCIDD is that of Board Member and Honorary Executive Director. Furthermore he is still consultant at the Department of Pediatrics, University Hospital Saint-Pierre, Brussels, Belgium. He has been honored several times and received two Honorary Doctorates.



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INTRODUCTION

The disorders induced by iodine deficiency (Iodine Deficiency Disorders, IDD[1]) belong to the history of Europe as only 4 European countries, namely Iceland, Finland, Norway and Sweden, were never exposed to this medical and socioeconomic scourge. Endemic cretinism, the most severe consequence of iodine deficiency, has been extensively reported from isolated and mountainous areas, for example from Switzerland, Austria, Italy, Bulgaria and Croatia[2]. The term «cretin of the Alps» has reached the popular vocabulary.

And yet, surprisingly, only limited attention has been paid to IDD in Europe.

IDD have been entirely eradicated in Switzerland thanks to the progressive implementation and sustained monitoring of a remarkable program of salt iodization initiated in 1922[3]. Probably because of the impact of this program on the medical world and also because legislations on iodized salt had become available in many additional countries, IDD seem no longer to have been considered an important public health problem in Europe during the next decades.

In 1960, the WHO published an exhaustive review on IDD in the world under the heading «Endemic goitre»[4]. Although this document included preliminary reports on Western countries, the information was scanty for the former USSR and especially for the Central Asia Republics[5], which are presently recognized as severely affected[6].

It is only in the late 1980's that the European Thyroid Association, in its reevaluation of the problem, clearly indicated that, with the exception 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]. This survey confirmed a lack of information on IDD from countries of the Eastern part of the continent.

At least in part under the influence of the International Council for Control of Iodine Deficiency Disorders (ICCIDD), a series of major decisive meetings on IDD and their control took place in the early 1990's, including the World Health Assembly (Geneva 1990) the World Summit for Children (New York 1990), the Policy Conference on Ending Hunger (Montreal 1991) and the International Conference on Nutrition (Rome 1992)[8]. At these meetings, most affected countries, WHO and UNICEF committed themselves to the virtual elimination of iodine deficiency disorders in the world, including in Europe, by the year 2000. In 1994, WHO, UNICEF and ICCIDD jointly published (and later updated) a technical document entitled «Indicators for assessing iodine deficiency disorders and their control through salt iodization». It has become the reference document for members of the health system, salt industry and national and international organizations and agencies in charge of the elimination of the disorders[9,10].

A next crucial evaluation of IDD in Europe took place in 1992: An international workshop entitled «Iodine deficiency in Europe: a continuing concern»[11] was organized in Brussels by the author of the present report and his colleagues. One representative from each European country summarized the latest IDD data from his country including the preventive measures. A report on the workshop has been produced in a former issue of Thyroid International[12]:

in 1992, iodine deficiency was under control in only 6 countries, namely Iceland, Finland, Norway, Sweden, Switzerland and Austria.

In 1997, a follow-up meeting entitled «Elimination of Iodine Deficiency Disorders (IDD) in Central and Eastern Europe, the Commonwealth of Independent States, and the Baltic States» was organized in Munich under the auspices of ICCIDD, UNICEF and WHO[6]. It provided an overview of IDD status, control programs and salt supplementation in the 28 countries of this part of the world. It emphasized the severity of the problem in many parts of Eastern Europe, including recurrence of goiter and occasionally of endemic cretinism in some countries such as Russia after interruption of former programs of salt iodization. The governments of the affected countries, their national delegates, the regions and sub-regions, agencies and non-governmental organizations all received appropriate recommendations. This meeting triggered massive efforts in the implementation or restitution of iodized salt programs, mainly by UNICEF with the financial support of Kiwanis International.

The objective of the present paper is to provide updated information on the status of iodine nutrition in the European region.

METHODS

This review is based mostly on the compilation of publications in peer reviewed journals and occasionally on information kindly provided as personal communications by prominent personalities in the field of IDD in the different European countries. These colleagues are usually also the national focal points of ICCIDD in their respective countries.

This paper provides also updated information on the regulations governing the use of iodized salt and marked shares of iodized household salt in Western and Central Europe. For this part, the information has been largely collected by Mr. Bernard Moinier, Secretary of the European Salt Producers Association, ESPA. Generally speaking, the part of the present review on Western and Central Europe constitutes a further development of a preliminary report on IDD in Europe prepared by F. Delange, H. Bürgi and B. Moinier and which is presently in press. The information on IDD and its control in Eastern Europe has been kindly provided by Doctor Gregory Gerasimov.

This review paper provides essentially clinical data such as the prevalence of goiter and the urinary iodine concentrations. Thus, it evaluates the present status of iodine nutrition. It will conclude that a country can be considered as iodine sufficient if,

Table 1. Epidemiological criteria for assessing iodine nutrition based on median urinary iodine concentrations in school-aged children

Median urinary iodine (µg/L)	Iodine intake	Iodine nutrition
< 20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Optimal
200–299	More than adequate	Risk of iodine-induced hyperthyroidism within 5–10 years following introduction of iodized salt in susceptible groups
> 300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid diseases)

From WHO/UNICEF/ICCIDD[10]

based on a national survey, the prevalence of goiter in the country is below 5 % and the median urinary iodine is within the normal range, i.e. between 100 and 200 µg/l[10] *(Table 1)*. A median above 200 µg/l is more than adequate with possible risks of side effects. The data presented in this report will not allow to state that iodine deficiency has been eliminated in a given country as the criteria proposed by WHO, UNICEF and ICCIDD[10] for reaching this conclusion are more exhaustive, including a proportion of household using adequately iodized salt above 90 %, less than 50 % of the urine samples containing below 100 µg/l iodine and at least 8 of 10 programmatic indicators dealing essentially with the administrative and political aspects of the organization of the programs at country levels. Interestingly enough, the prevalence of goiter has even disappeared from these criteria, essentially because the emphasis is put on the implementation of programs of iodized salt and probably also because of the uncertainties on the criteria used for establishing universal normative values for thyroid volume measured by ultrasound, and consequently for estimating the prevalence of goiter[13].

RESULTS

In 1999, WHO, UNICEF and ICCIDD reported that 18 countries in Western and Central Europe and 14 countries in Eastern Europe were still affected by iodine deficiency[14] *(Table 2)*. But data from the literature indicate that three additional countries in Western Europe, were also affected, namely Denmark[15], France[16] and Ireland[17], which makes a total of 21 affected countries in this part of the continent.

Control of IDD in these 35 countries has markedly improved even during the very recent years:

1. Western and Central Europe.

Table 3 summarizes the results of the latest nationwide evaluations of the prevalence of goiter and of the concentrations of urinary iodine in Western and Central Europe. Such surveys were conducted in 17 of the former 21 iodine deficient countries. As recommended by WHO/UNICEF/ICCIDD[9,10], most surveys were conducted in school-aged children (SAC). The prevalence of goiter was derived from measurements of thyroid volumes by ultrasound. Almost all urinary iodine assays were measured by using the colorimetric method of Sandell-Kolthoff[18]. Consequently, the results can be reasonably compared from one country to another.

An interesting case is Denmark, the only country in which iodized salt was prohibited until 1999[15,19]. Paradoxically, it was the high incidence of hyperthyroidism in the elderly (due to autonomous nodules in multinodular iodine deficiency goiters) that constituted the starting point for a very cautiously monitored program of salt iodization[15]. Germany was the first country to use a method of standardized

Table 2. European countries affected by Iodine Deficiency in 1999

Western and Central	Eastern, CIS* and Baltics
Albania	Armenia
Belgium	Azerbaijan
Bosnia Herzegovina	Belarus
Bulgaria	Estonia
Croatia	Georgia
Germany	Kazakstan
Greece	Kyrgyzstan
Hungary	Lithuania
Italy	Moldova
Luxembourg	Russian Federation
Macedonia	Tajiskistan
Poland	Turkmenistan
Portugal	Ukraine
Romania	Uzbekistan
Slovenia	
Spain	
Turkey	
Yugoslavia (Serbia)	

* CIS: Commonwealth of Independent States.
Adapted from WHO/UNICEF/ICCIDD[14]

Table 3. **Latest nationwide evaluations of iodine nutrition in Western and Central Europe**

Country	Year(s) of the survey(s)	Design, patients and methods	Findings	References
Belgium	1998	National survey Thyroid volume by ultrasound (criteria: Delange et al. 1997[55]) and UI in 2,855 SAC aged 6–12y from 23 sites.	TGR: 5.7 % (18.4 % in girls aged 12 y). Median UI: 80 µg/l < 100 µg/l: 67 % < 50 µg/l: 19 % Homogeneous. No gradient.	Delange et al. 1997[56] Delange et al. 2000[23]
Bosnia-Herzegovina	1999 (?)	National survey Prevalence of goiter (palpation) and UI in 5,523 SAC aged 7–14 y from all cantons	TGR:12.9 %–51.2 % Global UI <100 µg/l: 70 % < 50 µg/l: 34 %	Tahirovic et al. 2001[57]
Bulgaria	1998–2001	National survey: TGR and UI in 9,045 SAC aged 7–11 y.	TGR: <5–28 % (Total 13 %) Median UI: 88–165 µg/l National: 111 µg/l	Ivanova et al. 2000[58] Lozanov 2001[59]
Croatia	1995	National survey. TGR (palpation) and UI in 2,856 SAC.	TGR: 11–35 % Median UI: < 100 µg/l: 66–91 % < 50 µg/l: 14–52 %	Kusic et al. 1996[60]
	1996	National survey: TGR and UI in 2,054 SAC aged 7–11 y.	TGR: 5–18 % (Mean: 15 %) Median UI: < 100 µg/l: 30–59 % < 50 µg/l: 5–22 %	Antonic et al. 2000 (61)
	2002	Thyroid volume (US using the adapted Delange et al. criteria[13]) and UI in 540 SAC from four regional centers	Thyroid volume within the normal range Median UI: 131–147 µg/l < 100 µg/l: 24.7–32.8 % < 50 µg/l: 5.7–11.9 %	Kusic Personal communication
Czech Republic	2001	Thyroid volume (US) and UI in 467 randomly selected persons aged 6–65y.	Mean thyroid volume in adults: 15.7 ml Mean UI in: adults: 140 µg/l children: 168 µg/l < 50 µg/l: 1.1 %	Zamrazil, personal communication
		National survey Thyroid volume (US) and UI in ± 5000 children (6–13y), adolescents (14–18y) and adults (18–65y)	Mean thyroid volume Adults: 15.2 ± 7.4 (SD) ml Children: 4.5 ± 2.2 (SD) ml UI: Adults: 114 ± 57 (SD) µg/l Children: 136 ± 67 (SD) µg/l	Zamrazil 2000[62]
Denmark	1998–1999 (?)	Measurement of the iodine content of drinking water from 55 locations	Medians vary from <1 to 139 µg/l National median: 41 µg/l Correlation with 24-h UI measured in 1967 by Munkner[64]	Pedersen et al. 1999[63] Munkner 1969[64]
	1993–1999	TGR and UI measured in different locations and age groups	TGR in 391 women aged 15–60y: 17 %. Goiter stage II in 60-y old women: 3 %. Thyroid enlargment in 13.1 % of females and 6.2 % of males. Multinodular structure of the thyroid in 23 % of the population and solitary cold nodules in 2.4 %. Median UI vary from 38–110 µg/l Iodine intake stable over the last 30–40 years;	Nygaard et al. 1993[65] Knudsen et al. 2000[66] Knudsen et al. 1999[67]

Table 3 continued

Country	Year(s) of the survey(s)	Design, patients and methods	Findings	References
			Median UI in neonates vary from 16 to 59 µg/l (National median: 32 µg/l) and are correlated with the iodine content of breastmilk (22–55 µg/l).	Nohr et al. 1994[68]
	?	Thyroid volume, UI, serum TSH, T_4, T_3 Tg in 54 pregnant women and their neonates in east Jutland (UI:50 µg/L)	Serum TSH and Tg increase during gestation and are elevated on cord. Prevented by iodine supplementation.	Pedersen et al. 1993[69]
	1996–1997 (?)	Comparative epidemiological study of thyroid abnormalities in the elderly in Iceland (median UI 150 µg/L) and in Jutland (median UI 38 µg/L). n = 100 in Iceland ; 423 in Jutland. Mean age: 68 y.	Serum TSH < 0.40 mU/l: 9.7 % in Jutland (range: < 0.01 to 0.40) ; 0 % in Iceland. Serum TSH > 0.40 mU/l: 3.8 % in Jutland ; 18 % in Iceland.	Laurberg et al. 1998[70]
France	1999	National survey (SUVIMAX) TGR by ultrasound (method not described) and UI in 7,154 women and 4,860 men aged 35–60 y.	TGR: 13.9 % in women ; 11.3 % in men National median UI: 85 µg/l < 50 µg/l: 15–23 %	Valeix et al. 1999[16]
Germany	1993–1994	Thyroid volume determined by ultrasound and TGR in 5,932 individuals aged 1–89 y in 32 regions. Goiter defined by thyroid volume above 18 ml in adult females and 25 ml in adult males.	TGR in adults 18–70 y: 49 % in women and 51 % in males (NS) Frequency of thyroid nodules: 30% in women and 21 % in men (P < 0.001) Gradient North to South West to East	Hampel et al. 1995[20]
	1994–1995	Measurement of iodine content of food, urines, breastmilk and of thyroid volume by ultrasound in SAC	Iodine intake of adults increased from 46–66 µg/day to 99–139 µg/day. Iodine content of breastmilk increased from 36 µg/l in 1990 to 95 µg/l in 1995. UI in SAC reached 101 µg/g creat but TGR changed much less	Meng and Schindler[71]
	2000 (?)	National survey UI in 3,065 SAC aged 6–12 y from 128 sites	National median UI: 148 µg/l < 100 µg/l: 27 % < 50 µg/l: 7 % Homogeneous. No gradient	Hampel et al.[72]
Hungary	1994–1997	National survey TGR (palpation) and UI in 299,351 SAC aged 7–11 y.	National TGR: 15 % Median UI: 40–130 µg/l (+ 1 site: 250 µg/l) < 100 µg/l: 25–92 %	WHO, Dept. of Nutrition for Health and Development (NHD), personal communication
Italy	1978–1991	National survey including 71,112 SAC aged 6–14 y. Determination of the prevalence of goiter (palpation), UI and thyroid function.	TGR: 4–60 %. Below 5 % in only one site in one province. Urinary I/creat. ratio varies from 10 to 122 µg/g and is below 100 in 12/16 provinces examined. Serum TSH and T_4: within the normal range except in endemic areas (Sicily, Trentino Alto-Adige). Serum Tg can be elevated in the absence of elevated TSH	Pinchera et al. 1995[73]
	?	Neonatal thyroid screening in Calabria (22,384 infants)	Blood TSH > 5 mU/l in 14.4 %	Costante et al. 1997[74]
	?	Spectrum of thyroid disorders in Pescopagano (UI: 55 µg/l)	TGR: 16 % in children ; 59.8 % in adults. Thyroid nodularity: 0.5 % in children; 28.5 % in adults. Prevalence of hyperthyroidism in adults: 2.9 %.	Aghini-Lombardi et al. 1999[36]

Table 3 continued

Country	Year(s) of the survey(s)	Design, patients and methods	Findings	References
	?	Multicentre study on UIE in 1789 individuals from 28 centers (319 newborns and their mothers ; 223 infants aged 1–3 months ; 857 SAC aged 8–10 y).	Median UI: Newborns: 73 µg/l Mothers: 55 µg/l Infants: 69 g/l SAC: 122 µg/l (< 50 µg/l in SAC: 14 %)	Rapa et al. 1999[75]
Luxembourg	1999	National survey UI in 495 SAC aged 12–14 y.	National median: 77 µgI/g creat <100 µgI/24h: 60 %	Wagener and Hoffmann Personal communication
	2001	National survey UI in 514 SAC aged 12–14 y.	National median: 85 µgI/g creat.	Wagener and Hoffmann Personal communication
Macedonia	1995–1996	National survey: TGR (palpation + ultrasound) and UI in 11,486 SAC aged 7–15 y from 115 schools in 30 clusters.	TGR (n=11,486): 8–30 % (Mean:19%) Median UI (n=2,380) 117 µg/L < 100 µg/L: 26 % < 50 µg/L: 0 %	Karanfilski et al. 1998[76]
	2001	National survey: TGR and UI in 929 SAC aged 8–10 y. in 30 clusters and in 490 pregnant and lactating women	National TGR: 5 % Median UI: 165 µg/l < 100 µg/l: 16 % < 50 µg/l: 3 % UI in pregnant and lactating women 140 µg/l < 100 µg/l: 25 %	Karanfilski. Personal communication
The Netherlands	1995–1996	Thyroid volume by palpation and ultrasound (national reference values) and UI in 937 SAC aged 6–18y in two study sites, one of them in a formerly iodine deficient area.	TGR by palpation: 0.8 % and 2.6 % respectively. TGR by ultrasound: < 5 % Median UI: 154 µg/l	Wiersinga et al. 2001[77]
Poland	1999	Thyroid volume by ultrasound (criteria Delange et al. 1997[55]) and urinary iodine in 884 SAC aged 6–15 y from 12 primary schools in selected areas based on previous endemicity established during a national survey in 1994.	1994 | 1999 TGR 38.4 % | 7.0 % UI (µg/l) mean 60 | 96 % < 100 87 % | 64 %	Szybinski et al.[49]
Romania	1999–2002	National survey: SAC aged 6–16 y: TGR in ± 50,000 from all 41 counties UI in 7,509 from 30 counties Pregnant women: UI in 1,066 samples from 12 counties	SAC TGR: 5.2–22.0 % UI: > 100 µg/l: 6.3 % < 50 µg/l: 28.7 % (Barely unchanged as compared to survey in 1991–1992) Pregnant women UI > 100 µg/l: 0 % 50–100 µg/l: 84.0 % < 50 µg/l: 16.0 %	Simescu and Sbranca Personal communications
Slovakia	1994	UI in 900 children and adolescents	Median UI: 144 µg/l	Podoba Personal communications
Turkey	1997–1999	National survey: TGR (ultrasound, Delange et al. criteria (55)) and UI in 5,948 SAC aged 9–11 y from 20 city centers.	TGR: 6–58 % (Mean: 32 %) Median UI: 14–62 µg/l.	Erdogan et al. 2002[52]

TGR: Total Goiter Rate. UI: Urinary Iodine. SAC: School-aged children. US: Ultrasound. NS: Non significant difference.

evaluation of thyroid volume and prevalence of goiter by ultrasound[20]. This « ThyroMobil model » was further fitted for systematic collection of urine samples for iodine determination. It turned out to be one of the most efficient instruments for monitoring progress towards the elimination of IDD[21]. The Netherlands reached adequate iodine nutrition after phases of iodization of water and salt, especially for the bakery industry[22]. Belgium[23] and France[16] are among the very few European countries with no enforced programs of salt iodization so far and which remain similarly affected by mild iodine deficiency. Croatia, Macedonia, Poland and Turkey recorded substantial progress, especially after salt iodization was declared mandatory. In addition to the results of national surveys, local or regional studies on iodine nutrition showed spectacular progression towards iodine sufficiency in Greece[24] but persistence of pockets of iodine deficiency in Portugal[25] and Slovenia[26]. No data were available from Albania.

In summary *(Table 4),* based on the data from the literature, it can be considered that in 2002, 14 of the 31 countries of Western and Central Europe have reached a normal status of iodine nutrition. These countries are Austria, Bulgaria, Croatia, Czech Republic, Finland, Germany, Iceland, Macedonia, The Netherlands, Norway, Slovakia, Sweden, Switzerland and the United Kingdom (Although the data from the UK do not conclusively show national iodine sufficiency)[27]. Another three countries, namely Greece, Poland and Serbia, are close to iodine sufficiency. IDD persist in 13 of other countries: Belgium, Bosnia, Denmark, France, Hungary, Ireland, Italy, Luxembourg, Portugal, Romania, Slovenia, Spain and Turkey. Finally, data are missing for Albania. Thus, the data indicate a spectacular progress in the control of IDD as within the last ten years, i.e. between 1992 and 2002, the number of countries with iodine sufficiency increased from 6[11] to 14 and possibly to 17.

2. Eastern Europe and Central Asia

Doctor Gregory Gerasimov has very recently updated the information on IDD and their control through salt iodization in 15 countries of Eastern Europe and Central Asia, including 12 countries of the Commonwealth of Independent States (CIS) and the three Baltic States (BS) (Gerasimov, unpublished). This update is based not only on published reports but also on unpublished information, including country reports, data from agencies and personal communications. National IDD surveys were conducted in Armenia, Azerbaijan, Belarus and Uzbekistan. Regional surveys were conducted in Kazakhstan, Kyrgyzstan and Turkmenistan. A national baseline IDD survey is planned in Ukraine for 2002.

These different surveys indicate that substantial progress has been made in the region in the evaluation of the IDD status, in expanded production, supply and use of iodized salt. Some countries such as Armenia and Turkmenistan are very close to virtual elimination of IDD. However the goal of IDD elimination by the year 2000 has not been reached and additional efforts are needed to combat iodine deficiency in this part of Europe.

Table 4. Status of IDD Control in Western and Central Europe 2002. Summary.

Total number of countries in the region	31
Countries with nationwide evaluation of IDD during the past 10 years	17
Marked or slight improvement of iodine nutrition in most countries	
Countries with present iodine sufficiency (?)	14
Countries close to iodine sufficiency	3*
Countries with persisting IDD	13
Countries with no data on IDD available	1**

* Greece, Poland, Serbia ** Albania

PUBLIC HEALTH CONSEQUENCES OF IODINE DEFICIENCY IN EUROPE

The state of mild to severe iodine deficiency persisting in many European countries has important public health consequences, including on the intellectual development of infants and children. As an example, *Table 5* summarizes the situation in Belgium where the consequences of mild iodine deficiency on the main target groups, i.e. pregnant and nursing women, neonates and young infants, have been extensively investigated.

More generally speaking, the consequences of iodine deficiency in Europe can be summarized as follows:

In adults: the frequency of simple goiter is elevated in many countries and the cost of therapy of thyroid problems resulting from iodine deficiency in the adult population is enormous. For example, the cost for the diagnosis and treatment of goiter due to iodine deficiency in Germany for the year 1986 was estimated at 900 million DM (approximately 500 million $, or 8 $ per inhabitant per year)[28] while prevention by iodized salt would cost only 2–8 US cents per inhabitant and per year[29]. Thyroidal uptake of radioiodine varies markedly from one European country to another and is inversely related to the iodine intake[30]. Elevated thyroidal uptake due to iodine deficiency aggravates the risk of thyroid irradiation and development of thyroid cancer in case of a nuclear accident[31]. The best prophylaxis of nuclear hazards in case of radioiodine fallout is to increase the basal intake of iodine of the population[32].

Thyroid function is usually normal in young adults in European countries with borderline or low iodine supply. By contrast, it is frequently altered during pregnancy, when three synergistic mechanisms stimulate the thyroid gland: a) direct stimulation by the human chorionic gonadotropin, b) stimulation by TSH which rises because the higher thyroxine-binding globulin concentration lowers the free thyroxine, and finally, c) the overall enhancing role of limited iodine availability[33]. At least under conditions of borderline iodine intake, pregnancy is accompanied by a progressive decrease of serum free T_4 and consequently by an increase of serum TSH. This state of chronic TSH hyperstimulation results in the development of goiter in about 10 % of the pregnant women and in a progressive increase in the serum concentration of thyroglobulin. Goiter can persist after pregnancy in an important number of women[34]. Pregnancy, especially in conditions of borderline iodine intake, at least partly explains the higher frequency of thyroid problems in women than in men.

The consequences of marginal iodine deficiency during pregnancy in Belgium on the thyroid function of the neonate include even more elevated serum levels of TSH and thyroglobulin in cord blood than in the mothers and a slight enlargement of the thyroid gland[33]. The role played by iodine deficiency in these changes is demonstrated by the fact that they are prevented by iodine supplementation of the mothers during pregnancy[35] and that they do not occur in iodine replete areas in Europe such as The Netherlands[36].

Another consequence of longstanding iodine deficiency in the adult is the development of hyperthyroidism, especially in the elderly with multinodular goiters and autonomous nodules[15,37-39]. The mechanism involved is, as for iodine-induced hyperthyroidism, acceleration of thyrocytes proliferation which, in turn, triggers the development of cell clones harbouring activation mutations of the TSH receptors. It thus appears that both spontaneous and iodine-induced hyperthyroidism constitute additional aspects of the disorders induced by iodine deficiency.

In adolescents and children: Euthyroid pubertal goiter is especially frequent in adolescents and occasionally requires substitutive therapy by T_4 or iodide. Iodine metabolism is accelerated during this period of life[40].

A very important issue is that clinically euthyroid schoolchildren born and raised in moderately iodine deficient regions of Europe exhibit subtle or even overt neuropsychointellectual deficits when compared to iodine-sufficient controls living in other-

Table 5. **Functional consequences of mild iodine deficiency in Belgium**

Age groups	Recommended iodine intake (µg/day) WHO et al. 2001[10] US Ac. Sciences 2002[78]	Recommended urinary iodine concentration (µg/L)	Actual urinary iodine concentration (µg/L)	Functional consequences
Pregnant and lactating women	200	200–300	< 100 in 90 % of the cases	Increased thyroid stimulation. Goiter. Prevention of the anomalies by iodine supplementation Iodine content of breastmilk: 98 ± 5 µg/L (Mean ± SEM). Normal: 140-180 µg/L
Adults	150	100–200	51–60	Elevated thyroidal uptake of radioiodine. Increased risk of thyroid irradiation in case of nuclear accident
Adolescents	150	100–200	30–50	«Puberty» goiter
Children 6–12 years	120	100–200	55–80	Goiter (by ultrasound, method Delange et al. 1997[55]) 3.9-7.7 % (18.4 % in girls aged 12 years).
Infants 6–36 months	90	180–220	101 < 200 in 81 % of the cases	Risk for future intellectual development
Neonates	90	150	48–86 < 100 in 68 % of the cases	Elevated serum TSH and Tg on cord Blood. Thyroid hyperplasia. Until recently, elevated serum TSH and risk of transient neonatal hypothyroidism

Adapted from references [23, 33–35, 43, 56, 68, 79–82].

wise identical ethnic, demographic, nutritional and socio-economic populations. These deficits are of the same nature, although less marked, than those found in schoolchildren in areas with severe iodine deficiency and endemic mental retardation[41]. As demonstrated in severe iodine deficiency, these deficits most probably result from transient thyroid failure occurring during foetal or early postnatal life, i.e. during the critical period of brain development.

In neonates: The most important and frequent alterations of thyroid function due to iodine deficiency in Europe occur in neonates and young infants:

1) The frequency of transient primary hypothyroidism is almost 8 times higher in Europe than in North America[42]. This syndrome is characterized by postnatally acquired severe primary hypothyroidism lasting for a few weeks and requiring substitutive therapy[43]. The risk of transient hypothyroidism in the neonates increases with the degree of prematurity[44]. The specific role played by iodine deficiency in the etiology of this type of hypothyroidism is demonstrated by the disappearance of neonatal transient thyroid failure in Belgian preterms since they were systematically supplemented with 30 µg potassium iodide/day.

2) There is an inverse relationship between the urinary iodine concentrations in newborn populations in Europe and the frequency of serum TSH above 50 µU/ml at day 5, at the time of screening for congenital hypothyroidism[45], when it constitutes the criterion for recalling the babies under suspicion of congenital hypothyroidism. Consequently, the recall rate of neonatal thyroid screening appears as a particularly sensitive index of the presence of goitrogenic stimuli in the environment and neonatal thyroid screening can be used for monitoring iodine prophylaxis at a population level[46].

The reason for the particular sensitivity of newborns to the effects of iodine deficiency is their low iodine content of the thyroid with an extremely fast turnover rate of intrathyroidal iodine. By contrast, in adults, iodine deficiency, unless severe, does not affect the iodine stores of the thyroid[45].Therefore, thyroid failure is more likely to occur in neonates than in adults in conditions of iodine deficiency.

PREVENTION AND THERAPY OF IDD IN EUROPE

It is hard to accept that iodine deficiency, the most common preventable cause of mental deficiency in the world today[9], is still prevalent in Europe. The main cause of this situation is the lack of awareness and consequently of appropriate action by health authorities, including the medical doctors, and the public at large.

The strategy for the elimination of iodine deficiency in Europe must start with information and health education through appropriate channels, not only of the public, but also of the health professionals . Consumption of seafood, the main dietary source of iodine, must be encouraged, but is of limited value.

The major measure for the prevention of IDD in Europe clearly is through Universal Salt Iodization (USI), i.e. the fortification of all salt for human and animal consumption and for the food industry[9,10,29]. Possible side effects of iodine supplementation delivered by salt should be openly addressed, but without causing undue concern[47,48]. Also, programs should clearly avoid the impression that they do advocate a higher salt intake.

In 1992, iodized salt was available in most European countries, usually nation-wide, with the exception of Denmark where it was prohibited up to 1999[19]. It was compulsory in 8 countries, including Austria, and voluntary in all the others, including Switzerland. The price was most usually barely higher than non iodized salt; it was even lower in France.

From 1992 onwards, and especially following the endorsement by WHO Euro of the recommendations resulting from the Brussels meeting[11] to appoint national iodine committees in all countries and to promote the use of iodized salt, quite significant progress has been achieved in many European countries *(see Table 6)*. National programs have been organized, which could result, as for example in Poland[49], in an exhaustive re-evaluation of the situation and in practical measures aiming at the implementation of USI.

The level of iodization of salt must be adapted at regular intervals to compensate for changing salt intake. For example, in Switzerland, because of the progressive decline in salt intake, the iodine intake slightly decreased in the seventies. In 1980, the level of salt iodization was therefore increased from 7.5 to 15 ppm. This resulted in an increase of iodine intake from a borderline value of 90 µg/day to a perfectly adequate value of 150 µg/day. Rather unexpectedly, this change was not accompanied by any significant increase in the incidence of iodine-induced hyperthyroidism but rather, by a steady decline in the incidence of both toxic nodular goiter and Graves' disease[50]. European countries which are actually in a state of moderate iodine deficiency thus may expect to make the transition to iodine sufficiency not only with no ill effects, but with the unexpected large benefit of a marked decrease of the incidence of hyperthyroidism in the elderly in addition to the disappearance of euthyroid goiter[15,37–39].

In their report published in 1999[14], WHO/UNICEF/ICCIDD indicated that iodized salt was then available in all 18 iodine deficient countries in Europe and that legislations on iodized salt were available in 12 of them.

Table 6 summarizes the latest information available on the use and legal status of iodized salt in Western and Central European countries. Most countries have created a legal basis or even established a monitoring and/or promotional program. Iodized salt is now compulsory in 12 countries. It is voluntary in 17, and the status of enforcement is unknown in the last

Table 6. **Regulations governing iodised salt in Western and Central Europe and market shares of iodized household salt**

	Latest revision	Legal status	Compound (iodate or iodide)	Iodine amount (ppm)	Market share of household salt (%)
Albania	1999		(iodide)	(25)	56
Austria	1999	C	both	15–20	95
Belgium	1992	V	both	6–45	(10)
Bosnia	1998	C	iodide	5–15	(37)
Bulgaria	1997	C	iodate	22–58	90
Croatia	1999	C	iodide	25	90
Czech Republic	1999	C	iodate	20–34	90
Denmark	1999	V	iodide	8–12	
Finland	1998	V	iodide	25	>90
France	1997	V	iodide	10–15	55
Germany	2001	V	iodate	15–20	84
Greece	2000	V	iodide	40–60	18
Hungary	1999	C	both	10–20	
Ireland	1992	V	iodide	25	
Italy	1997	V	both	24–42	3
Luxembourg	2000	V	both	10–25	
Macedonia	1999	C	iodate	20–30	100
The Netherlands	1999	V	both	30–40 househ. 70–85 bakers	(60)
Norway	1992	V	iodide	5	
Poland	1999	C	iodide	20–40	(90)
Portugal	1996	V	iodate	25–35	I
Romania	2002	C	iodate	34±8	25
Slovakia	1999	C	iodide	15–35	85 (imports; 70)
Slovenia	1998	C	iodide	5–15	
Spain	2000	V	both	51–69	(16)
Sweden	1999	V	iodide	40–70	
Switzerland	2002	V	both	20–30	94
Turkey	1999	V	both	25–70	20–30
United Kingdom	1992	V	Iodide	10–22	2
Yugoslavia (Serbian Rep.)	2000	C	Iodide	20	73

V: voluntary. C: compulsory. Information in brackets is tentative. Void cases: no information available.
Updated from F. Delange, B. Moinier and GH. Bürgi (unpublished).

2 countries, Albania and Iceland. 15 countries require iodide, 6 require iodate, and 9 countries allow both iodide and iodate. The level of salt iodization for household salt ranges from 5 to 70 ppm. The figures for the market share of iodized packed salt sold to the households vary from 1 % in Portugal to at least 90 % in Austria, Bulgaria, Croatia, the Czech Republic, Finland, Macedonia and Poland. These figures must be considered with great caution, since salt producers unwillingly divulge sales figures, and regular household surveys are tedious to perform. Even when iodized salt is enforced by law, its market share may remain low, because of lack of political will, non-compliance of retailers, distribution of cottage-salt or low price imports. Market shares for the salt for food industry are even more difficult to estimate. The staggering diversity of legal arrangements shown in Table 6 results from several factors:

- Enforced use of iodized salt facilitates the management of a program, but in many countries it is unacceptable on constitutional grounds.
- Even though iodate is preferable because of its greater stability, many countries have had no problem with iodide or even prefer it, because it is cheaper, and because the long-term safety of iodate should be established according to actual standards[51].
- Iodine intake may vary from one country to another, depending on dietary habits and legal provisions *(Table 3).* In highly industrialized countries, the share of household salt is smaller, because most salt comes from pre-processed food bought in supermarkets.
- It is clearly preferable to have all salt for human consumption (i.e. household and food industry) iodized, but some countries find it difficult to enforce iodized salt on food industry.

Clearly then, international European legislations would be of great help but presently, in spite of efforts of representatives of individual countries or of the salt industry, the European Union has not issued global recommendations or legislations on iodized salt in Europe. Rather, the Union has issued a draft guideline which would allow direct supplementation (i.e. not via salt) of food with iodine. This would not allow the judicious dosing and necessary control of iodine supplementation that iodized salt affords. If enacted, this guideline would be a disaster for iodized salt programs and for monitoring iodine nutrition in Europe.

As long as USI is not systematically implemented in Europe, special attention has to be devoted to the protection of the two main target groups to the effects of iodine deficiency, i.e. pregnant and nursing women, neonates and young infants. If iodine deficient, these age groups should be supplemented with physiological quantities of iodine, for example by including iodine to the multivitamins prepared for them. Moreover, the iodine content of formula milk should be increased in Europe above the classical recommendation of 5 µg/dl. The present recommendations, endorsed by WHO Euro and by ICCIDD, are 10 µg/dl milk for fullterms and 20 µg/dl for preterms[11].

In some European areas affected in the past by overt endemic cretinism, iodine deficiency was and remains severe, for example in parts of Turkey[52] and Romania (unpublished), with impairment of neonatal thyroid function and, consequently, with potentially harmful consequences for brain development. In such situations, emergency and transient more drastic measures can be justified from a public health point of view, such as the oral administration of iodized oil.

It is now demonstrated that in many industrialized countries such as the United States, Great Britain and Northern European countries, the main source of dietary iodine is neither iodized salt nor seafoods but dairy milk[27]. This results either from the use of iodophors in the industrial processing of milk or from iodine supplemented diets for the animals, or from both. European rules for monitoring the iodine content of milk and a precise evaluation of the possible role of milk as a substrate for iodine supplementation in Europe are desirable.

Iodinated water has proved to be efficient in the control of iodine deficiency in developing countries in situations where iodized salt is hard to implement,

where the access to water is well localized, for example by wells, and where most of the water is used for human and animal consumption (Review in ref. 53). These conditions are probably rarely met in European countries.

Finally, it is conceivable that in exceptional circumstances where iodide or iodate are not accepted as sources of iodine for salt iodization for personal reasons, the use of natural seaweeds as a source of iodine could be considered[54].

CONCLUSION

This review underlines major improvement of iodine nutrition in Europe. However, the goal of sustainable elimination of IDD has not yet been reached, especially in Eastern Europe. In 1999, Europe was the less efficient region in the world in terms of access to iodized salt at household level in iodine deficient countries[14]. In spite of the progress achieved since, further efforts have to be developed in order to insure the recommended daily intake of iodine for age in all inhabitants of Europe, i.e. 90 µg/day from 0 to 59 months, 120 g/day between 6 and 12 years, 150 µg/day in adolescents and adults and 200 µg/day in pregnant and lactating women[10]. This has to be achieved principally through implementation of efficient programs of salt iodization without undue concern to the possible side effects of the increase of iodine intake[47,48].

The main impact of iodine deficiency is on pregnant and lactating women and young infants due to the role of maternal, fetal and neonatal hypothyroxinemia in the development of brain damage resulting in irreversible mental retardation[55]. In addition to programs of salt iodization in iodine deficient populations, iodine supplementation to these target groups have to be considered temporarily in iodine deficient populations until programs of salt iodization have insured normal iodine stores within the thyroid of females during the child bearing age and consequently of the pregnant and lactating women and of their fetuses and young infants.

Iodine deficiency is the leading cause of potentially preventable mental retardation in childhood. Its elimination is within reach and would constitute an unprecedented public health success in the field of non communicable diseases. Additional efforts have to be developed in Europe in order to reach the goal of sustainable elimination of iodine deficiency. These include communication and education at all levels resulting in increased political will and coordination of the legislations on iodine supplementation, regular monitoring of iodine nutrition, increased protection of mother and child and concern about uncontrolled iodine supplementation by food fortification.

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1. The prize is to exclusively and directly honour special scientific work in the field of the thyroid gland and serves also to recognize and encourage young scientists. Euro 10,000 per year are available. In exceptional cases, the jury may decide to divide the prize.

2. Young scientists who are domiciled in Europe and have not completed their 40th year of life may apply for the prize. Employees of industrial firms are exclused. The candidates are to hand in manuscripts of (original plus nine copies) their as yet unpublished works to the President of the German Society of Endocrinology by October 31 of the year prior to the prize-giving.

3. In addition to basic research, work involved in both diagnostic as well as therapeutic problems in this specific field also may be considered for the prize. The submitted reports must not exceed 25 type-written pages à 30 lines. The number of figures and tables is to amount to no more than 1/3 of the complete report. The manuscript, in either English or German, must be drawn up according to the regulations of a scientific journal. All rights are exclusively in the control of the author. After confirmation of receipt, the author may offer his work to a journal for publication.

4. The prize project should not include more than two authors. If more authors have cooperated in a project, the team should decide on the two main authors to be named for the prize project; if necessary, the remaining authors must give their consent in writing. The curriculum vitae stating the scientific career of the author(s) must be enclosed with the prize project. The author(s) must affirm in writing that at the time of submission the manuscript had not been published or handed in for publication in a journal (exception: published abstracts).

5. A jury decides on who is to receive the prize. The jury may decide not to donate the prize if the manuscripts received are not worthy. The decision of the jury is mandatory for all participants and is not subject to judicial inquiry. If not awarded, the prize may in exceptional cases be made available in the following year for additional manuscripts which are worthy.

6. The jury comprises: The President and two members of the Board of the German Society of Endocrinology, the speaker and two members of the Thyroid Section nominated by the Board of the German Society of Endocrinology and one representative from the Pharmaceutical Section of Merck KGaA, Darmstadt. Other experts (without the right to vote) may be included in the assessment. The chairman of the jury is the President of the German Society of Endocrinology.

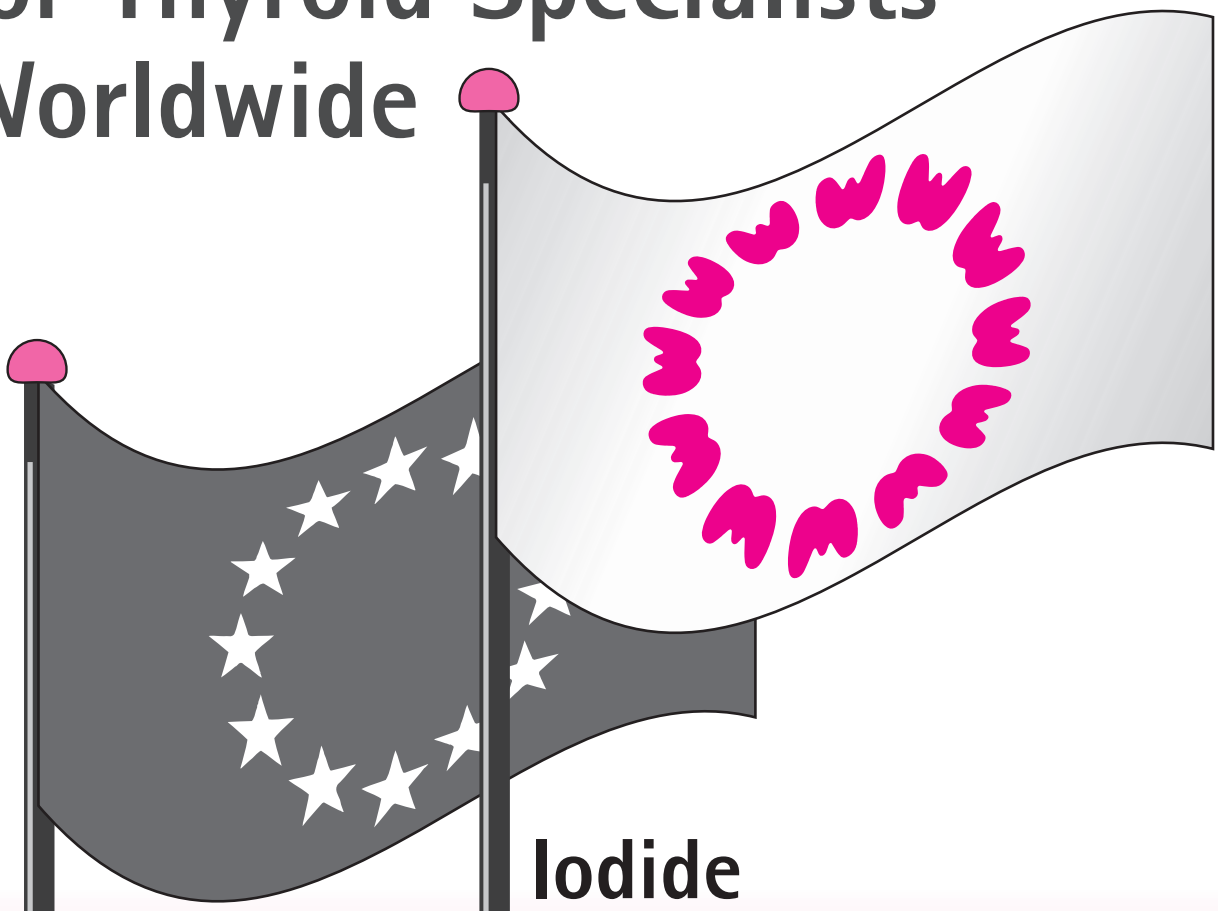
7. The jury decides with a 2/3 majority. In exceptional cases, decisions given in writing form absent jury members may be considered. A member of the jury may not take part in assessing a manuscript if it originates from his working circle. In this case, the President calls another member of the Society from the same field to the jury.

8. The prize is usually awarded once a year at the annual meeting of the German Society of Endocrinology.

9. The President of the Society will invite applications for the prize for the subsequent year at the annual meeting. The secretary and press agent of the Society will arrange announcements in several languages for the competition to be advertised in medical journals.

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