Iodine Nutrition: Iodine Content of Iodized Salt in the United States

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Adequacy of iodine nutrition in the United States has lately been of concern. A major source of dietary iodine for the U.S. population is iodized salt. The U.S. Food and Drug Administration (USFDA) recommends 60–100 mg KI/kg salt, equivalent to 46–76 mg I/kg salt. All U.S. iodized salt contains 45 mg I/kg according to labels. We collected samples of table salt from freshly opened containers from U.S. volunteers. A sample was sent to us when the can was first purchased. Subsets of volunteers sent further samples when the salt container became half-empty through normal use and a further final sample when the container was nearly finished. We also looked at iodine distribution homogeneity within individual containers, loss of iodine from salt upon exposure to humidity and sunlight, and upon short-term heating (dry and in solution) as may be encountered in cooking. Measurements were made in 0.01% w/v salt solutions by induction coupled plasma−mass spectrometry with ^{72}Ge as an internal standard. The median and mean (±sd) I content in freshly opened top-of-the-can salt samples was 44.1 and 47.5 ± 18.5 mg/kg (n = 88, range 12.7–129 mg I/kg) and geometric mean and standard deviation of 44.70 and 1.41. Forty-seven of 88 samples fell below the USFDA recommended I content while 6 exceeded it. The homogeneity in a single can of salt varied greatly: in 5 samples taken from the same container from different depths, the iodine content varied by as little as 1.2× (8.3% coefficient of variance (CV)) to as much as 3.3× (49.3% CV) from one container/brand to another. Iodine is significantly lost upon high humidity storage but light or dry heat has little effect. There is much recent literature on iodine sufficiency and uptake inhibitors; there is also much misinformation and disinformation. We review the relevant literature and discuss our results with reference to the United States.

Introduction

In humans iodine is needed by the thyroid gland to produce indispensable thyroid hormones. Although only vertebrates have the thyroid gland and the iodinated hormones, iodine is believed by some to be essential for all life (*1*). In humans, ∼60–80% of the total iodine is extrathyroidal (*2*); their complete role is unknown. When oxygen first appeared in the terrestrial atmosphere, iodinated compounds may have played a central role to scavenge and thus detoxify reactive oxygen species (*3*).

Discovery, Early History, and Goiter. Rosenfeld (*4*) summarized the discovery and early uses of iodine. In 1811, Courtois serendipitously discovered iodine by heating seaweed ash with sulfuric acid (*5*). Inadequate intake leads to iodine deficiency disorders (*6*), the most visible manifestation being the enlargement of the thyroid gland, called goiter, observed not only in man but also in animals (*7*). Although "iodine" itself was unknown, Chinese medical writings advocated treating goiter with seaweed and burnt sea-sponge, nearly 4 millennia ago (*4*). In 1831, Boussingault (*8*) discovered that goiter can be completely cured by administering naturally iodized water or minerals containing iodine. Although Goiter was particularly prevalent in the Midwest and the Great Lakes States (known as the Goiter Belt (*9, 10*)], such iodine therapy would not be practiced in the United States until the next century (*11*). Primarily due to recommendations of Marine (*11*), U.S. salt iodization was instituted in 1924; beneficial effects on thyroid disorders began to be recorded almost immediately (*12*).

Politics and Technology of Salt Iodization. Unlike some 120 countries (including Canada and parts of Mexico) (*13, 14*), which adapted mandatory iodization of all food grade salt, salt iodization is voluntary in the United States. Veteran congresswoman Frances Bolton once attempted to legislate mandatory salt iodization; the salt producers association prevailed with the argument that this is *medication by legislation* (*15*). Failing mandatory iodization, the U.S. Public Health Service launched a nationwide educational program in 1949 for consumers to ask specifically for iodized salt at the grocery. The USFDA approves KI (0.006–0.01%) and CuI (0.01% maximum) as iodization vectors (*16*), while the World Health Organization (WHO) prefers KIO_3 due to its greater stability (*17*). As iodine stabilizers, ingredients approved by the USFDA for iodide as additive include dextrose (no limit, typ. 0.0374%) and $Na_2S_2O_3 \cdot 5H_2O$ (0.1% max) as well as $NaHCO_3$, Na_2CO_3, and $Ca_3(PO_4)_2$ as buffering agents that also help prevent iodine loss.

Iodine Intake in the West, Especially the United States. Iodine intake has decreased in recent decades in the west in general (*18–20*) and the United States in particular (*21–23*). Salt is a major vector for iodine in the United States. But because excessive sodium intake can increase hypertension risks, many agencies now recommend reduction of salt intake (*24–26*). A 1995 report found 58% of men and 68% of women having reported never using salt, using "lite" salt, or rarely using ordinary table salt (*27*). More recently, the American Medical Association has taken the extraordinary position to suggest that the USFDA remove salt from the *Generally Recognized as Safe* list (*28*).

The U.S. Institute of Medicine (IOM) recommended daily allowance (RDA) or adequate intake (AI) of iodine for different population groups range from 90 μg I/day for 1–8 year olds to 290 μg/day for a lactating mother; a detailed list appears in Table S1 in Supporting Information (SI) (*29*). In most adults, iodine input and output is believed to be in stasis, 90–100% of the input iodine is presumed to appear in the urinary output. A hypothetical 70-kg adult produces a urinary output of 1.2 L with a creatinine content of 1.3 g (*30*). (More recent numbers for both men [median 1.65 L (*31*)] and women [1.73 L (*32*)] suggest a greater daily urinary volume but presently we will assume the traditional value of 1.2 L.) Iodine intake at the recommended level will thus be reflected in a urinary iodine concentration (UI) of 11–12.5 μg/dL (∼104 μg/g

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creatinine) for a regular adult (RDA 150 μg/day) to 18 and 24 μg/dL for a pregnant and lactating woman, respectively.

Iodine intake in the U.S. diet has decreased since the early 70s. The U.S. median UI was 32 μg/dL in 1971–74 vs 14.5 μg/dL in 1988–1994, suggesting a ~50% reduction in dietary iodine intake. The more recent study shows no statistical change, the median value of urinary iodine was 16.1 μg/dL (*33*). In a 2004 study of 100 pregnant mothers in Boston, Pearce et al. (*23*) report that 49% of pregnant women were taking iodine below the RDA (assumed to correspond to an UI of 15 μg/dL) and 9% had UI classifiable as iodine-deficient.

At least in young children, milk/dairy products were previously a major source of iodine. While milk iodine levels do show seasonal variation (being highest in the winter *7, 34, 35*), the average iodine content of U.S. dairy whole milk decreased from a high of 602 ± 184 μg/L in 1978 to 155 ± 19 μg/L in 1989–90 (*34*). More recent limited measurements indicate an average value <100 μg/L (*36, 37*). Food basket data (*38*)]show how precipitously iodine intake in the US has fallen, across all age groups (Figure S1).

Why Have Iodine Intake Levels Decreased? About three decades ago, there was a concern that the U.S. population may be getting too much iodine. Although no study ever established that such "excess iodine" caused a problem, certain practices were changed. Specifically, the two major factors contributing to lowered U.S. iodine intake since the 1970s are the reduced use of iodine-based disinfectants/iodine in feed supplement in the dairy industry, and the reduction/elimination of iodate (IO_3^-)-based conditioners in bread (*21, 35, 38*). The link between the milk iodine content and iodine use in the dairy industry (as well as that between the discontinuation of this practice in countries that emulated the United States and the decline in iodine nutrition there) is well established (*39–43*). Udder/teat disinfection by iodine-based disinfectants actually results in absorption and re-expression (*44*). In several countries, the cessation of use of iodine compounds in the dairy industry and the re-emergence of iodine insufficiency have led to calls for universal/mandatory iodization of all salt (*19, 41, 45, 46*). In the United States, children drink much less milk today than they did in the past decades (*22*).

Regarding bread, Pearce et al. (*35*) reported on 20 types of bread marketed in the Boston area. The practice is remarkably non-uniform: 15 brands added an insignificant amount of iodine to the intake (6 ± 4 μg/slice), two had an intermediate level of iodine (~30–55 μg/slice), and the other three contained iodine at 2–4 times the RDA per slice.

Goitrogens, Salt, and the Iodine Content of Salt. It is established that transport of iodide into the thyroid or into milk of mammals is mediated by a membrane protein, the sodium-iodide symporter (NIS) (*47*). It has long been known that certain other ions, especially those that are large and polarizable like thiocyanate (significant amounts result from tobacco smoking and the consumption of certain vegetables) and perchlorate, act as competitive inhibitors to iodide (*48*); these are often termed goitrogens. Perchlorate is particularly potent; it displays 30 times the affinity for the human NIS than does iodide (*49*). In the wake of the discovery that perchlorate is widely present in our environment (*50*), in our food and beverages (*51*) and milk, human or bovine (*36, 37, 52, 53*), there has been much concern about inhibition of iodine uptake (*54*), regardless of whether perchlorate originates from natural, rocket propellant, Chilean nitrate fertilizer, or other sources (*50, 55, 56*). If one begins with poor iodine nutrition, removing goitrogens from one's diet will not restore iodine nutrition.

Japan is one of the few countries where salt is *not* iodized because the Japanese diet contains large amounts of iodine-rich seaweed (*57*). One study reported the average urinary excretions in Japan to range between 700 and 3200 μg/d (*58*); this is considerably over what U.S. doctrine would regard as the maximum safe level. Nevertheless, thyroid health in Japan is excellent; there is no excess incidence of autoimmune thyroiditis that supposedly results from excess iodine consumption (*59*). In nations where salt is assumed to be a significant source of iodine, the precise iodine content of the salt is of obvious interest. It is a myth (often also false advertising) that "natural" sea salt contains significant amounts of iodine. The iodide content of seawater is only 64 μg/kg or 2.1 mg I/kg NaCl. In evaporatively prepared salt, the iodide/chloride ratio is even lower because of iodine loss; crystallization processes leave iodide selectively in the mother liquor. Aquaron (*60*) examined 81 "natural" salt samples from 21 countries: all contained ~<0.7 mg I/kg with the exception of Nigerian samples (1.4–6.5 mg I/kg) made from underground brine. He also examined iodized salts from many countries. Although a limited number of samples were analyzed, it cannot be reassuring to the U.S. population that the United States and Spain were the only two countries where the salt samples consistently fell below the respective recommended iodization levels.

In a newborn, the thyroid holds only a 24 h reserve of the necessary iodine (*61, 62*); fresh supplies of iodine must come from the feed. Iodine is critical to allow production of thyroid hormones that govern neurodevelopment in the infant and young children. Sufficient iodine is essential to prevent mental retardation: the World Health Organization (WHO) maintains that on a worldwide basis, iodine deficiency is the most common cause of cretinism and is the most easily preventable (*63*). When we consider that links between iodine deficiency and attention deficit disorders (ADD (*64*)) have been reported and the diagnosed incidence of ADD in the United States is now at an all-time high (an estimated 3–5% of all children (~2 million) have ADD (*65*)), we wanted to assess if salt iodization is being properly carried out.

Experimental Section

Sample Collection. Rather than purchase only locally available salt, we undertook a salt solicitation campaign. The solicitation went out to friends and professional colleagues and the senior author made a pitch for salt contribution at whichever scientific conference he attended. Briefly, we solicited 20–25 g of salt from the top of a fresh container, to be put in a thick-walled zip-lock bag, excluding air as best as possible when sealing the bag. The bag was then to be wrapped with aluminum foil on the outside before being mailed to the researchers along with the following information: city and store bought, date bought, manufacturer or supplier or brand name, product label batch code (from bottom of container) and any stated iodine content information, sender's name and contact information. We also solicited, if possible, for volunteers to send a second sample when the salt container was about half-empty and a final third sample when the salt container was nearly exhausted. An excerpt from the solicitation letter appears in SI. In each case upon receipt, the sample was logged in with a receipt date and stored at −20 °C in the dark until analysis. A few samples were damaged in the mail and were not analyzed. We received 88 samples from freshly opened containers, 50 samples from half-empty containers, and 30 samples from the bottom of the container. The samples came from 40 of 50 states, plus the District of Columbia; the greatest number (17) was from TX; Table S2 in SI details the number distribution of the samples from the different states. It may be useful to augment the present study with another where an even greater number of samples are directly purchased by investigators.

Effect of Humidity. The effect of humidity and other iodine stability experiments on salt samples were all con-

ducted with a brand of salt that contained dextrose as a stabilizer. The salt sample was thoroughly homogenized before the experiments. Sulfuric acid solution (~100 mL) was put at the bottom of a 500 mL beaker. A weighted down 25-mL beaker was used as a pedestal inside the larger beaker to hold up a watch glass on which a ~5–10 g salt sample was distributed in an even layer. Water-impermeable Parafilm was used to seal the larger beaker. Three concentrations of H_2SO_4 solution were chosen based on equilibrium relative humidity (RH) values tabulated in standard compilations; the actual RH was measured with a high-precision digital hygrometer (model RH-45400, Extech Instruments) to be 90.1%, 81.8%, and 67.6% at the laboratory temperature of 22 ± 1 °C. In addition, the same measurement was made at ambient laboratory humidity (36 ± 4% RH). The assembly was stored in the dark and periodically salt samples were removed and analyzed.

Effect of Light Exposure and Simulated Cooking. Salt samples were stored at a RH of 36 ± 4% RH at 22 ± 1 °C in darkness and under 24 h exposure to fluorescent lighting. Salt aliquots were periodically withdrawn and analyzed. To simulate dry and wet cooking, we respectively heated a salt sample by placing it in an oven kept at 200 °C and boiled a salt solution, both for 5 min.

Homogeneity Determination. Iodine is added to table salt as KI in dry form or more typically by spray from a solution. There are no extant reports as to how homogeneously the iodine is distributed in marketed iodized salt. To study this, four brands of iodized salt were investigated. The salt container was put on its side and holes were punched in the wall to extract samples (~1.25 g each) from the top, bottom, and three more equally spaced locations between.

Analysis. All chemicals used were analytical reagent grade and 18.3 MΩ deionized (DI) water (Milli-Q) was used throughout. For preparation of calibration standards, 5.000 g of reagent grade NaCl was dissolved in 90 mL water, and 1 mL of 1000 mg I/L (0.1307 g KI/L) standard was added and water added to make up to 100 mL. This contains 10 mg I/L in a 5% w/v NaCl matrix. This solution was blended with a 5% w/v pure NaCl solution to make different concentrations of iodide (0–10 mg I/L, corresponding to 0–200 mg I/kg in the original salt) in a 5% w/v NaCl matrix. Samples were prepared the same way; except that 0.500 g was dissolved in 10 mL of water and filtered through a 0.45-μm nylon membrane syringe filter to remove any insoluble material. For analysis, an internal standard stock solution was first prepared. The internal standard was made from GeO_2 (99.999%, www.strem.com); a stock solution was made by dissolving 0.37 g GeO_2 in 100 mL of 40 mM NaOH. A working internal standard solution was prepared by 1000× dilution of this solution. To 9.8 mL of Milli-Q water, 0.1 mL of the 5% salt sample or calibration standard and 0.1 mL of the diluted Ge standard was added. The actual samples and standards analyzed thus had a 0.05% NaCl matrix. Specifically ^{72}Ge (natural abundance 27.54%) was used as the internal standard.

Samples and standards were loaded into the autosampler rack (Cetac, ASX-520) and the automated analysis procedure was initiated. The peristaltic pump built into the X-series II induction coupled plasma−mass spectrometer (ICP−MS, Thermo Electron Corp.) was used to prime the sample into the Peltier-cooled nebulizer at 1.6 mL/min for 45 s and then continuously deliver the sample to the nebulizer at 0.8 mL/min. Each measurement cycle consisted of a 20-s qualitative mass survey scan followed by three 32-s long quantitative mass scans. Once the sampling was complete, the autosampler probe was washed in DI water for 1 min before storage. Detailed operating conditions of the ICP−MS are given in SI (Table S3).

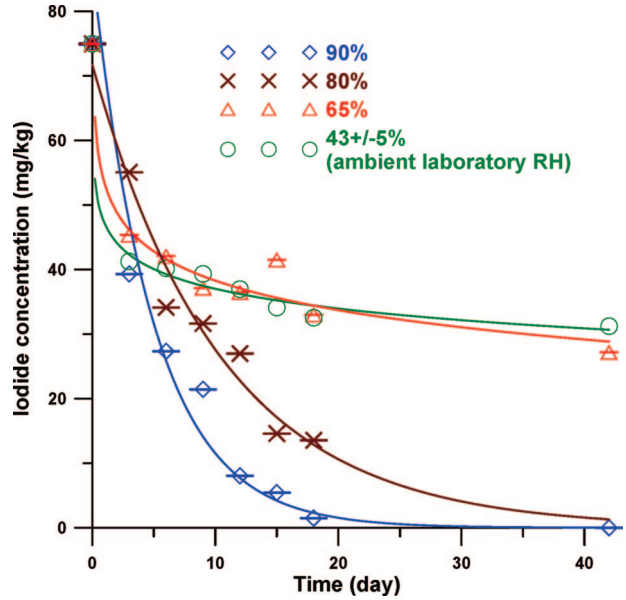

FIGURE 1. Loss of iodine over time with exposure to air with specified humidity levels, no light, 22 ± 1 °C.

Results and Discussion

Analytical Performance. Measurement of iodide or iodate by ICP−MS with Ge as an internal standard reportedly exhibits excellent performance parameters (*66*). We routinely obtained a limit of detection (LOD, 3σ, where σ is the standard deviation of the blank) of 0.047 μg/L, corresponding to ~0.9 mg I/kg salt. Iodide spike recovery (0–15 mg I/kg equivalent added to a Brand M salt sample containing 32 mg I/kg) was 100.0 ± 1.2% and the linear correlation coefficient (r^2) was 0.9985 (six different spike levels, including none) with an intercept statistically indistinguishable from zero.

Stability as a Function of Storage Humidity. In air, iodide is oxidized to iodine that can readily sublime. Heat and moisture also cause loss of iodine; microencapsulation reduces such loss (*67, 68*). However, few quantitative results are available on the rate of iodine loss from U.S. iodized salt. We chose a salt formulation that contained dextrose, the most commonly used stabilizer in our samples. The data shown in Figure 1 indicate that for RH values up to 65% at our test temperature of 22 ± 1 °C, the iodine loss does *not* follow an exponential loss pattern and is virtually the same, regardless of humidity. The initial loss rate is steep but after that it stabilizes such that little further loss occurs over time (the two best-fit lines shown are log–log fits). In contrast, at >80% RH, the loss proceeds exponentially ($r^2 > 0.95$ in both cases). These data suggest that the iodine on the surface is rapidly oxidized. At lower RH, the crystal is solid and the rate determining process is the migration of iodide to the surface to be oxidized. The deliquescence point of NaCl is 75% RH (25 °C), a liquid phase is present on the surface at humidities higher than this. Iodide migration to the surface and air oxidation is facilitated above the deliquescence point. With increasing RH beyond this, for the solution phase, the equilibrium water content increases and the viscosity decreases, facilitating diffusive migration. It is remarkable that at 80 and 90% RH (admittedly extreme conditions), the corresponding iodine half-lives are only 7.25 and 3.4 days. Even at low humidities the loss can be significant over long periods. Biber et al. (*69*) report 58.5% loss at 30–45% RH over 3.5 years in sealed paper bags.

Effect of Heat and Light. We found only a minor acceleration of decay on exposure to light at low humidities; Figures S2 and S3 in SI show the results and are not further discussed. Biber et al. (*69*) observed a 41% loss on 24-h

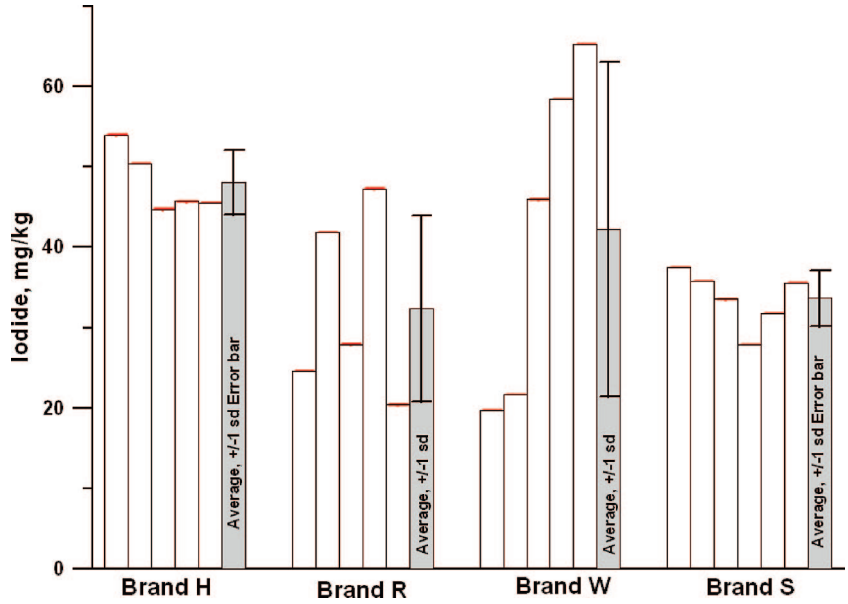

FIGURE 2. Homogeneity of iodine distribution in four individual cans of salt. Left to right bars: top to bottom, followed by the average. The respective coefficients of variance were 8.3, 35.7, 49.3, and 10.3%, respectively.

exposure to 200 °C; this is more extreme than may be encountered. Of 4 brands of salt examined (all stabilized with dextrose), we did not find any statistically significant iodine loss upon 5 min exposure to 200 °C for two of the samples ($p = 0.96$ and $p = 0.68$), the third showed an apparent 8.5% loss on heating (barely statistically significant, $p < 0.25$), but the fourth, an "iodized sea-salt" sample, showed 25.9% loss ($p < 0.01$), see Figure S4.

Wang et al. (*70*) examined iodine retention by cooked food from added iodized salt; 14–63% was lost. Because of the matrix, its native iodine content, and the use of a simple spectrophotometric procedure, the reliability of these data is uncertain. We chose to simply determine iodine loss upon boiling a 5% salt solution for 5 min; 21–68% was lost ($p <$ 0.001 for all), see Figure S5. As some retention by the food matrix, especially those containing antioxidants, will be expected, this may be an upper limit.

Homogeneity of Iodine Distribution in a Single Can of Salt. All U.S. iodized salt containers typically state: One serving ($^1/_4$ tsp, 1.5 g) contains 45% of the daily RDA of iodine. With current U.S. adult RDA being 150 μg/day, this translates to an iodine content of 45 mg/kg. A consumer implicitly assumes that the iodine is homogeneously distributed within a can of salt. In reality, there are no publicly available data on this. The distribution of iodine in individual cans of salt from four brands is shown in Figure 2. The standard deviations of the individual measurements *are* shown but are generally too small to be visible in the figure. The distribution was reasonably uniform for the particular brand H and S cans studied but this was not the case for the other two samples. In brand R, the iodine content randomly varied from top to bottom. In brand W, the iodine content steeply increased from top to bottom, resulting in a ~50% coefficient of variance.

Iodine in Freshly Opened Containers of U.S. Iodized Salt. In China all salt is iodized; Wang et al. (*70*) studied commercial food-grade salt and salts intended for household consumption. Of the latter samples, 72% were found to be in compliance with the Chinese national standard (20–50 mg/kg). No similar study is available for the United States. Figure 3 shows the results for freshly opened top-of-the-can U.S. samples. Some 46 samples (52%) fell below the USFDA-suggested iodization range (which is admittedly higher than that in most other countries) while 6 of 88 samples (7%) exceeded the recommended range. The median (44.1 mg I/kg) was just below the recommended range and was essentially the same as the manufacturer-stated 45 mg I/kg. The mean was 47.5 mg I/kg with a substantial standard deviation of 18.5 mg I/kg (39% RSD). Some 49 of the 88 samples were brand M, presumably with the largest market share. With a median of 41.6 mg/kg, brand M iodine content was not markedly different and the variance was in fact higher (mean ± SD: 48.4 ± 20.8 mg/kg). Brand M samples were statistically indistinguishable from the complete set of samples.

Several other salt samples had ambiguous labels. Some stated that it "contains iodine, an essential nutrient" but did not state an exact content. A "garlic salt" sample contained 4.3 ± 0.3, a "Kosher" salt sample contained 2.6 ± 0.0, and a "real salt" sample contained 2.3 ± 0.2 mg I/kg. Two other batches of the same brand of "real salt" samples supplied by other volunteers contained no iodine detectable by us (<0.9 mg I/kg).

As a matter of allied interest, we analyzed a few salt samples from UK, Canada, Brazil, The Netherlands, Singapore, Thailand, China, India, Belgium, Australia, and Japan. Salt is not iodized in Japan and this iodized salt was actually imported; iodine content was detectable but low at 14 mg/kg. All of the other samples except one from Australia fell within the levels of iodization recommended by the individual countries.

Serial Samples. The analysis of serially obtained samples was intended to reveal loss over time. The discovery of substantial inhomogeneity within an individual can made conclusions about temporal loss difficult. Similar to the brand W sample in Figure 2, one admittedly extreme case of a brand M sample registered 56 mg/kg at the top ($t = 0$), 106 mg/kg from midcan ($t = 218$ days), and 220 mg/kg at the bottom ($t = 251$ days). Clearly these results are dominated by inhomogeneity issues; loss, if any, cannot be ascertained. However, the totality of the data suggests that loss probably does occur during use. We use the following designation with respect to the measured iodine concentration: *123* connotes sample 1 (top) > Sample 2 (middle) > Sample 3 (bottom). For cases where only two samples were turned in, *12* ($n = 16$) was far more frequent than *21* ($n = 7$). For three samples turned in, the situation was similar; the occurence of *123* ($n = 14$) outnumbered all others: *213* and *321* ($n = 3$ each), *312* and *132* ($n = 2$ each) and *231* ($n = 1$). However,

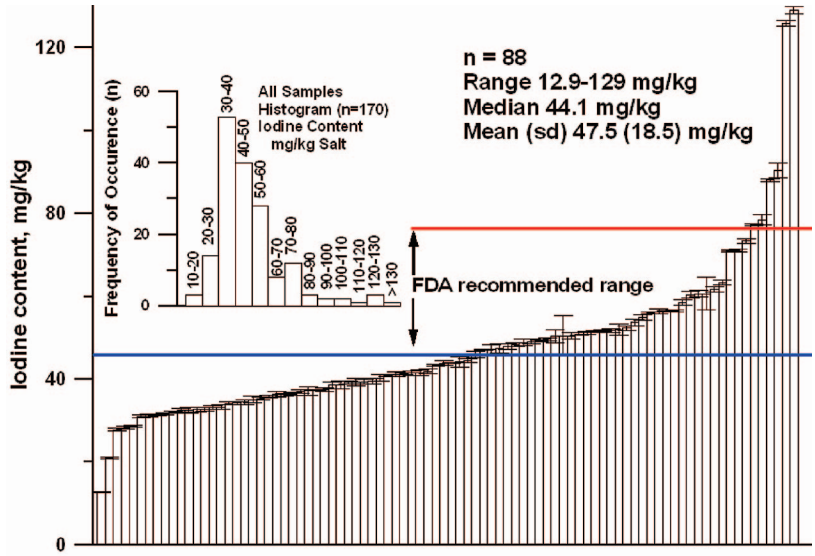

FIGURE 3. Iodine content of freshly opened top-of-the can U.S. iodized salt samples. Inset: Frequency distribution of iodine content of all U.S. iodized salt samples examined.

given the inhomogeneity issue, these data do not merit a further quantitative discussion of loss.

How Much Iodine Do We Get from Salt? The Iodine Gap. Some of the serial salt donors regarded themselves as "low salt consumers" and followed our advice of simulating use by periodically throwing away a handful to complete the study in a reasonable period. However, 17 donors consumed the salt in a "normal" manner. The median time for complete consumption was 201 days (range 61–640 d). Based on the number of people in the respective households and the time taken for a can (737 g) to be emptied, the average salt consumption ranged from 0.34 to 4.03 g/d, with an average(±SD) of 1.47(±0.94) and a median value of 1.24 g/d, without accounting for the amounts sent to us as samples (that would reduce the consumption figures by ~10%). Several participants noted that much of the salt was used in baking events where products were largely consumed by others, or that the salt was added to water for boiling, e.g., pasta, where the liquid bearing much of the salt was discarded, etc. These data suggest that iodine intake from salt (containing 45 mg I/kg) would fall substantially short of meeting iodine requirements. If one indeed adopts a diet that is sodium-healthy, and consumes no more than 5 g of salt per day as per WHO recommendations (*26*), the approximate iodine intake from salt would still be of the same order, 45 μg (assuming the salt contained 45 mg I/kg) *because only one-fifth of the salt consumed in the United States is iodized.*

Contrary to popular belief, the vast majority of salt in the U.S. diet is not iodized. Approximately 70% of the salt is used commercially—virtually none of the salt used by the prepre-pared or the fast food industry is iodized. Approximately 70% of the remaining 30%, sold to consumers in grocery stores, is iodized, representing one-fifth of the total salt consumed (*14, 71*). Others have recognized the emerging iodine deficiency issue (*72, 73*). Satin (*73*) suggested that the restaurant/food service trade must demand and use iodized salt so that meals consumed away from home provide the same iodine level as at home. If all salt was iodized, a 5-fold increase in iodine intake can occur *without increasing salt intake*. Whether consumer demand can persuade the food industry to do so or legislation is needed is not a scientific issue. A large number of countries have chosen the route of mandatory universal salt iodization. In the United States, an affluent country, another issue that ironically underlies the *iodine gap* is the unseen discrimination based on economic classes. To paraphrase Stephen (*74*), there is no disease worse than poverty. Consumption of prepackaged or fast food is much greater among the less affluent (*75–78*), leading to, and perhaps even perpetuating, the *iodine gap*.

Other Iodine Vectors. Information and Disinformation. The WHO has adopted in some countries a yearly dose of slow-release iodized oil, especially for children. In Spain, tablets containing 200 μg of iodine are made available to pregnant and lactating women through the national health system (*79*). Many travelers and others use iodine for water disinfection for which the recommended upper limit is 2 mg/day and a maximum period of 3 weeks (*80*).

Regarding the minimum requirement, optimum dose, and maximum permissible safe amount for iodine, it is difficult to separate fact from fiction. At one extreme, Abraham (*81*) believes that while 50 μg/day may be sufficient to prevent goiter, the actual optimum iodine requirement has never been proven and it may be a thousand times higher. He claims that triiodide (I_3^-) is the best vector for iodine and argues that salt is a poor choice because iodide is obligatorily added with a much larger amount of competing chloride. Considering the high chloride concentration normally present in gastric juice, this argument seems moot. Few question that iodization of salt has made a major difference to human health. In May 2007, World Health Assembly unanimously approved a resolution to continue efforts to foster universal salt iodization (*82*). Satin (*73*) calls it the most effective dietary intervention of the 20th century and laments that the Centers for Disease Control barely mentions it among the 10 greatest public health achievements of the 20th century when discussing safer and healthier foods. Kurlansky's voluminous treatise on salt (*83*) barely mentions iodization. Much worse, however, are active detractors—for which the web, where information and disinformation are accessible with equal ease, has no parallel. Here one finds self-proclaimed nutri-tionists who argue that iodized salt is the vehicle for the West's ultimate plan to inflict AIDS on India (*84*), hailing cessation of mandatory salt iodization in that country. Perhaps it is more troubling that one reads expert culinary pronouncements that iodized salt imparts a bitter taste (*85*) or that noniodized salt is preferred in some particular culinary exercise (*86*). It becomes really worrisome when one reads in 2007 that . . . *years ago, salt was iodized to make up for once common iodine deficiencies. Today, if you eat plenty of dairy products and seafood, you probably do not need to use*

iodized salt, especially when such proclamations come with the *Good Housekeeping* seal (*87*).

Walking a Thin Line? What Path Forward? The median value of the presently found levels of iodine in U.S. iodized salt approximately meets the level targeted by manufacturers. However, the distribution is broad. If we take all our salt samples, regardless of whether they came from top, middle, or bottom of the can, this reflects actual iodine consumption by consumers and the median value of 43.2 mg I/kg (n = 170) is only slightly less than top-of-the-can samples. Note that the correspondence of this median is only to the manufacturer's stated iodine levels—it falls far short of the middle of the iodization range that the USFDA suggests. The mode is in the 30–40 mg/kg range as shown in the inset of Figure 3 (the same is true for the top-of-the-can samples), suggesting that the salt does not *often* contain the stated amount of iodine.

As pointed out before, two of the four salt cans we examined using multiple samples had serious homogeneity problems. It is also obvious that the average content varies greatly. Of 49 donors who supplied serial samples, there were 5 cases where the highest concentration sample contained at least twice as much iodine (in the worst case, four times) as the lowest concentration sample from the same can. Inhomogeneity is not therefore rare; the large inhomogeneity found in some samples is worrisome. Although a similar study has not been conducted in the United States, an extensive study in Nepal showed that as salt iodine content varies as a function of season (decreasing in more humid weather), a similar variation in UI is observed (*88*) suggesting that salt is an important source of iodine. If salt does supply a significant portion of the iodine intake of a pregnant/lactating woman in the United States (note that a large fraction of pre- or postnatal vitamins contain no iodine) and she is unfortunate enough to pick a can of salt that is low in iodine or in which iodine distribution is greatly inhomogeneous, there is potential for serious harm. Transient hypothyroxinemia in the first week after birth is a risk factor for cerebral palsy in premature infants (*89*). Hypothyroidism during fetal and neonatal development may result in hearing impairment with an inability to distinguish particular sound frequencies (*90*), possibly resulting in future reading disabilities. Between 20 and 30% of hypothyroid neonates suffer residual hearing impairment despite early treatment (*91*). Fetal or neonatal hypothyroidism may result in permanent defects, despite the proper development of the fetal thyroid, establishment of normal thyroid functioning, or prophylactic treatment after birth. Persistent functional deficits in children identified as hypothyroid at birth include memory and attention deficits, poor sensorimotor coordination, and difficulty in processing visual-spatial information (*92*). Minimal brain damage is still observed in approximately 20% of children who received early treatment for hypothyroidism (*93*). Adverse behavioral and/or cognitive effects of infant hypothyroidism have been shown to persist at least through adolescence despite neonatal prophylaxis (*94*). Even in euthyroid children, maternal hypothyroidism has been associated with neuropsychological impairment (*95*).

In their appropriately titled article, Lee et al. (*21*) talk about the dilemma of too little vs too much iodine. They point out that since the introduction of iodized salt and the near-magical disappearance of goiter, the collective American belief is that iodine deficiency has been permanently eliminated. While the adult RDA is 150 μg I/day, the upper safe limit is considered to be 1100 μg/day (*29*). Even at 290 μg/day the RDA for a lactating woman is substantially below these upper safe limits. Recently Utiger has persuasively argued that the RDA for men and women should be raised to 300 and 400 μg/day, although agreement on this is not universal (*79, 96*). Backer and Hollowell (*80*) surveyed the extensive extant literature and concluded that *the strongest data suggests that low levels of iodine (1–5 mg/d) are safe for most people for years*. At the same time they pointed out that any increase in iodine intake for a population generally will result in some increase in hyperthyroidism or thyrotoxicosis where there was some underlying thyroid disease, even iodine deficiency. Morreale de Escobar and Escobar del Rey (*97*) have reviewed iodine needs during pregnancy, lactation and infancy. Decreased availability of maternal thyroxine to the fetal brain decidedly causes impairment of neuropsychological development (*98*). They advocate active prophylaxis: *It appears urgent to ensure the use of iodine supplements from before or very early in pregnancy, and to screen all women for hypothyroxinemia as early as possible* (*99*). They have proven that fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development (*100*); cerebral cortex cytoarchitecture is affected by hypothyroxinemia even without any frank hypothyroidism (*101*), concluding that (*102*) . . . *as mild−moderate iodine deficiency is still the most widespread cause of maternal hypothyroxinemia in Western societies, the birth of many children with learning disabilities may already be preventable by advising women to take iodine supplements as soon as pregnancy starts, or earlier if possible*. Clearly, for these authors and iodine nutrition, *more is better* (*79, 96*).

Based on UI evaluation, U.S. women of childbearing age may already be borderline iodine-deficient (*23*). Extensive data show that for U.S. women with UI <100 μg/L, perchlorate in urine, reflective of intake, was a significant negative predictor of thyroxine ($p < 0.0001$) and a positive predictor of TSH ($p = 0.001$) (*103*). This effect may be further potentiated by smoking and thiocyanate derived therefrom (*104*). Human milk iodide and maternal UI appear to be well correlated (*105*) and at least according to some reports (*37, 53*), median breastmilk iodide in U.S. samples have become low enough to be of concern. Salt iodization remains one of the assured sources of iodine that is presently used only partially in the United States. Whether or not it will ever be an ample vector or is the best vector, this is the best we have been able to do. The ultimate question for future generations pondering the too much vs too little iodine dilemma may be simple: if we have a right to have children, do children have a right to be born with their full potential (*106*)?

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Supporting Information Available

Excerpt from salt solicitation letter; table of recommended values of iodine intake in the U.S.; statewise listing of salt samples analyzed; ICP-MS operating conditions and measurement parameters; salt donors; fall of iodine intake over the years in different age groups ; loss of iodine with and without exposure to fluorescent room light at 36% RH and 65% RH; loss of iodine from different brands of salt upon dry heating for 5 min at 200 °C; loss of iodine on boiling a 5% w/v salt solution. This material is available free of charge via the Internet at http://pubs.acs.org.

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