Evidence Needed to Inform the Next Dietary Reference Intakes for Iodine[1,2]

Paula R. Trumbo*

Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, College Park, MD

ABSTRACT

In 2001, Dietary Reference Intakes (DRIs) for iodine were set for the different gender and life-stage groups by the Institute of Medicine. Because of the serious consequences of iodine deficiency for the developing fetus and infant, there is particular interest in further understanding optimal iodine nutrition and improving the monitoring of iodine status, particularly during infancy, pregnancy, and lactation. This review discusses the basis for the current DRIs for iodine and the evidence that may be needed for considering and conducting the reevaluation of one or more of the DRIs. *Adv. Nutr. 4: 718–722, 2013.*

Introduction

The Office of Dietary Supplements of the NIH organized a symposium at the 2103 Experimental Biology meeting entitled "Iodine Insufficiency—A Global Health Problem?" and which has been summarized (1). As part of this symposium, information was provided on the approach used to set the current DRIs for iodine (2) and the type of information needed to consider the reevaluation of these DRIs. This review includes information provided at this symposium. The DRIs include 4 types of reference intake levels that are set for the U.S. and Canadian population by the Institute of Medicine: Adequate Intake (AI)[3], Estimated Average Requirement (EAR), RDA, and Tolerable Upper Intake Level (UL). DRIs have been established for various age and both gender groups and are used in part to plan diets for or assess nutrient intake inadequacy of individuals (e.g., the RDA) or groups (e.g., the EAR) (3,4). The review of the evidence to establish the DRIs for the various nutrients included information on the nutrient's role in the development of chronic disease (e.g., AI for potassium) (5), as well as evidence on the daily needs of a nutrient (e.g., RDA for iodine) (2).

AI for Infants

The AIs for iodine were set at 110 and 130 μg/d for young (0–6 mo) and older (7–12 mo) infants, respectively (2). Breast milk was considered to be sufficient in meeting the iodine requirements during infancy in the United States and Canada. Therefore, the AI for young infants was set primarily on the basis of the average consumption of iodine by young infants exclusively fed breast milk using 3 studies (6–8). Average nutrient consumption was the general approach used to set the AI for vitamins and minerals during early infancy. For older infants, the AI for a number of nutrients was determined by extrapolating from the AI for young infants, as was the case for iodine. The AI of 130 μg/d is similar to the iodine intake range determined by using the 2003–2004 FDA Total Diet Study, which estimated an average intake range of 144–155 μg/d for infants 6–11 mo of age (9).

A limitation of the use of the AI is that it is not possible to make any assumption about the extent of intake inadequacy, whereas the proportion of a group with usual intakes below the EAR can be used to estimate the prevalence of inadequate intakes (4). Because of the importance of iodine in fetal and infant development, a summary from an NIH workshop identified the need to replace the AI with an EAR for iodine during infancy (10). Whereas the EAR could be used to estimate the prevalence of inadequate intakes in infants, NHANES currently does not estimate iodine intake because the USDA Nutrient Data Laboratory does not provide information on the iodine content of foods. Furthermore, NHANES does not collect nutrient intake data from breast milk during infancy and sometimes other relevant sources (e.g., iodine from iodized salt added to foods).

[1] Presented at the symposium "Iodine Insufficiency—A Global Health Problem?" held 21 April 2013, at the ASN Scientific Sessions and Annual Meeting at Experimental Biology 2013 in Boston, MA. The symposium was sponsored by the American Society for Nutrition (ASN). A summary of the symposium was published in the September 2013 issue of *Advances in Nutrition*.

[2] Author disclosures: P. R. Trumbo, no conflicts of interest.

[3] Abbreviations used: AI, Adequate Intake; EAR, Estimated Average Requirement; LOAEL, lowest-observed-adverse-effect-level; TSH, thyroid-stimulating hormone; UF, uncertainty factor; UL, Tolerable Upper Intake Level.

* To whom correspondence should be addressed. E-mail: paula.trumbo@fda.hhs.gov.

The FDA Total Diet Study collects information on the iodine content of ~280 foods; however, the content amount in foods does not reflect the variability of iodine in different brands of foods nor iodized salt use in food preparation. An RDA, used for assessing intakes of individuals, could estimate the iodine intake of individual infants without relying on national survey data. Furthermore, urinary iodine concentration is a reliable indicator of intake sufficiency for groups but not for individuals (11).

Unlike most vitamin and minerals, including iodine, breast milk was not considered to provide adequate amounts of iron and zinc to meet the needs of older infants, and therefore average consumption from breast milk was considered an inappropriate approach for setting an AI. Because data for factorial analysis to estimate the daily requirements of iron and zinc for older infants were available, an EAR, rather than an AI, was set (1). The U.S. and Canadian government DRI committees have recently posted information that would be useful in considering the need for a new or reevaluation of nutrient DRIs (12). One element that is being considered is whether there is significant, new, and relevant scientific information available for the nutrient of interest. Similar to iron and zinc, information would need to be available to indicate that breast milk consumed by United States and/or Canadian infants does not provide adequate amounts of iodine for young and/or older infants, and therefore average iodine consumption is an unacceptable approach for setting an AI. Furthermore, scientific evidence on daily requirements would need to be available to determine the EAR for young or older infants, as was the case for iron and zinc.

EARs and RDAs for Children and Adolescents

An EAR and RDA for iodine were set at 65 and 90 μg/d, respectively, for children 1–8 y of age (1) using data from balance studies (13,14). Because of the lack of sufficient experimental data on older children and adolescents (9–18 y), the EAR was determined by extrapolating from the adult EAR based on metabolic body weight. This extrapolation process was commonly used for setting EARs and RDAs for children and adolescents due to the lack of experimental data on nutrient requirements for these age groups. The EAR and RDA were set at 73 and 120 μg/d for children aged 9–13 y, respectively, and at 95 and 150 μg/d for adolescents aged 14–18 y of age, respectively.

Evidence was available on the urinary iodine concentrations associated with a 2% prevalence of goiter in children 6–15 y of age (15), which could directly estimate an RDA because the RDA is an estimate of the requirements for ~98% of a population group and urinary iodine is a proxy for iodine intake. An EAR, however, could not be determined by using goiter as an endpoint because urinary iodine data associated with a 50% prevalence of goiter for a group were not available. It is difficult, if not impossible, to use clinical endpoints of nutrient deficiency diseases (e.g., goiter), as well as for chronic disease risk (e.g., coronary heart disease), for establishing EARs because there seldom exists a high prevalence of such diseases in the vast majority of a population group, which is needed to determine the intake amount needed to reduce the incidence for 50% of the population (16).

The estimated average iodine intake range for children and adolescents was determined by using the FDA Total Diet Study (2003–2004) (9). Although the distribution of iodine intake was not determined, the lower and upper bound average ranged from 178 to 353 μg/d, suggesting that children and adolescents did not consume iodine at amounts below the EARs of 65 and 73 μg/d, respectively.

EARs and RDAS for Adults

The EAR and RDA of 95 and 150 μg/d, respectively, were set for adults using data published in the 1950s and 1960s on thyroid iodine accumulation and turnover as an indicator for daily iodine needs (17–22). Similar to iodine, most EARs for vitamins and minerals were based on data that estimated average daily needs (e.g., balance data, factorial analysis, status biomarkers).

For most nutrients for which an EAR could be established, the RDA is equal to the EAR plus 2 SDs of the EAR. Therefore, the RDA was calculated as the EAR plus twice the CV [i.e., RDA = EAR + 2 (%CV $\times$ EAR)] to cover the needs of 97–98% of individuals in a gender and life-stage group. For most nutrients, there was insufficient information to calculate a percentage CV, which is used to determine the RDA. When such information was lacking, the CV was assumed to be 10% based on the variation in the basal metabolic rate (23). A %CV for thyroid iodine accumulation and turnover could be calculated and was determined to be 40%. It was assumed that half of this large variation was due to the complexity of the experimental design and the calculations used to estimate thyroid iodine turnover, and therefore a CV of 20% was used instead. If such methods for estimating thyroid iodine accumulation and turnover have improved since the 1960s, then a more accurate EAR and RDA could possibly be determined.

Based on the FDA Total Diet Study (2003–2004), the lower and upper bound average iodine intakes ranged from 138 to 284 μg/d for adults (9). The lower bound of this range exceeds the EAR of 95 μg/d, suggesting that there is a low prevalence of inadequate iodine intake for adults.

EARs and RDAs for Pregnant and Lactating Women

An EAR and RDA of 160 and 220 μg/d, respectively, were set to meet the needs of pregnant women on the basis of data from balance studies (24,25), iodine supplementation studies (26–28), and the thyroid iodine content of newborns (29,30). The results of these 3 types of data indicated that the iodine requirement during pregnancy ranged between 160 and 170 μg/d. For lactating women, the EAR and RDA were set at 209 and 290 μg/d, respectively, by using the EAR for adult women plus the loss of iodine in breast milk. Many studies have evaluated the impact of iodine intake during pregnancy on fetal development and outcomes,

such as intelligence quotient (31). The EARs and RDAs for nutrients, however, have been set to meet the needs of pregnant and lactating women, rather than based on intake amounts to meet the needs of the developing fetus and newborn infants. Most recent information indicates that the incidence of congenital hypothyroidism in the United States is ~3.86 cases per 10,000 births (32), for which the most common cause is some form of thyroid dysgenesis (33). In populations with severe iodine deficiency and endemic goiter, the incidence of congenital hypothyroidism is much higher (34).

Urinary iodine concentration is typically used to assess iodine intake, and therefore iodine status of populations, and is measured in NHANES. On the basis of NHANES data, it has been concluded that iodine status of U.S. pregnant women may be insufficient (35), and this in turn could have a negative impact on fetal and infant development. Whereas iodine intake is generally not determined using NHANES data for the reasons previously discussed, the FDA determined iodine intake by using iodine food composition data from the FDA Total Diet Study, adjusted for iodized salt used in cooking, and food and dietary supplement consumption data from What We Eat in America, NHANES (2003–2008). The FDA determined that the mean iodine intake from food during pregnancy was ~315 μg/d (WY Juan, JKC Ahuja, K Egan, J Gahche, P Trumbo, unpublished results). Based on the distribution of this intake data and using the EAR, the prevalence of inadequate iodine intake was 8.5% among U.S. pregnant women, which is markedly lower than the percentage of pregnant women with inadequate urinary iodine concentrations (56%) using the WHO cutoff concentrations (36). This discrepancy may be due, in part, to the meaning of the EAR versus the cutoff values for urinary iodine concentration provided by the WHO. The WHO cutoff for urinary iodine concentration for pregnant women (<150 μg/L is indicative of insufficient iodine intake) is based on every 100 μg of iodine ingested being equivalent to 60 μg/L (37) and with the use of the WHO Recommended Nutrient Intake of 250 μg/d, which is equivalent to an RDA rather than an EAR. The EAR, not the RDA, is used to estimate the prevalence of inadequate intakes in groups (4). Using an RDA for assessing populations will overestimate nutrient inadequacy.

Endpoints of thyroid function, such as hypothyroidism, can help ascertain whether insufficient iodine intake is of public health concern in the United States. Based on NHANES (1999–2002) data, the incidence of hypothyroidism, of which insufficient iodine intake is one of several causes, was 3.1% for all women of reproductive age and 6.9% for pregnant women (38). In addition to significant, new, and relevant scientific information, the U.S. and Canadian government DRI committees are also considering whether a new or reevaluation of a DRI would help address an important public health concern (12). If inadequate iodine intake is a public health concern in the United States or Canada, then it would be important to know, for example, whether new scientific information suggests that the current EAR and RDA for pregnant women are too low and therefore underestimate inadequate iodine intakes during pregnancy, assuming that national survey data on iodine intake would become available.

Tolerable Upper Intake Levels

Several adverse effect endpoints were considered in setting a Tolerable Upper Intake Level (UL) for iodine, including subclinical hypothyroidism as defined by an elevation in serum thyroid-stimulating hormone (TSH) concentration, goiter as a result of increased TSH stimulation, and thyroid papillary cancer (1). Elevated TSH concentration was chosen as the adverse effect endpoint because it is an indicator for increased risk of developing clinical hypothyroidism and because dose-response data were available (39,40).

One study (39) provided 500, 1500, or 4500 μg/d of supplemental iodine to men. Baseline serum TSH concentrations significantly increased for those who consumed 1500 and 4500 μg/d of supplemental iodine. In a similar study (40), when supplements provided 250, 500, or 1500 μg/d of iodine, thyroid-releasing hormone–stimulated serum TSH concentration significantly increased for those who consumed 1500 μg/d of iodine. It was estimated that the amounts of iodine consumed from the diet in these 2 studies were ~200 and 300 μg/d, resulting in a total iodine intake of 1700 and 1800 μg/d, respectively, for those who had increased TSH concentrations.

On the basis of the findings of these 2 studies (39,40), it was determined that the lowest-observed-adverse-effect-level (LOAEL) was 1700 μg/d. To determine a UL, the LOAEL is divided by an uncertainty factor (UF). The UF was determined to be 1.5 and is relatively low compared with UFs determined for other nutrients, in part, because dose-response clinical trial data in humans were available and therefore there was little uncertainty about the LOAEL. On the basis of a LOAEL of 1700 μg/d and a UF of 1.5, the UL was set at 1100 μg/d for adults (1). As was the case for a number of other nutrients, data were lacking in children, adolescents, and/or pregnant and lactating women to directly set a UL for these groups. Therefore, the UL was set for these groups by extrapolating from the adult UL on the basis of body weight. The ULs for children aged 1–3 y, 4–8 y, and 9–13 y and adolescents aged 14–8 y are 200, 300, 600, and 900 μg/d, respectively (1). The UL for pregnant and lactating women is 1100 μg/d.

The proportion of a group with usual intakes above the UL can be used to estimate the percentage of the population at potential risk of adverse effects from excessive nutrient intake (4). The 95th percentile of intake is usually compared with the nutrient UL, as was the case for iodine using iodine intake data from the FDA Total Diet Study (1991–1997) (1). Although the distribution of iodine intake was not provided, it was determined by using the more recent FDA Total Diet Study (2003–2004) that the upper bound average intake did not exceed the ULs for any of the groups except for children 2 y of age for whom the UL is 200 μg/d and the estimated lower and upper bound average iodine intake was 225 to

247 μg/d (9). Because NHANES has been measuring urinary iodine and measures of thyroid function in individuals ≥6 y of age, NHANES data are not available to further evaluate the iodine intake data for children 2 y of age. Furthermore, most of the published data on urinary iodine from NHANES have focused on inadequate amounts (e.g., urinary iodine <100 μg/L) rather than providing the full distribution of urinary iodine concentration. Excessive intakes of iodine, however, generally do not appear to be a public health concern in the United States.

Conclusions

Like many vitamins and minerals, the iodine AI for infants was set on the basis of the average intake from breast milk. Research that could better inform the need for reevaluating the AI for infants includes evidence to indicate that breast milk consumed by U.S. and/or Canadian infants does not provide adequate amounts of iodine for young and/or older infants and evidence to determine the EAR for young or older infants. For other age groups and pregnant and lactating women, significant, new, and relevant data, as well the need to reevaluate the DRIs for iodine to address a public health concern in the United States and/or Canada, would be useful to the DRI government committees for consideration. New and relevant data on iodine could be based on studies that used the same endpoints for setting the current DRIs or different endpoints for which the totality of the evidence could be used for updating the DRIs for iodine.

Acknowledgments

The sole author had responsibility for all parts of the manuscript.

Literature Cited

1. Swanson CA, Pearce EN. Iodine insufficiency: a global health problem? Adv Nutr. 2013;4:533–5.
2. Institute of Medicine. Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington: National Academies Press; 2001
3. Institute of Medicine. Dietary Reference Intakes: application in dietary planning. Washington: National Academies Press; 2003.
4. Institute of Medicine. Dietary Reference Intakes: applications in dietary assessment. Washington: National Academies Press; 2000.
5. Institute of Medicine. Dietary Reference Intakes for water, potassium, sodium, chloride, and sulfate. Washington: National Academies Press; 2005.
6. Gushurst CA, Mueller JA, Green JA, Sedor F. Breast milk iodine: reassessment in the 1980s. Pediatrics. 1984;73:354–7.
7. Etling N, Padovani E, Fouque F, Tato L. First-month variations in total iodine content of human breast milks. Early Hum Dev. 1986;13:81–5.
8. Johnson LA, Ford HC, Doran J, Richardson VF. A survey of the iodide concentration of human milk. N Z Med J. 1990;103:393–4.
9. Murray CW, Egan SK, Kim H, Beru N, Bolger PM. US Food and Drug Adminstration's Total Diet Study: dietary intake of perchlorate and iodine. J Expo Sci Environ Epidemiol. 2008;18:571–80.
10. Swanson CA, Zimmerman MB, Skeaff S, Pearce EN, Dwyer JT, Trumbo PR, Zehaluk C, Andrews KW, Carriquiry A, Caldwell KL, et al. 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. Am J Clin Nutr. 2012;142 Suppl:1175S–85S.
11. Delange F, de Benoist B, Burgi H; ICCIDD Working Group. Determining median urinary iodine concentration that indicates adequate iodine intake at population level. Bull World Health Organ. 2002;80:633–6.
12. U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Nomination for new Dietary Reference Intakes reviews. 2013 [cited 2013 Sept 24]. Available from: http://www.health.gov/dri/Default.asp.
13. Ingenbleek Y, Malvaux P. Iodine balance studies in protein-calorie malnutrition. Arch Dis Child. 1974;49:305–9.
14. Malvaux P, Beckers C, de Visscher M. Iodine balance studies in nongoitrous children and in adolescents on low iodine intake. J Clin Endocrinol Metab. 1969;29:79–84.
15. Delange F, Benker G, Caron P, Eber O, Ott W, Peter F, Podoba J, Simescu M, Szybinsky Z, Vertongen F, et al. Thyroid volume and urinary iodine in European schoolchildren: standardization of values for assessment of iodine deficiency. Eur J Endocrinol. 1997;136:180–7.
16. Trumbo PR. Challenges with using chronic disease endpoints in setting dietary reference intakes. Nutr Rev. 2008;66:459–64.
17. Fisher DA, Oddie TH. Thyroidal radioiodine clearance and thyroid iodine accumulation: contrast between random daily variation and population data. J Clin Endocrinol Metab. 1969;29:111–5.
18. Fisher DA, Oddie TH. Thyroid iodine content and turnover in euthyroid subjects: Validity of estimation of thyroid iodine accumulation from short-term clearance studies. J Clin Endocrinol Metab. 1969;29:721–7.
19. Riggs DS. Quantitative aspects of iodine metabolism in man. Pharmacol Rev. 1952;4:284–370.
20. Berson SA, Yalow RS. Quantitative aspects of iodine metabolism: the exchangeable organic iodine pool, and the rates of thyroidal secretion, peripheral degradation and fecal excretion of endogenously synthesized organically bound iodine. J Clin Invest. 1954;33:1533–52.
21. Ermans AM, Dumont JE, Bastenie PA. Thyroid function in a goiter endemic: I. Impairment of hormone synthesis and secretion in the goitrous gland. J Clin Endocrinol. 1963;23:539–49.
22. DeGroot LJ. Kinetic analysis of iodine metabolism. J Clin Endocrinol Metab. 1966;26:149–73.
23. FAO/WHO/United Nations Association. Energy and protein requirements report of a Joint FAO/WHO/UNA expert consultation. Geneva: WHO. Technical Report Series No.724. 1985.
24. Delange F, Bourdoux P, Vo Thi LD, Ermans AM, Senterre J. Negative iodine balance in preterm infants. Ann Endocrinol (Paris). 1984;45:77.
25. Dworkin HJ, Jacquez JA, Beierwaltes WH. Relationship of iodine ingestion to iodine excretion in pregnancy. J Clin Endocrinol Metab. 1966;26:1329–42.
26. Romano R, Jannini EA, Pepe M, Grimaldi A, Olivieri M, Spennati P, Cappa F, D'Armiento M. The effects of iodoprophylaxis on thyroid size during pregnancy. Am J Obstet Gynecol. 1991;164:482–5.
27. Pedersen KM, Laurberg P, Iversen E, Knudsen PR, Gregersen HE, Rasmussen OS, Larsen KR, Eriksen GM, Johannesen PL. Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation. J Clin Endocrinol Metab. 1993;77:1078–83.
28. Glinoer D. Iodine supplementation during pregnancy: Importance and biochemical assessment. Exp Clin Endocrinol Diabetes. 1998;106:S21.
29. Delange F, Ermans AM. Iodine deficiency. 6th ed. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's the thyroid: a fundamental and clinical text. Philadelphia; J.D. Lippincott; 1991;368–89.
30. Delange F. Research in iodine nutrition and congenital hypothyroidism. In: Delange F, Fisher DA, Glinoer D, editors. Research in congenital hypothyroidism. New York: Plenum Press; 1989. p. 5–13.
31. Zhou SJ, Anderson AJ, Gibson RA, Makrides M. Effect of iodine supplementation in pregnancy on child development and other clinical outcomes: a systematic review of randomized controlled trials. Am J Clin Nutr. 2013 Sep 11. [Epub ahead of print].
32. U.S. Department of Health and Human Services; Center for Disease Control and Health Promotion. Pediatric genetics, data and statistics. Newborn screening and related conditions. 2011 [cited 2013 Sept 24]. Available from: http://www.cdc.gov/ncbddd/pediatricgenetics/data.html.

33. Kaye CI; Committee on Genetics. Newborn screening fact sheets. Pediatrics. 2006;118:e934–63.
34. Delange F. Iodine nutrition and congenital hypothyroidism. In: Delange F, Fisher DA, Glinoer D, editors. Research in Congenital hypothyroidism. New York: Plenum Press; 1989. p 173–85.
35. Sullivan KM, Perrine CG, Pearce EN, Caldwell KL. Monitoring the iodine status of pregnant women in the United States. Thyroid. 2013;23: 520–1.
36. Caldwell KL, Pan Y, Mortensen ME, Makhmudov A, Merril L, Moye J. Iodine status in pregnant women in the National Children's Study and in U.S. women (15–44 years), NHANES 2005–2010. Thyroid. 2013;23: 927–37.
37. WHO Secretariat on behalf of the Participants of the Consultation. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutr. 2007; 10:1601–11.
38. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). Thyroid. 2007;17:1211–23.
39. Gardner DF, Centor RM, Utiger RD. Effects of low dose oral iodine supplementation on thyroid function in normal men. Clin Endocrinol (Oxf). 1988;28:283–8.
40. Paul T, Meyers B, Witorsch RJ, Pino S, Chipkin S, Ingbar SH, Braverman LE. The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism. 1988;37:121–4.