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Supplement: Shaping the Development of an Iodine Research Initiative for the US

Summary of an NIH Workshop to Identify Research Needs to Improve the Monitoring of Iodine Status in the United States and to Inform the DRI[1–3]

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Abstract

The Office of Dietary Supplements (ODS) at the NIH sponsored a workshop on May 12–13, 2011, to bring together representatives from various NIH institutes and centers as a first step in developing an NIH iodine research initiative. The workshop also provided an opportunity to identify research needs that would inform the dietary reference intakes for iodine, which were last revised in 2001. Iodine is required throughout the life cycle, but pregnant women and infants are the populations most at risk of deficiency, because iodine is required for normal brain development and growth. The CDC monitors iodine status of the population on a regular basis, but the status of the most vulnerable populations remains uncertain. The NIH funds very little investigator-initiated research relevant to iodine and human nutrition, but the ODS has worked for several years with a number of other U.S. government agencies to develop many of the resources needed to conduct iodine research of high quality (e.g., validated analytical methods and reference materials for multiple types of samples). Iodine experts, scientists from several U.S. government agencies, and NIH representatives met for 2 d to identify iodine research needs appropriate to the NIH mission. J. Nutr. 142: 1175S–1185S, 2012.

Introduction

Given the serious consequences of iodine deficiency and uncertainty regarding the iodine status of the most vulnerable population groups in the US (i.e., pregnant women and infants), the Office of Dietary Supplements (ODS)[16]at NIH convened a workshop to shape the development of an iodine research initiative with NIH institutes and centers. The overarching goal of the meeting was to identify the research areas that would inform future public health activities and policy related to the identification, prevention, and remediation of iodine deficiency disorders. Vulnerable populations in the US and Canada were

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[3] Speakers and participants included representatives from the U.S. Department of Health and Human Services, NIH, CDC, USDA, FDA, National Institute of Standards and Technology, and Health Canada, and internationally recognized experts in iodine nutrition, nonfederal stakeholders, national and international organizations, and professional clinical societies.

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emphasized. Recommending specific changes to the dietary reference intake (DRI) for iodine was beyond the scope of this workshop, but the US and Canada will work collaboratively in the future to further refine the DRI, which was last revised in 2001 (1). In the interim, relatively little research relevant to iodine and human nutrition has been conducted by investigators in the US or Canada, but researchers from other countries have been actively engaged in this area.

This summary will focus on iodine adequacy and mild deficiency because these categories are considered most likely to be relevant to North America. Although the US and Canada are often described as iodine sufficient, mild deficiency still exists in a surprisingly large number of other industrialized countries (2). Further, investigators with the CDC recently raised concerns about the adequacy of iodine status of pregnant women in the US (3). Moderate and severe deficiency also will be reviewed, primarily to emphasize the more serious and sometimes irreversible health consequences of clearly inadequate iodine intake. Various international agencies and organizations[17] have made enormous progress in reducing the prevalence of iodine deficiency disorders around the world, yet iodine deficiency remains the primary preventable cause of mental retardation among children (4). At the other end of the exposure spectrum, our understanding of the health effects of excessive iodine intake appears to be inadequate.

History of Iodine Deficiency

The iodine concentration of foods for human consumption is primarily determined by the concentration of iodine in the soil where plants grow and animals graze. For this reason, iodine deficiency undoubtedly dates back to earliest man (5). Simple goiter, a clinical manifestation of iodine deficiency, was recognized in classical times and depicted in early Christian iconography. As reviewed by Zimmermann (6), the cause was unknown, but goiter was treated with seaweed and tinctures from sponges, both rich in iodine. For centuries, many European countries experienced both endemic goiter and cretinism, the latter being the most severe form of iodine deficiency characterized by mental retardation, deaf-mutism, stunted growth, delayed sexual maturation, and a variety of complications due to neurological abnormalities. In the late 1870s, research chemists and physicians in Western Europe identified the unifying characteristic of patients with goiter and cretinism as a thyroid that was low in iodine.

History of iodine deficiency in North America. Evidence of widespread goiter in the US was documented around World War I, owing in part to the results of physical examinations associated with the draft. The condition was prevalent around what came to be known as the Goiter Belt, including areas around the Great Lakes and Pacific Northwest regions of the US and Canada. Growth failure and reproductive problems associated with iodine deficiency in humans were observed among farm animals in the same areas. After extensive lobbying and education efforts by nutrition scientists, and in spite of strong opposition from local, state, and federal authorities, intervention studies were eventually conducted by Dr. David Marine et al. (7,8) between 1917 and 1919 and clearly demonstrated the efficacy of iodine supplementation among teenage girls with endemic goiter.

Metabolism and Function

Metabolism. Iodine present in food and supplements occurs both as salts and in organic forms. Kelp is often used as a source of iodine in dietary supplements available in the US (9). After ingestion, inorganic and organic sources of iodine are converted to iodide and absorbed by the gut. A sodium-iodine symporter expressed by the apical membrane of enterocytes mediates intestinal absorption of iodine (10). Absorption of oral doses is estimated to range from 85 to 90% (11,12). The sodium-iodine symporter, located on the basolateral membrane of thyrocytes, mediates uptake of circulating iodide and its concentration in the thyroid. Absorbed iodine is cleared from the circulation primarily by the kidneys and thyroid. Fractional renal clearance appears to be constant (13). In contrast, thyroidal uptake of iodine varies substantially and increases when intake is low (11). In iodine-sufficient areas, the adult thyroid retains ~60 μg/d iodine to compensate for loss in feces and sweat and also to maintain thyroid hormone (TH) synthesis. Thyroid stores are estimated to range from 20 μg in severely deficient populations to ~10–20 mg, depending on usual iodine intake (11).

Biological role. The only known function of iodine is as a component of TH. The multiple physiological effects of iodine are attributed to the pleiotropic effects of TH. Most circulating TH is bound to plasma proteins, particularly to thyroxine (T4)-binding globulins (14). Only ~0.1% of circulating TH is unbound and therefore active. There are 2 forms of active TH, T4 and triiodothyronine (T3). In peripheral tissues, T3 is the more active form and critical for neurodevelopment (15). Like other endocrine systems, thyroid homeostasis is maintained by a negative feedback loop. When circulating TH is low, the pituitary gland increases production of thyroid-stimulating hormone (TSH), also known as thyrotropin, resulting in increased synthesis of TH. Similarly, when the TH concentration is too high, TSH production is reduced.

Factors affecting iodine utilization. Several dietary and environmental factors affect the absorption and utilization of iodine, including consumption of foods containing goitrogens, exposure to perchlorate, and the presence of other micronutrient deficiencies. Goitrogens such as isothyocyanates are substances that interfere with the uptake of iodine in the thyroid gland. Isothyocyanates are present in cassava, cabbage, broccoli, cauliflower, and other cruciferous vegetables. When ingested at high levels, isoflavones found in soy products also can inhibit TH formation (16). Healthy individuals exposed to dietary goitrogens do not usually develop goiter unless other factors are present, such as low iodine intake (1). Perchlorate, a chemical contaminant found in many public drinking-water supplies, also inhibits the transport of iodine into the thyroid gland (17). However, like most goitrogenic substances, perchlorate at usual intake levels does not appear to have a clinically significant effect unless there is a coexisting iodine deficiency (18).

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[16] Abbreviations used: AI, Adequate Intake; DRI, dietary reference intake; DSID, Dietary Supplement Ingredient Database; EAR, Estimated Average Requirement; IOM, Institute of Medicine; IQ, intelligence quotient; MVMM, multivitamin-multimineral; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; NIST, National Institute of Standards and Technology; ODS, Office of Dietary Supplements; RCT, randomized clinical trial; RMP, reference measurement procedures; SRM, Standard Reference Material; T3, triiodothyronine; T4, thyroxine; TH, thyroid hormone; TSH, thyroid stimulating hormone; UI, urinary iodine; UL, tolerable upper intake level.

[17] WHO/Pan American Health Organization/UNICEF/International Council for the Control of Iodine Deficiency Disorders.

Deficiencies of selenium, iron, and vitamin A can exacerbate iodine deficiency by interfering with normal thyroid function. Selenium, for example, is a component of the deiodinase enzymes required for the activation of T4 to T3. New Zealand has a history of both selenium and iodine deficiency. In a recent study of older New Zealand residents with marginal status of both nutrients, joint supplementation improved selenium and iodine status but did not have a synergistic effect (19). Children in developing countries often suffer from coexisting deficiencies of iron and iodine. Thyroid peroxidase, the enzyme that catalyzes the first 2 steps of TH synthesis, requires an iron-containing heme prosthetic group. Thus, iron deficiency impairs activity of this enzyme and could blunt the effects of administered iodine in populations with goiter (20). In a controlled intervention trial of Moroccan children, administration of salt fortified with both iodine and iron dramatically reduced the prevalence of anemia and also increased the efficacy of supplemental iodine (21). Vitamin A deficiency, through its effects on the promoter region of the pituitary TSH gene, may increase risk for goiter in iodine-deficient children (22). It seems likely that additional interactions between iodine and other nutrients remain to be discovered, especially as our understanding of nutrient-gene and nutrient-nutrient interactions evolves.

Consequences of Insufficient Iodine Intake

Iodine is required for normal growth and development of humans and animals. Severe deficiency in humans is associated with goiter and poor pregnancy outcome (e.g., fetal death, stillbirth, prematurity, stunted growth, and impaired cognitive and motor function) (23). The nature and severity of adverse effects associated with iodine deficiency are related to the timing, degree, and duration of insufficient intake.

Vulnerable groups. Women whose diets are iodine sufficient before pregnancy have substantial iodine reserves in their thyroids, ~15–20 mg (4); this is roughly enough to provide 50–70 μg/d over the course of a 280-d pregnancy. Iodine requirements increase with pregnancy and are associated with increased maternal metabolism, increased loss of urinary iodine (UI), and transfer of iodine to the fetus throughout pregnancy for synthesis of TH (24). Maternal reserves and continued sufficient intake of iodine during pregnancy are needed to meet fetal requirements and the later needs of newborns and developing infants who are breastfed.

The effects of insufficient iodine intake on the developing fetus are described as the most serious of any population group, because the damage is permanent, particularly if the deficiency is severe. The potential benefit of treating infants exposed to severe deficiency in utero has been studied in countries with high rates of endemic cretinism. Although the findings are not completely consistent, it appears that interventions with iodine must occur early in pregnancy to reduce the risk of prematurity, stillbirth, and subsequent cognitive impairment during infancy and childhood (23).

Infants (i.e., birth to 24 mo) are the population most at risk of iodine deficiency, because they have the highest requirements per kilogram of body weight of any age group (11). Clinical signs of severe iodine deficiency during infancy include growth retardation and impaired cognitive function (23). In developing countries, iodine insufficiency of infants is often further complicated by inadequate intake of other micronutrients.

In areas in which the general population has adequate iodine intake, exclusively breast-fed infants may be at risk of iodine insufficiency. Andersson et al. (25) reported that breast-fed infants in Switzerland were borderline deficient with the exception of those fed iodine-fortified complementary foods. This suggests that even in iodine-sufficient areas, breast milk may not provide adequate iodine and/or home-prepared complementary foods may be low in iodine. Both fortified complementary foods and iodine-fortified infant formula make substantial contributions to total iodine intake (26,27).

Observational and intervention studies: progress and challenges. In the last century and particularly in the last 20 y, assessment of population iodine status provided evidence of iodine deficiency, which led to iodine intervention programs and facilitated the transition of many severely and moderately iodine-deficient countries to iodine sufficiency (4). Relatively few investigators have conducted observational epidemiologic studies to assess the relation between iodine intake and health outcomes. Investigators in Italy studied the association between UI excretion and intake of selected food items in relation to the intelligence quotient (IQ) of >1200 school children in Spain (28). UI excretion, as a proxy for total intake, was inversely associated with IQ. Intake of noniodized salt and infrequent consumption of milk were also related to increased risk of lower IQ. A small prospective cohort study of 26 children born to mothers living either in iodine-deficient or -sufficient areas of Spain indicated increased risk of attention deficit and hyperactivity disorders among children in the low-iodine areas (29).

Randomized clinical trials (RCT) are less common, usually due to cost considerations, but are generally considered at the top of the hierarchy of study designs. Two RCT related to iodine deficiency and neurological deficits were conducted decades apart and in very different settings. The first was conducted in Papua New Guinea at a time when severe iodine deficiency was common in that country. Pharoah et al. (30) observed that motor skills improved among children born to mothers who received injections of iodized oil and further hypothesized that cognitive function might also be enhanced by supplementation. In 2009, New Zealand school children with mild iodine deficiency were recruited to participate in a controlled trial. Those supplemented with 150 μg iodine daily for 7 mo had improved cognition and intellectual performance compared with controls (31).

DRI for Iodine

Reference intake levels for iodine and other nutrients are established by the Food and Nutrition Board at the Institute of Medicine (IOM) of the National Academies (**Table 1**). These reference values, collectively referred to as DRI, include the Adequate Intake (AI), Estimated Average Requirement (EAR), RDA, and Tolerable Upper Intake Level (UL) (1). Other publications provide definitions of these terms and guidance for appropriate interpretation and application of DRI values (32,33).

Intake recommendations. Most DRI values require estimates of nutrient requirements. EAR are particularly important, because RDA are calculated from them. For adults, the IOM panel relied on iodine turnover studies in which the mean uptake, distribution, and release of iodine from body compartments was measured (1). Based on data from these studies, the committee set the EAR for adult women and adult men at 95 μg/d. For children age 4–18 y, limited data from balance studies and

extrapolation from adult values yielded an EAR that varied from 65 to 95 μg/d, depending on age.

As noted earlier, pregnant women have increased iodine requirements (24). The EAR for pregnancy was set at 160 μg/d based primarily on data from a limited number of balance studies. Similarly, the iodine requirement also increases during lactation to compensate for iodine excretion in breast milk. The EAR for lactation was based on the EAR for adolescent girls and nonpregnant women plus the average daily loss of iodine in human milk, resulting in a value of 209 μg/d.

Perhaps the most important gap in the DRI is the lack of data to establish an EAR for infants. Due to lack of experimental data, the AI for both younger and older infants (110 and 130 μg/d, respectively) were based on mean iodine intake of infants aged 0–12 mo exclusively fed breast milk. The AI cannot be used to assess inadequacy of population groups, and thus establishing an EAR for infancy should be an important goal of future research. Consideration should also be given to the iodine intake of infants fed infant formula, because this represents a large percentage of infants in the US.

UL. In setting the UL, the IOM committee considered adverse effects of excess iodine, including goiter, hypothyroidism, and elevated TSH levels (1). Paradoxically, these effects include some of the same symptoms as those associated with iodine deficiency, because excess iodine can inhibit TH synthesis and thereby increase TSH stimulation (34,35). The IOM committee also considered other adverse effects of excess iodine, including thyroiditis, papillary cancer of the thyroid, and goiter and hypothyroidism in newborn infants (1). Because an elevated TSH is one of the first signs of excess iodine intake, it was selected as the critical adverse effect upon which to base the UL. Dose response data for elevated TSH, combined with an estimated uncertainty factor of 1.5, yielded a UL of 1100 μg/d for adults, with corresponding lower amounts for other age groups.

Evidence indicates that healthy individuals are usually tolerant to iodine intakes up to ≥1 mg, because the thyroid gland is able to regulate the production of TH within a wide range of iodine intakes (36,37). However, in a recent RCT conducted in China, healthy euthyroid adults receiving iodine supplements of 400 μg/d (providing a total daily iodine intake of ~800 μg) showed signs of subclinical hypothyroidism after 4 wk of supplementation (38). Although these findings are of uncertain clinical importance, the researchers recommend revisiting the current upper limit for this population.

It is well established that certain individuals, including those with autoimmune thyroid disease and iodine deficiency, may respond adversely to intakes below the UL (1,36,37). Doses of iodine in the milligram range or lower may cause hypothyroidism in people with damaged thyroid glands, because the normal downregulation of iodine transport into thyroid cells does not occur and the intracellular concentration of iodide remains high, inhibiting the formation of TH (36,37,39). In individuals with iodine deficiency, administration of iodine, even at levels well below the UL, can precipitate iodine-induced hyperthyroidism (40–42). This may occur because nodules within goiters overproduce TH when presented with sufficient iodine (37). For these reasons, caution is warranted when introducing an iodine fortification program to address iodine deficiency in a population. Workshop participants experienced with iodine fortification programs reported that gradually increasing the level of fortification using incremental dosing has been used to help prevent iodine-induced hyperthyroidism.

TABLE 1 DRI for iodine in various groups[1]

	AI	EAR	RDA	UL
Infants			*μg/d*	
0–6 mo	110			nd[2]
7–12 mo	130			nd[2]
Children				
1–3 y		65	90	200
4–8 y		65	90	300
9–13 y		73	120	600
14–18 y		95	150	900
Adults		95	150	1100
≥19 y				
Pregnant women		160	220	900
≤18 y				
≥19 y		160	220	1100
Lactating women		209	290	900
≤18 y				
≥19 y		209	290	1100

[1] AI, Adequate Intake; DRI, dietary reference intake; EAR, Estimated Average Requirement; UL, tolerable upper intake level.
[2] nd, not determined; Intake should be from food or formula only.

Iodine Exposure

Individuals ingest iodine from a variety of sources, making exposure to iodine difficult to assess. The variable concentration of iodine in individual foods complicates the assessment of intake, as does the variable use of iodized salt. In addition, supplement use is widespread in the US, so it is essential to consider intakes from both foods and supplements when assessing total iodine intake (43). The contribution of adventitious sources of iodine further complicates the assessment of iodine intake and it is likely that these sources contributed substantially to the iodine concentration of milk and dairy products in the US prior to the late 1980s (44). Iodophores were used to sanitize cow udders prior to milking and also were used during the subsequent milk production process. These agents did not eliminate bacteriophage and were eventually replaced with more appropriate compounds. Iodine also is found in some medications (e.g., povidone) and typically in amounts well beyond usual intake.

Food sources of iodine. Seaweed is one of the richest iodine food sources, but it is highly variable in its concentration (45); other good sources include marine fish and other seafoods, dairy products such as milk, and eggs (46). Fruits and vegetables provide iodine, but the amounts can be highly variable depending on the iodine content of the soil, the type of fertilizer used, and irrigation practices (1). Variation in the iodine content of animal fodder, including supplemental salts, also influences the iodine content of meat and dairy products available to humans (46).

Iodine is present in human breast milk (1), but concentrations vary depending on the mother's iodine status and intake during pregnancy and lactation (47,48). Recently, Pearce et al. (49) reported that the median iodine concentration of breast milk samples from healthy women in the Boston, MA area was 155 μg/L[18], with median values from other analyses in the US ranging from 34 to 146 μg/L (1,50–52).

[18] To convert from g iodine/L to μmol iodine/L, multiply by 0.0079.

The composition of infant formula is regulated in the US and must provide 5–75 μg iodine/100 kcal (~150 mL) of formula (53). Infant formula regulations in Canada are similar, with a required minimum of 5 μg iodine/100 kcal of formula (54). Measured iodine concentrations of 17 infant formulas have been reported to range from 84 to 224 μg/L (49) (~13–34 μg/100 kcal). These data indicate that infant formulas meet FDA and Canadian minimal requirements but are also highly variable in iodine concentration.

Iodized salt. Unlike Canada and most other industrialized countries, the US does not mandate fortification of salt with iodine; iodization is voluntary (55,56). About 70% of the salt in the U.S. diet comes from processed food and food eaten outside the home, neither of which is iodized (57). It appears that food providers (e.g., food manufacturers, fast-food establishments, and other restaurants) do not use iodized salt because of perceived undesirable effects on food flavor. However, there is no published evidence regarding this concern. It is not clear how much of the salt used in U.S. households (i.e., at the table or in cooking) is iodized, but iodized salt must be labeled as such and is required to contain iodine at a concentration of 45 mg/kg. Specialty forms of salt, such as sea salt and Kosher salt, are not usually iodized. Most U.S. consumers do not appreciate that iodine in household salt, which is typically in the form of potassium iodide, is not stable and sublimates over time under conditions of high humidity and heat (57). In other parts of the world, potassium iodate is frequently used to iodize salt because it is more stable, particularly in tropical climates (58).

Dietary supplements. Dietary supplement use among a representative sample of the U.S. population is monitored as part of NHANES. Use of individual ingredients such as calcium or supplement categories such as multivitamins-multiminerals (MVMM) is assessed. In a recent NHANES survey, 53% of adults reported the use of at least one dietary supplement in the last 30 d and the majority reported daily use (43). MVMM are the most widely used of all the supplement categories (59). Use of dietary supplements containing iodine can be calculated from recent NHANES data and those analyses are in progress.

Prenatal supplements. Pregnant women are encouraged to take a prenatal dietary supplement, and the American Thyroid Association recommends 150 μg of supplemental iodine daily for all women who are pregnant, lactating, or planning a pregnancy (60). In a brief report of NHANES data collected between 2001 and 2006, ~70% of pregnant women in the US reported supplement use, but only 20% reported use of a product that contained iodine (61).

Assessment of Iodine Intake

In the US, the assessment of nutrient intake must include contributions from foods and dietary supplements, particularly if the contribution from supplement ingredients of interest is substantial (62). Both FFQ and 24-h recalls are used to collect qualitative and quantitative information about what people eat and also to assess their use of supplements to estimate total intake. Intake of iodine and other nutrients from supplements can be estimated based on label information provided by study participants, as is done in NHANES (63). However, it is not currently possible to link information about usual intake of iodine from foods to food composition tables, because comprehensive information on the iodine content of foods is not yet available in the US or Canada. Therefore, the exposure of interest currently cannot be directly measured and a surrogate biomarker, usually UI, is used to estimate intake. UI has been used as a proxy for recent intake based on reasonable correlations between iodine intake and its excretion in urine (11). In industrialized countries, where people consume a wide variety of foods, UI provides no information on the primary sources of iodine within populations. This information would enhance surveys and the planning and conduct of observational studies and interventions.

In the US, 2 government agencies, the FDA and the USDA, currently conduct studies to estimate the iodine content of foods. These efforts could lead to the development of food composition tables for iodine if a number of obstacles can be overcome. Both groups have identified a number of foods for analysis. The FDA determines iodine levels in >250 foods collected as part of the FDA Total Diet Study (27). These sample units are collected from 3 locations in each of 4 regions in the US and composites are prepared and analyzed in an FDA laboratory. Annual trends of iodine intake and the major contributors to total intake are identified. These estimates, however, do not include data about the variability of iodine in different brands of foods that are collected in a given year. To evaluate the variability of iodine in selected foods that are important sources of iodine, the USDA Nutrient Data Laboratory is now commissioning preliminary analyses of archived food samples that were collected as part of the National Food and Nutrient Analysis Program. These foods are also included in the Total Diet Study and include products such as fluid milk, ready-to-eat breakfast cereals, and white bread. After review and statistical analysis to assess variability, results will be compared with those obtained by the FDA. This approach is promising for a variety of reasons, including the successful development of food composition tables for selenium (64). Like iodine, the selenium concentration of foods is highly dependent on its concentration in the soil and is largely determined by geography. Although the ongoing iodine food composition work is encouraging, no decision has been made to develop a food composition table for iodine to assess intake using NHANES data.

Eventually, it may be possible to conduct observational epidemiologic studies (case-control or cohort) to assess the relation between iodine intake and health outcomes of interest (e.g., pregnancy outcome) in otherwise healthy populations. In preparation for a cohort study, investigators in Norway validated multiple FFQ and diet records as determinants of dairy intake (65). It was known beforehand that dairy products would be high in iodine, because fortification of cattle fodder is mandatory in Norway. The validity coefficients for total consumption of dairy products were higher for the food diary instrument (0.94) than the more easily administered FFQ (0.65). A coefficient of 0.52 was reported for 24-h UI excretion, which also can be used as a biomarker of total iodine intake. A group from Denmark (66) provided data suggesting that the validity coefficient associated with UI as a biomarker of dairy intake and potentially total intake could be improved by using two 24-h urine collections.

Dietary Supplement Ingredient Database. The Nutrient Data Laboratory, Beltsville Human Nutrition Research Center, Agricultural Research Service, USDA, has collaborated with ODS and other federal agencies to plan and develop a Dietary Supplement Ingredient Database (DSID) to evaluate levels of ingredients in dietary supplement products. The data are unique in that the values are analytically validated rather than obtained

from label information. A publicly available database has been released that includes data on values for adult MVMM (67) and is being expanded to include other products of public health importance (63,68).

A study evaluating the vitamin and mineral content of over-the-counter prenatal MVMM is currently underway (69). A sampling plan was developed to obtain a representative sample of products and was based on information from NHANES, the *Nutrition Business Journal*, published studies, and store surveys. Retail products were purchased in 6 regions of the US in mass markets and vitamin and health food stores. Direct sales products were purchased via the Internet and through multilevel marketing channels. Multiple lots of ~70 representative products were obtained, ~80% of which contained a label claim for iodine. The label amounts ranged from 25 to 300 μg iodine/serving, with the most commonly labeled value of 150 μg/serving, which is 100% of the Daily Value for labeling purposes. Approximately one-half of the supplements listed potassium iodide as the iodine source and the rest listed kelp.

The purchased supplements were chemically analyzed for iodine using both a titration (70) and inductively coupled plasma MS method of analysis (71). Both methods were evaluated over time against the National Institute of Standards and Technology (NIST) Standard Reference Material (SRM) 3280, a MVMM tablet containing a certified level of iodine. Each method provided mean results within the certified range. The inductively coupled plasma MS method was determined to be superior, because it was more precise and will be used exclusively for DSID studies. For the 55 over-the-counter prenatal products analyzed for the DSID study, preliminary results show a mean percent difference from label values of 25% above, with a range of 30% below label to 116% above. Approximately two-thirds of the analyzed products exceeded the labeled values.

Analytical Methods

The development of any database that is dependent on chemical analysis requires implementation of analyses that are fit-for-purpose, validated, accurate, and can be reproduced by others. The goal of these activities is harmonization of methods of analysis to ensure integrity of the data and to allow pooling and comparison of data across studies.

Harmonization of methods. There are several options available when considering harmonization and the path depends to a great extent upon the available resources (72). The best option requires the availability of reference materials and one or more reference measurement procedures (RMP). RMP can be used to assign values to reference materials, which are then employed by laboratories to assess measurement accuracy of specific analytes. RMP also can be used as a reference point when evaluating the accuracy of routine methods. A side-by-side comparison of the results of an RMP and a routine method can provide an estimate of measurement bias associated with the routine method.

The development of SRM has been a major program within the NIST Analytical Chemistry Division, with an inventory now approaching 1000 matrix-based or pure materials. With the objective of providing improved quality assurance support and the provision of traceability for iodine status monitoring and dietary intake, a new measurement program has been initiated to increase the inventory of SRM with measured values for iodine. SRM 2670a, a freeze-dried urine, is already available and certified for iodine concentration (88.2 μg/L). This will be supplemented soon with a new material, SRM 3668, which is a 2-level, fresh-frozen urine having a certified iodine concentration of 142.7 μg/L in Level I and 279 μg/L in Level II.

Assessment of iodine intake and monitoring change in exposure following iodine supplementation is an important area in the assessment of iodine status and nutrition of populations around the world. Two relevant SRM are currently available with certified values for iodine, consisting of SRM 1548a, Typical Diet, with a certified value of 0.759 mg/kg, and SRM 3280, a multivitamin supplement, with a certified value of 0.1327 mg/g. A program to add iodine values to other important nutritional SRM, namely SRM 3233 (fortified breakfast cereal), SRM 1549a (whole milk powder), SRM 1845a (whole egg powder), SRM 1849a (infant/adult nutritional formula) (73), SRM 2383a (baby food composite), and SRM 1954 (fortified human milk), is underway.

Iodine supplementation by means of the addition of iodine compounds (either potassium iodide or potassium iodate, depending on the region) to table salt has been a predominant mechanism for ensuring sufficient iodine nutrition in many countries (11). The currently accepted reference method for analytical determination of iodized salt is titration (74), but there are no matrix reference materials yet available for quality assurance of such measurements. With this in mind, 2 new SRM, consisting of SRM 3530, iodized table salt (iodide) and iodized table salt (iodate), are being developed.

Assessment of Iodine Status

UI concentration. In most circumstances, the iodine status of individuals participating in observational or intervention studies is not estimated by assessing dietary iodine intake. Instead, urine is the biospecimen most frequently collected for assessing iodine status. For 2 physiological reasons, UI concentration is almost universally used as a proxy for iodine intake. First, the absorption of iodine is typically in the range of 85–90% across a wide range of intakes (11,12). Second, renal fractional clearance of circulating iodide is reported to be constant, making UI an appropriate estimate of recent iodine intake (75). Pregnant women appear to be an exception to the rule given the pronounced increase in glomerular filtration rate during gestation (76).

Due to the expense and practical difficulties associated with 24-h urine collections by free-living populations, spot urine collections (casual urine samples) are usually collected instead. Some investigators recommend timed urine collections, because there could be a difference between fasting urine samples and those collected during other parts of the day (77). In addition, there are various ways of expressing UI, including UI concentration and UI concentration adjusted for creatinine. Nearly all variations of UI are expressed per liter of urine.

The WHO developed reference ranges for UI concentration and those values are widely used to evaluate iodine nutritional status, ranging from severe deficiency to excessive intake (**Table 2**) (58). Reference ranges were established for various stages of the life cycle, including the groups most vulnerable to iodine deficiency. The WHO UI criteria for children and nonpregnant, nonlactating adults are based on the correlation between rates of endemic goiter in populations and the corresponding median 24-h UI excretion (78).

In preparation for a planned national sodium reduction initiative in the US and subsequent monitoring of progress, the CDC and other federal partners are analyzing data from a recent pilot study designed to determine if timed urine samples can be used to replace the current gold standard of 24-h urine

collections for determination of daily sodium excretion. Using 24-h urine collections would be too expensive in a large national survey (i.e., NHANES) designed to determine whether the sodium reduction initiative is effective. Additional urine samples from the pilot study have been collected for measurement of iodine to determine if timed urine samples are an adequate substitute for 24-h collections. This study is expected to provide important new data on the adequacy of casual urine samples for the assessment of iodine intake. The results for sodium and iodine will be available in 2012.

U.S. and Canadian population surveys of iodine status. The US and Canada conduct national population surveys to assess and monitor iodine status. UI concentration (μg/L) has been the proxy index of iodine intake used in NHANES. Median values are evaluated against the WHO reference values (Table 2). In 1998, Hollowell et al. (79) noted a dramatic decline in median UI concentration from NHANES I (1971–1974) to NHANES III (1988–1994). The median concentration of the population decreased from 320 to 145 μg/L between the 2 surveys and increased slightly to 167.8 μg/L in a subsequent survey (NHANES 2001–2002) (80). A variety of factors, including reduced use of iodophores by the dairy industry, were proposed as contributors to the initial decline of ~50% but were never clearly identified.

Iodine status of pregnant women has been monitored in several surveys and median values compared with WHO criteria for adequacy (150–249 μg/L) (Table 2). NHANES is a very large multipurpose survey of the U.S. population that is not specifically designed to emphasize pregnancy and does not include a large number of pregnant women. In NHANES I (1971–1974) and NHANES III (1988–1994), median UI concentrations of pregnant women were 327 and 141 μg/L, respectively, but were greater than those of nonpregnant women (79). In a subsequent report based on NHANES data from 2001–2006 (3), the median UI concentration of 326 pregnant women was 153 μg/L and dairy products contributed substantially to iodine intake. Most recently, Caldwell et al. (81) reported NHANES data from 2005–2008; the median UI concentration of 184 pregnant women was 125 μg/L. Although the decline in median UI concentrations of pregnant women after 1994 is of concern, a much larger sample size would be needed to adequately evaluate changes over time in this critical population group.

UI concentration and iodine intake in Canada also are being assessed using data from 2 different surveys: the Canadian Community Health Survey and the Canadian Health Measures Survey (82). The studies are in a relatively early phase and the data on intake and iodine status are not yet published.

Assessing iodine exposure at the population level: statistical considerations. Assuming that UI concentration is a reliable measure of daily iodine exposure from a large sample of individuals, the median UI concentration of the population is frequently the statistic of immediate interest. To obtain additional and more useful information from the distribution of population exposure, within-person variability in iodine excretion should be determined. This step requires 2 or more independent UI concentrations from at least a subsample of individuals representing age, gender, and other categories of interest. Ignoring the within-person variance in exposure decreases the precision of UI estimates in the most essential areas of the distribution curve, the tails. Recent studies (66,83–85) indicate that the within-person variability in iodine excretion is non-negligible relative to the between-person variability. Further, the failure to assess and adjust for within-person variability may bias the proportion of persons with excretion below or above given thresholds (i.e., <150 or >500 μg/L among pregnant women) (86,87). In general, the proportion of individuals in the lower part of the distribution will be overestimated and the proportion in the upper end of the distribution tail will be underestimated.

Functional indices of iodine status. Given that iodine is intimately associated with thyroid function, it is not surprising that various biomarkers of thyroid function have been used to assess iodine status in addition to the more commonly used measure of UI concentration. Some investigators have reported that TH concentrations (e.g., free T3 or T4) are not adequately sensitive to change in iodine status (88,89). Thyroglobulin, however, has emerged as a promising biomarker of iodine nutrition status (90). Other investigators are actively pursuing the development of dried blood-spot thyroglobulin as a means to study iodine nutrition, especially in populations where laboratory and storage resources are limited (91). The ODS Analytical Methods and Reference Materials Program works with a variety of groups to support methods development for many ingredients found in dietary supplements. The program also involves a collaboration with NIST to develop SRM, including one for blood-spot thyroglobulin.

Biomarkers of Nutrition for Development initiative. Nutritional status is often assessed by measuring exposure and/or functional indices of nutrient adequacy or excess. Ideally, one or both approaches will have predictive value for the health outcomes of interest. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) at NIH is actively engaged in developing a research initiative in this area with a focus on biomarkers (92). The program, Biomarkers of Nutrition for Development, is intended to meet the increasing need for discovery, development, and implementation of reliable and valid biomarkers to assess nutrient exposure, status, function, and effect. Iodine is 1 of 6 nutrients currently being developed under the Biomarkers of Nutrition for Development initiative (93).

Summary of Research Needs

The workshop provided an opportunity to identify and prioritize research likely to advance the assessment of iodine status of the U.S. population, with emphasis on the most vulnerable populations. Additional details are provided below. Intervention studies are not mentioned as a high-priority research need (**Table 3**), given the extent of preliminary research needed to even consider an RCT. Only one DRI is mentioned to emphasize what was felt to be the most important gap to be addressed to inform future DRI.

Assessment of total iodine intake. The assessment of total iodine intake is important, because it represents the exposure of interest. Dietary assessment instruments are regularly administered to individuals participating in a variety of observational studies, including population surveys, but food composition tables for iodine are not available. The USDA and FDA are collaborating to develop such tables for the U.S. population and are working on another database providing the iodine content of dietary supplements. A successful effort would provide an opportunity to obtain better estimates of the total iodine intake of various segments of the U.S. population and to

TABLE 2 Epidemiological criteria for assessing iodine nutrition in a population based on median and/or range of UI concentrations[1]

Population	Iodine intake	Iodine nutrition
School-aged children[2]		
<20 μg/L	Insufficient	Severe iodine deficiency
20–49 μg/L	Insufficient	Moderate iodine deficiency
50–99 μg/L	Insufficient	Mild iodine deficiency
100–199 μg/L	Adequate	Optimal
200–299 μg/L	Above requirement	May pose a slight risk in the overall population, but likely to provide adequate intake for pregnant/lactating women
>300 μg/L	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)
Pregnant women		
<150 μg/L	Insufficient	
150–249 μg/L	Adequate	
250–499 μg/L	More than adequate	
≥500 μg/L	Excessive[3]	
Lactating women[4]		
<100 μg/L	Insufficient	
≥100 μg/L	Adequate	
Children <2 y old		
<100 μg/L	Insufficient	
≥100 μg/L	Adequate	

[1] To convert from μg iodine/L to μmol iodine/L, multiply by 0.0079. Reproduced with permission from (94). UI, urinary iodine.
[2] Also applies to nonpregnant and nonlactating adults.
[3] The term ''excessive'' means in excess of the amount required to prevent and control iodine deficiency.
[4] In lactating women, the figures for median UI are lower than the iodine requirements because of the iodine excreted in breast milk.

determine the relative contributions from various sources for a variety of age-gender groups.

UI. In the absence of food composition tables, UI concentration is the most commonly used surrogate for total iodine intake. It is important to determine whether UI concentration is an appropriate proxy for 24-h urine collections and daily iodine intake. The first question will be answered when the results of the previously mentioned pilot study designed by the CDC and other federal partners are made available. This study will also be useful for assessing the validity of the multiple correction factors used to estimate total daily UI excretion based on a determination of UI concentration.

Information about intra-individual variation of UI concentration is also needed to obtain additional information from the distribution of population exposure. This is particularly important, because the tails of the distribution curve reflect the exposures of interest, i.e., deficiency and excess. This requires at least 2 urine collections and 2 UI determinations per participant and is rarely done.

Indices of iodine status related to thyroid function. Thyroglobulin appears to be a promising index of iodine status and should be evaluated in more studies of pregnant women and infants. As a relatively new index of iodine status, tests of sensitivity and specificity would be useful. Low concentrations

TABLE 3 Summary of an NIH workshop to identify research needed to improve the monitoring of iodine status in the US and to inform the DRI[1]

Research need	Use
Assessment of iodine intake	
Develop food composition tables for iodine	Dietary assessment instruments
Develop dietary supplement database for iodine	Assess contribution of supplements to total intake
Evaluate UI concentration as an index of 24-h excretion	Assess UI as a proxy of daily iodine exposure
Refine population distribution curves by assessing intra-individual variation of UI concentration	Obtain critical information from the tails of the distribution curve
Evaluate TH as indices of iodine status	Resolve current controversy regarding sensitivity and specificity of TH
Continue to develop validated analytical methods and SRM for a variety of matrices	Quality control which will facilitate comparison between studies and allow pooling of studies related to iodine nutrition.
Modeling studies	If additional iodine fortification is contemplated, predictive mathematical models would be very useful for assessing potential impact on all segments of the population.
DRI	
EAR for infants	To establish a RDA for a high risk population

[1] DRI, dietary reference intake; EAR, Estimated Average Requirement; SRM, Standard Reference Material; TH, thyroid hormone; UI, urinary iodine.

of circulating TH are sometimes equated with iodine insufficiency without providing a more direct measure of iodine status. In addition, questions about TH sensitivity and specificity should also be addressed.

Analytical methods. Many basic research tools needed for conducting iodine research are now available. These include validated analytical methods for measuring iodine concentration of various samples (e.g., urine, baby formula, milk) and a variety of important SRM produced by NIST. Development of methods for assessing iodine in foods is not as far advanced but is progressing. In addition, it is essential for investigators to provide details in publications about the analytical methods employed, including information about quality control.

Modeling studies. If additional fortification with iodine is someday considered for the US, mathematical modeling of the proposed intervention could be very useful. Ideally, the development of methods to simulate changes in iodine intake from a fortified food or foods would minimize the prevalence of both inadequate and excessive intake of the population and various subgroups.

Intervention studies. Many industrialized countries are defined as mildly iodine deficient, but few studies have been conducted to evaluate iodine supplementation of pregnant women and subsequent health effects on their children. A better understanding of the effect of mild iodine deficiency on subsequent cognition and motor function of children is needed. No such intervention studies have been conducted in the US or Canada, but until more data on the iodine status of pregnant women in these countries are available, these studies would be premature. Nonetheless, it is important to begin to develop the research questions to be addressed and also develop the most cost-efficient research designs.

DRI. The formulation of an EAR for infants is the most pressing DRI issue. In addition, the EAR of specific age and gender groups should be less dependent on extrapolation of data. Additional studies examining the effects of high-iodine intakes on thyroid disorders and other adverse effects are also needed.

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