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IODINE DEFICIENCY AND EXCESS IN CHILDREN: WORLDWIDE STATUS IN 2013

Running title: Worldwide iodine status

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ABSTRACT

Objective: Assessing iodine nutrition at the population level is usually done by measuring urinary iodine concentrations (UICs) and, in some countries, by estimating household coverage of adequately iodized salt (HHIS). Using these indicators, the objective of this review is to assess global and national iodine status in 2013.

Methods: The most recent data on HHIS were obtained from UNICEF. The most recent data on UICs were obtained from the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) Global Network and the World Health Organization (WHO). Median UIC was used to classify national iodine status based on the current WHO classification system, but with a modification: the 'adequate (100-199 μg/L)' and 'more than adequate (200-299 μg/L)' categories of median UIC in SAC were combined into a single category of 'adequate' iodine intake (100–299 μg/L).

Results: Over the past decade, the number of countries that are iodine deficient has fallen from 54 to 30, the number iodine sufficient has increased from 67 to 112, while the number with excessive iodine intakes has increased from 5 to 10. In most countries with excess intakes, this is due to over-iodization of salt and/or poor monitoring of salt iodization. Out of 128 countries with HHIS data, in 37, at least 90% of households consuming adequately iodized salt, but in 39 countries, coverage rates are below 50%. Overall, ≈70% of households worldwide have access to iodized salt.

Conclusion: There has been substantial recent progress in the global effort to control iodine deficiency. But iodized salt programs need to be carefully monitored to ensure adequate iodine intakes while avoiding iodine excess.

***Key words*:** Urinary iodine, iodine deficiency, iodine excess, salt iodization

INTRODUCTION

Iodine is an essential dietary nutrient for the synthesis of thyroid hormones that are critical for normal reproduction, growth and development. Iodine deficiency (ID) has multiple adverse effects on health, all due to inadequate thyroid hormone production, that are termed the iodine deficiency disorders (1). ID in utero and during childhood damages the developing brain leading to the loss of millions of IQ points globally, making it one of the most important preventable causes of brain damage worldwide (2).

In 1952, the World Health Organization (WHO) recommended iodization of all ‘food salt’ in iodine deficient areas, and, in 1980, estimated 20-60% of the global population was iodine deficient and/or goitrous (3). But little attention was paid to ID in public health programs in most countries— goiter was considered a lump in the neck primarily of cosmetic concern. This gradually changed during the period of 1970-1990: controlled studies in iodine-deficient regions showed that iodine supplementation not only eliminated new cases of cretinism, but also reduced infant mortality and improved cognitive function in the rest of the population (4).

Before 1990, only a few countries —Switzerland, some of the Scandinavian countries, Australia, the United States and Canada— were completely iodine sufficient. In 1990, at the U.N. World Summit for Children and the World Health Assembly, and again in 1991 at the Conference on Ending Hidden Hunger, world leaders adopted the ambitious goal of eliminating ID as a public health problem (5-7). Fortunately, through salt iodization, ID is among the simplest and least expensive of nutrient deficiencies to prevent (2). The annual costs of salt iodization are estimated at only 0.02-0.05 US$ per child covered, and the costs per child death averted are US$ 1000 and per DALY gained are US$34-36 (8). Programs against ID have clear political appeal because the health, economic and social consequences can be averted by a lowcost intervention. This has spurred remarkable progress in the global effort to eliminate ID over the past two decades, as detailed in this review. However, ID still affects may regions and in 2007, the International Child Development Steering Group re-emphasized that ID remains one of four key global risk factors for impaired child development (9).

Salt iodization programs, like other public health interventions, require effective, long-term monitoring systems. In 2005, the World Health Assembly called on national governments to report on their iodine nutrition every three years (10). Periodic measurement of population iodine status is important because both ID and iodine excess can have adverse health effects (4).

METHODS

Classification of country iodine status based on the national median UIC

Because more than 90% of dietary iodine eventually appears in the urine, UIC is an excellent biomarker of recent iodine intake (11). UIC data do not provide direct information on thyroid function, but they are a reliable measure of exposure, and a low or a high median value suggests a population is at higher risk of developing thyroid disorders. UIC surveys are usually done in school aged (children 6-12 y old) children (SAC) because they are a convenient population, easy to reach through school based surveys and usually representative of the general adult population (2), although not of pregnant women (12,13). WHO/UNICEF/ICCIDD recommend the use of spot UICs from SAC in nationally representative surveys, expressed as the median in µg/L, to classify a population's iodine status (2). More countries are beginning to carry out studies in high-risk population groups, i.e. pregnant women, however data is limited and the majority of countries still conduct routine iodine monitoring in SAC (13).

For this review, updated country data on UIC compiled in the WHO Vitamin Mineral Nutrition Information System (VMNIS) (14) was used, as well as data from on-going or

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unpublished surveys provided by the ICCIDD Global Network (15). The sampling frame was surveys conducted between 1993 and March 2013. Only surveys with a cross-sectional population-based sample frame that used standard UIC assay techniques and reported the median and/or mean UIC (µg/L), or the proportion (%) of the population with UIC <100 µg/L, were included. SAC were assumed to serve as a proxy for the general population (2). If no national data were available subnational data was used; if two or more subnational surveys in SAC of the same administrative level were available from different locations, the surveys were pooled into a single weighted summary measure. For countries where no UIC data was available, no national estimates were made. Additional details have been published on this approach to analysis of national iodine data (16).

For this review, the median UIC obtained from the survey data was used to classify countries according to the international criteria of public health importance of iodine nutrition from WHO/ICCIDD/UNICEF (WHO 2007), with a modification (17). A large international multicenter study in SAC has recently confirmed there is no increase in the prevalence of thyroid dysfunction and/or antithyroid antibodies comparing children across the current ranges of 'adequate' (UIC range of 100–199 µg/L) and 'more than adequate' iodine intake (UIC range of 200–299 µg/L) (17). These findings indicate iodine intakes in SAC resulting in UICs in the current WHO category of 'more than adequate' intake (200–299 µg/L) are likely safe. Thus, for the purposes of this review, the acceptable range of median UIC has been widened and a single category of 'adequate' iodine intake in the range of 100–299 µg/L for SAC has been applied **(Table 1**).

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Assessing the coverage of iodized salt programs by measuring the percentage of households using iodized salt

Since the mid-1990s, UNICEF assists countries in collecting health data through its international household survey initiative the Multiple Indicator Cluster Surveys (MICS). Countries may also participate in other standardized household survey programs, such as the Demographic and Health Surveys (DHS) program from the US Agency for International Development (USAID). These surveys have large sample sizes (usually between 5,000 and 30,000 households) and typically are conducted about every 5 years, to allow comparisons over time. One of the nutrition indicators in these programs is iodization of household salt.

An adequate iodine level in household salt is defined as salt containing 15 to 40 ppm of iodine (2). Testing of the iodine content in household salt samples is usually done with simple rapid test kits (RTKs). Data on household coverage with iodized salt is updated and summarized yearly by UNICEF in their State of the World's Children Reports. The data compiled by UNICEF are mainly from developing countries and countries in transition, as household coverage data from industrialized countries are limited. The data on household coverage with iodized salt in this review are drawn from the 2012 Report (18) and the UNICEF Child info database (19).

RESULTS

Nationally representative UIC surveys are available for 121 countries, and for 31 countries, subnational surveys are used to make the estimates. Globally, the overall data quality and coverage of UIC surveys is high, and although data are lacking for 41 countries, these countries (mostly smaller islands) contain only 2.2% of the world's population of SAC. Larger countries still without adequate UIC survey data include the Israel, Iraq and the Syrian Arab Republic. Available UIC data now cover 97.8% of the world's population of SAC.

Two decades of progress against ID are shown in **Figures 1** and **2.** Figure 1 shows the global situation in 1993 when countries were classified according to degree of public health importance of iodine nutrition based on the goiter rate in SAC. In 1993, WHO estimated that 110 countries were affected by goiter and ID (20). Figure 2 shows the situation in mid-2013, with countries classified according to degree of public health importance of iodine nutrition based on the median UIC. In 2013, iodine intake is adequate in 112 countries. Iodine intake is deficient in 30 countries, with nine are classified as moderately deficient and 21 classified as mildly deficient (**Table 2**). Iodine intake is excessive in 10 countries (Table 2).

Household coverage with iodized salt

Data on household coverage with iodized salt is available for 128 out of 196 UNICEF member states, most of which are low-income countries. Out of 128 countries with data, 37 countries have salt iodization coverage that meets the international goal of at least 90% of households consuming adequately iodized salt (3). Fifty-two countries have coverage rates of between 50 and 89%, and 39 countries have coverage rates of <50%. The world map in **Figure 3** shows countries classified by their household coverage rates. Overall, approximately 70% of households worldwide have access to iodized salt. Those with the greatest access are living in the WHO regions of the Western Pacific and the Americas, and those with the least access are residing in the Eastern Mediterranean region.

DISCUSSION

At the national level, there has been major progress in correcting ID: from 2003 to 2013, using the national median UIC, the number of countries with adequate iodine intake increased

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from 67 to 112, and currently, only 30 countries remain iodine deficient. Large populous countries that remain iodine deficient include several developing countries (e.g., Ethiopia, Mozambique, Angola), countries in transition (e.g., Russia, Ukraine) and industrialized countries (e.g., United Kingdom, Italy). This emphasizes that ID, unlike many other micronutrient deficiencies, is not limited to low-income settings and populations with poor dietary quality.

There are several limitations to the estimates of national iodine status presented in this review. For 31 countries subnational data was used; this represents 32% of the global population in 2013. For 8 countries, including India, Italy, Japan, Russia and Spain, multiple subnational data within the country were pooled and weighted based on the sample size of the study to obtain an estimate of the national median UIC. Because large regional differences in ID prevalence may exist within countries, subnational prevalence estimates can either over- or underestimate national prevalence. In addition, estimates for many of the countries that remain classified as iodine deficient in 2013 are based on older studies conducted between 1994-1999 (e.g. Central African Republic, Algeria, Gambia, Guatemala, Ireland, Morocco, Hungary, Lebanon). Finally, only a small number of countries have completed nationally representative UIC surveys in pregnant women and women of reproductive age, who are important target groups. This is a major constraint of the current estimate because although the median UIC in SAC may be used to represent iodine status of most of the population, it should not be used as a proxy for iodine status in pregnant women (12,13).

The percentage of households covered by adequately iodized salt increased from <10% to 66% between 1990 and 2002, but progress has slowed in the last decade (3). Inconsistent production or limitations in quality-controlled iodization technology at the factory, poor packaging and ineffective transport channels may be explanations for varying iodine levels and iodine losses, resulting in inadequate amounts of iodine in salt at the households. Further obstacles to the implementation of effective iodized salt programs are difficulties in enforcing legislation on iodized salt, problems caused by having a high number of small-scale salt producers and the absence of an effective monitoring system. Reaching the remaining one-third of the global population not yet covered with iodized salt will not be easy. Although the key factors to successful national programs have been identified, reaching disadvantaged groups living in remote areas and convincing the food industry and small scale salt producers to use and to iodize their salt are major challenges.

The marked improvement in iodine nutrition around the world over the past decade as measured by the number of countries with a median UIC indicating iodine sufficiency has not been paralleled by comparable increases in iodized salt coverage. This is due in part to the generally longer lag time in data reporting of iodized salt coverage as household surveys are generally carried out only every 3-5 years, so that recent initiatives to improve iodization programs may not be yet visible in the global statistics. Other reasons for the difference are that salt iodization data are available from only 128 countries while UIC data are available from 150 countries. The salt iodization data are mainly from developing countries and countries in transition, whereas the UIC data also include industrialized countries in Europe and North America. Also, the salt iodization data do not take all dietary iodine sources into account, particularly the contribution of salt in processed foods and dairy products that are important sources in many countries, as well as iodine-rich groundwater found in some regions.

In 2013, of the 30 countries with ID, all are classified as mild-to-moderately deficient, and none as severely deficient. Whether mild-to-moderate ID in children has adverse effects has long been debated. Several older randomized, controlled trials in SAC have tried to measure the

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effect of iodized oil on cognition; three of the studies found no effect (21-23), while one found cognition improved with treatment (24). However, two of the studies were confounded by a significant improvement in iodine status in the control group (21,24), while in the other two, the treated group remained iodine deficient at retesting (22,23). Two recent randomized, placebo controlled, double-blind intervention trials in mild-to-moderately deficient SAC have shown clear benefits of iodine on cognitive and motor function (25,26). Moderately iodine deficient 10-12 y-old children (n=310) in Albania were randomized to receive either 400 mg of iodine as oral iodized oil or placebo (25). Compared to placebo, iodine treatment significantly improved performance on tests of information processing, fine motor skills, and visual problem solving. The second placebo-controlled, double-blind trial was conducted in mildly iodine deficient New Zealand SAC (n=184) randomly assigned to receive 150 μg I daily or placebo for 28 wk (26). The overall cognitive score of the iodine-supplemented group was 0.19 SDs higher than that of the placebo group (P = 0.011).

A recent systematic review (27) examined the effects of iodine supplementation and/or status on mental development of children ≤5 y. Organized by study design, average effect sizes were: a) 0.68 (2 randomized controlled trial with iodine supplementation of mothers); b) 0.46 (8 non-randomized trials with iodine supplementation of mothers and/or infants); c) 0.52 (9 prospective cohort studies stratified by mothers' iodine status); and d) 0.54 (4 cohort stratified by infants' iodine status). Overall, this translated into 6.9 to 10.2 lower IQ points in iodine deficient children compared with iodine-replete children (27). Thus, the available data, although limited, suggest ID of mild-to-moderate severity in SAC and in children ≤5 y has adverse effects on cognitive/motor performance and likely prevents children from attaining their full intellectual potential.

On the other hand, iodine excess may also have detrimental consequences of thyroid function during childhood. Although the healthy thyroid can adjust to a wide range of intake to regulate the synthesis and release of thyroid hormones (28,29), in individuals with past or present thyroid abnormalities, even modest increases in iodine intake can precipitate thyroid disorders (4). Also, the fetus and the newborn are especially vulnerable to iodine excess, and excessive maternal iodine intake can cause neonatal goiter and hypothyroidism (30). In children, excess dietary iodine has been associated with goiter and thyroid dysfunction. In coastal Japanese children (31), consumption of iodine-rich seaweed with intake of >20 mg iodine per day was associated with a prevalence of visible goiter of 3%–9%, but no cases of clinical hypo-or hyperthyroidism. Chinese children consuming iodine-rich drinking water have elevations in mean serum TSH and increased rates of goiter (32,33). A recent multicenter study in SAC in 12 countries (n=2512) found a significantly higher prevalence of elevated blood thyroglobulin values in children with UIC ≥300 µg/L but no significant change in the prevalence of hypo- or hyperthyroidism (17). In a study in Chinese SAC with iodine excess due to high iodine in groundwater, the goiter prevalence was elevated at 8.0% in the areas with an iodine concentration >150 µg/L in the drinking water and median UICs >300 µg/L (34). In a large international study of 6- to 12-year-old children, chronic dietary iodine intakes >500 µg/d were associated with an increase in thyroid size by ultrasonography (35). These studies suggest the onset of mild thyroid hyperstimulation (as indicated by an increased blood thyroglobulin) above the currently recommended threshold for the median UIC indicating excess iodine intake of 300 µg/L UIC, and the appearance of goiter in children when iodine intake increases above 400–500 µg/d. These data emphasize the importance of avoiding iodine excess, as indicated by a median UIC >300 µg/L in SAC (2).

Of the 10 countries where SAC have excessive iodine intakes (Table 2), the high intakes are due to varying sources. Excessive intake in Japan is associated with frequent consumption of foods with naturally high iodine content, including Laminaria, a type of kelp commonly labeled as kombu (36). In regions of China, and perhaps in Somalia, high iodine in groundwater is a contributing factor in iodine excess (34, 37). But in most countries with iodine excess, high iodine intakes are due to excessively iodized salt combined with high household coverage, as for example in Georgia (38) and in Brazil (39). In Chile in the 1990's, iodine concentrations in iodized salt were set too high, at ≈80 ppm, resulting in excessive iodine intake and a median UIC of 540 µg/L in SAC. These results led the national program to change the iodized salt law to reduce the iodine content of salt to 20-60 ppm, which resulted in a normalization of iodine intakes in most regions of the country (40). Thus, it is important that surveillance systems for iodine programs not only monitor iodine intakes in the population, but also regularly assess the quality of salt iodization and other sources of dietary iodine.

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LEGENDS

Fig.1. National iodine status in 1993 based on total goiter rate in school age children.

TGR; Total goiter rate

Fig. 2. National iodine status in 2013 based on median urinary iodine concentration in school age childen.

UIC; Urinary iodine concentration

Fig. 3. Coverage of households with adequately iodized salt (data from references 18, 19).

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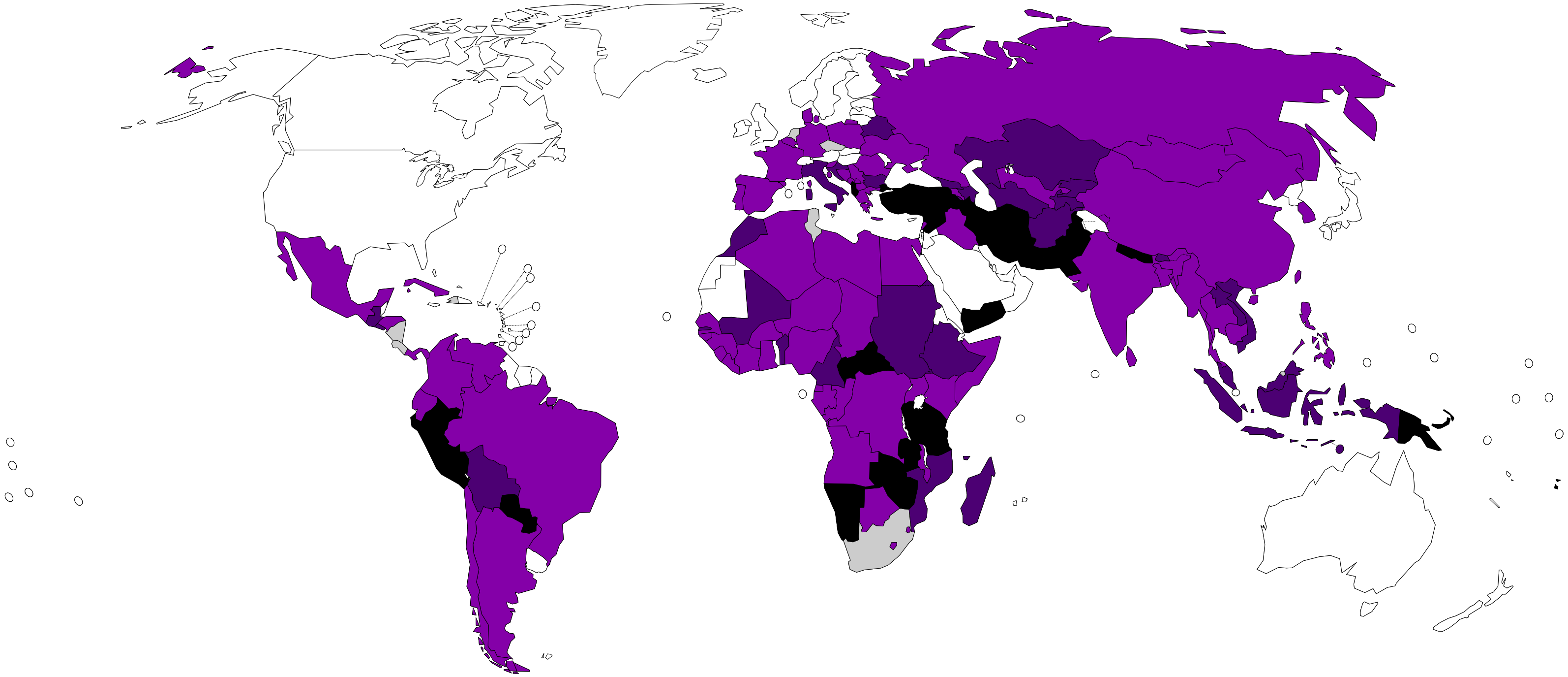
Table 1. Epidemiological criteria for assessing iodine nutrition based on median urinary iodine concentrations of school-aged (6-12 y-old) children (from references 2 and 17).

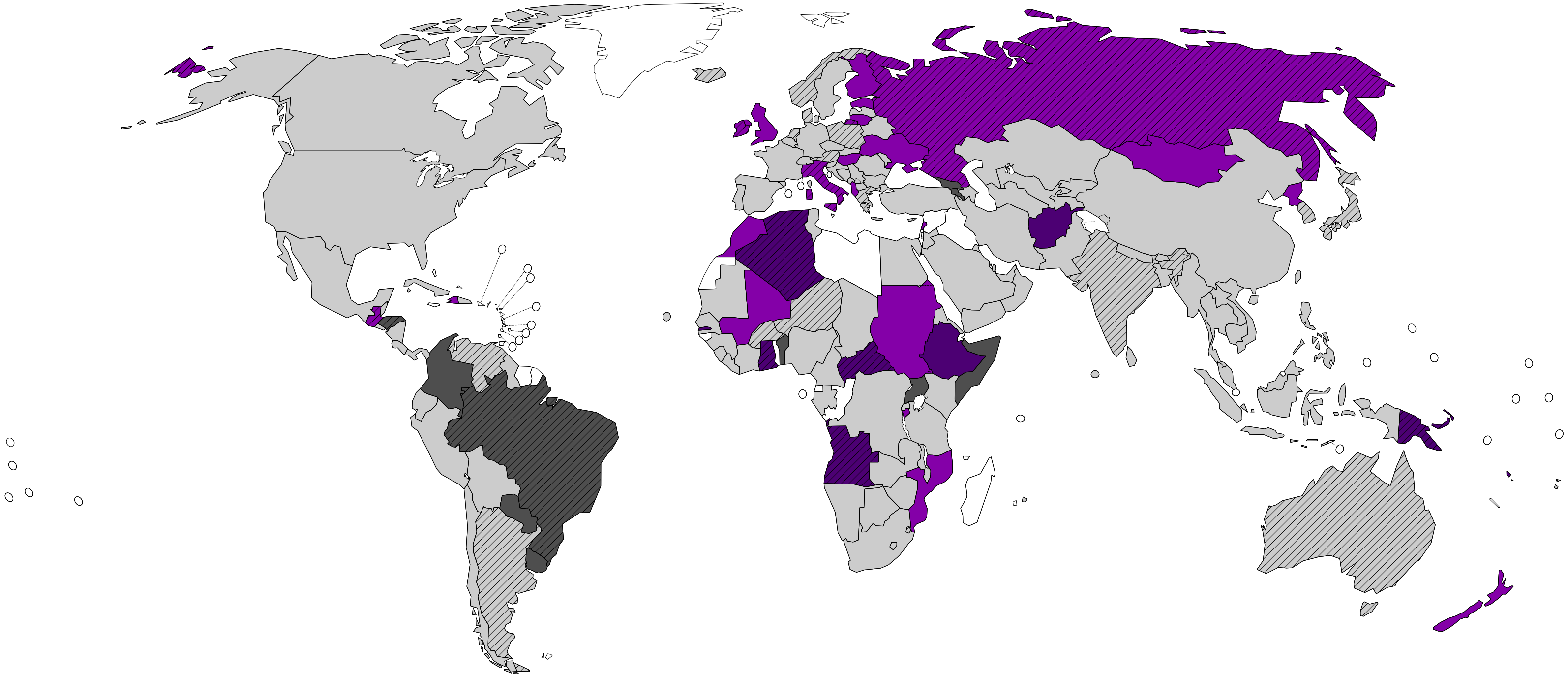
Median urinary iodine (µg/L)	Iodine intake	Iodine nutrition
<20	Insufficient	Severe iodine deficiency
20-49	Insufficient	Moderate iodine deficiency
50-99	Insufficient	Mild iodine deficiency
100-299	Adequate	Optimal
≥300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)

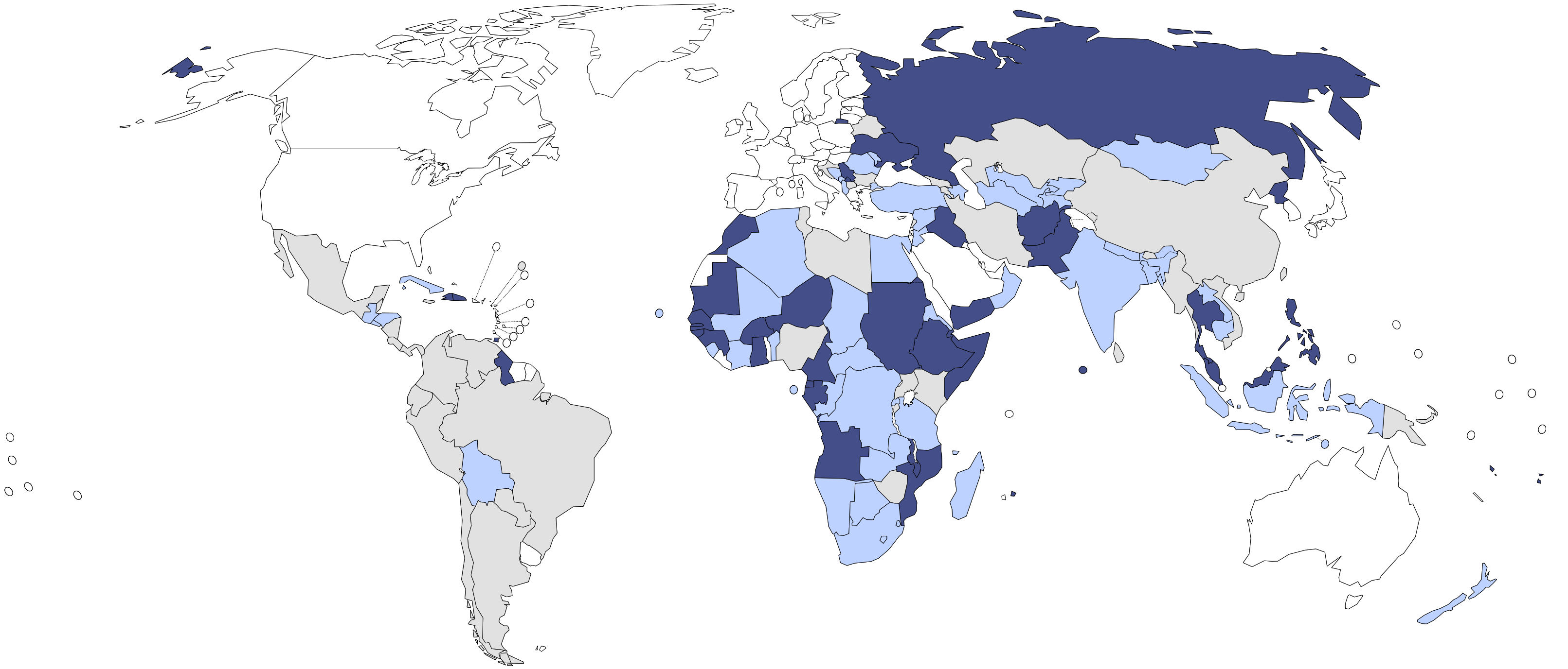
Table 2. Countries in 2013 who are mildly or moderately iodine deficient or have excessive iodine intakes, based on the median urinary iodine concentration. Countries are listed alphabetically in each category.

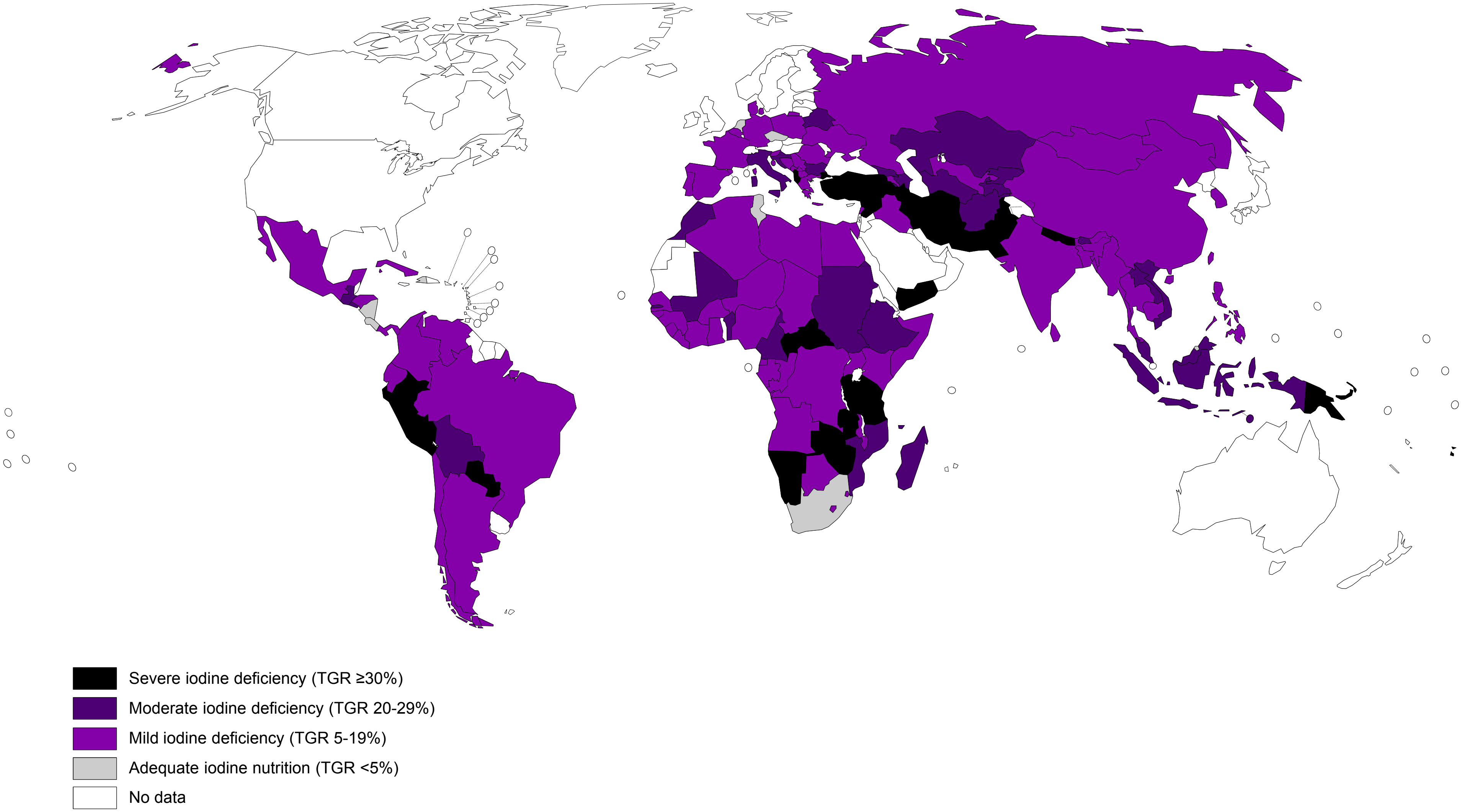
Moderately iodine deficient (median UIC 20-49 µg/L)	Mildly iodine deficient (median UIC 50-99 µg/L)	Excessive iodine intake (median UIC >300 µg/L)
Afghanistan Algeria Angola Central African Republic Ethiopia Gambia Ghana Papua New Guinea Vanuatu	Albania Burundi Democratic People's Republic of Korea Estonia Finland Guatemala Haiti Hungary Ireland Italy Lebanon Lithuania Mali Mongolia Morocco Mozambique	Armenia Benin Brazil Colombia Georgia Honduras Paraguay Somalia Uganda Uruguay

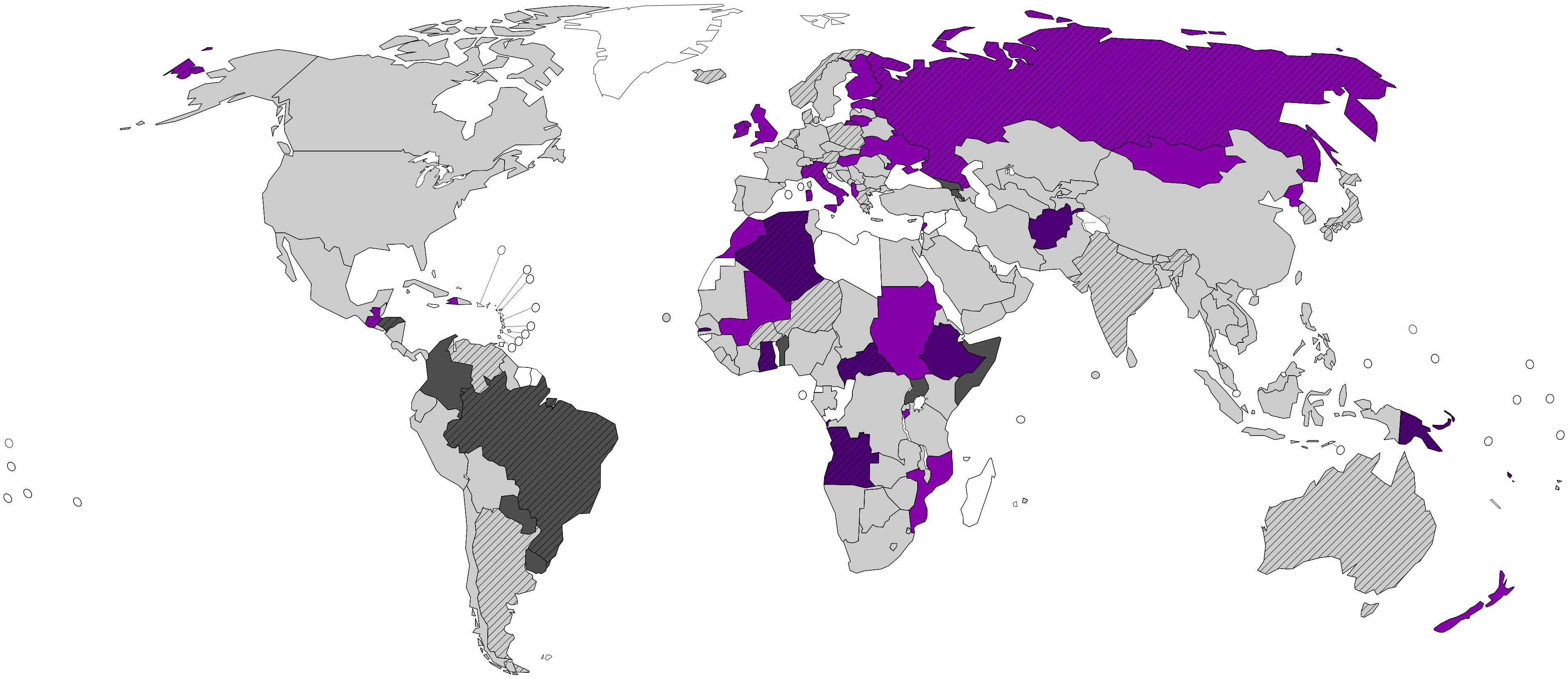
	New Zealand Russian Federation Sudan Ukraine United Kingdom	





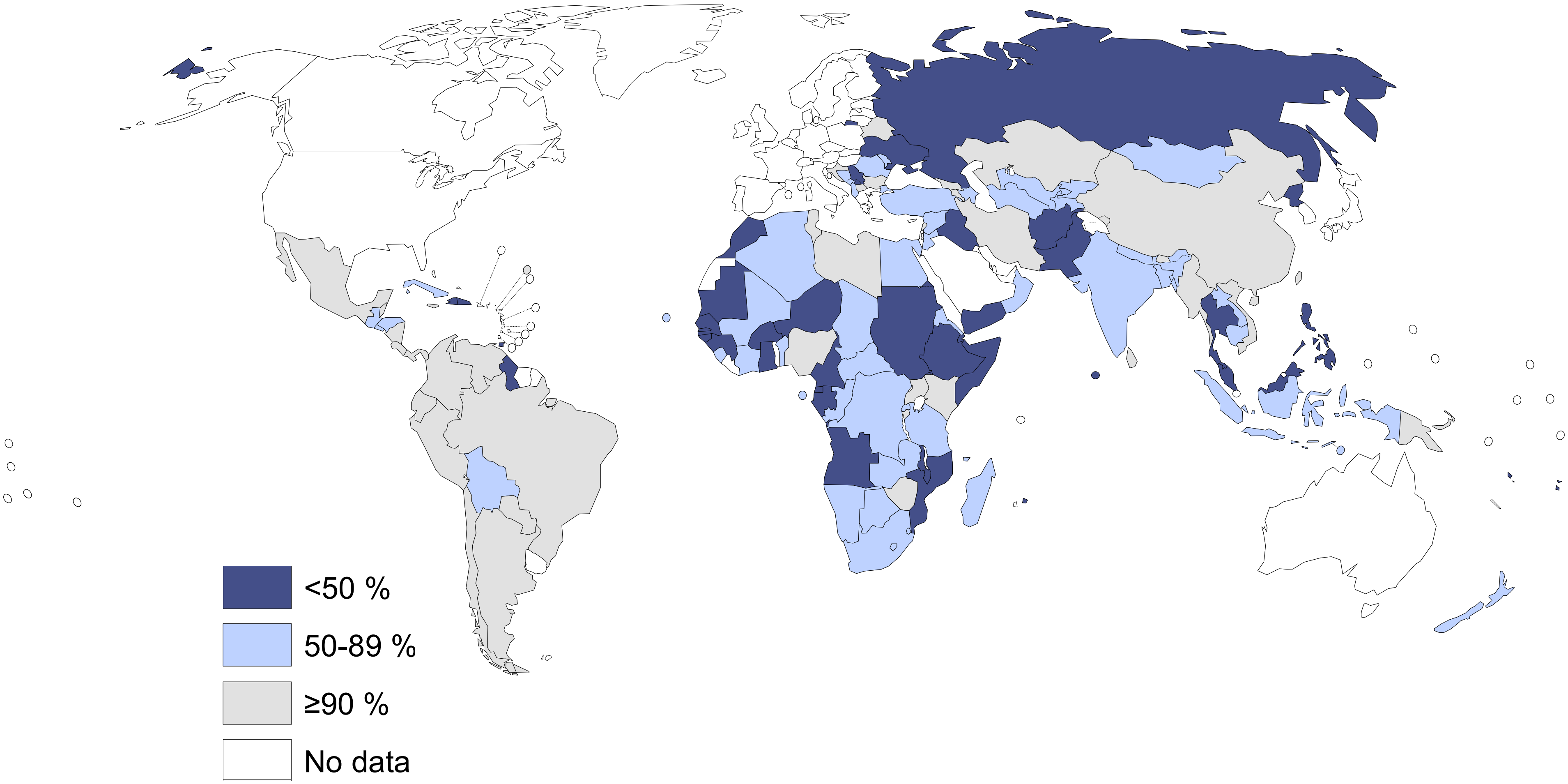



Severe iodine deficiency (TGR ≥30%)
Moderate iodine deficiency (TGR 20-29%)
Mild iodine deficiency (TGR 5-19%)
Adequate iodine nutrition (TGR <5%)
No data



- ■ Moderate iodine deficiency (UIC 20-49 µg/L)
- ■ Mild iodine deficiency (UIC 50-99 µg/L)
- ■ Adequate iodine nutrition (UIC 100-299 µg/L)
- ■ Excess iodine intake (UIC ≥300 µg/L)
- ▨ Subnational[a]
- ☐ No data

[a] The country estimates in the cross -hatched countries are based on subnational data. The national coverage of iodized salt in these countries may be incomplete and there may be large variations in the iodine intake.


<50 %
50-89 %
≥90 %
No data