



A review of iodine toxicity reports. Jean A.T. Pennington.
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Abstract:

In this article, case reports and research studies from the literature on the unfavorable effects of excessive exposure to iodine are reviewed; the reports cover the past 100 years. Exposure to excessive iodine levels may occur through consumption of foods or dietary supplements, application of certain medications to the skin, or exposure to iodine-containing contrast media, which are radioactive substances used in certain X-ray procedures. Excessive iodine in the body may cause thyroiditis (inflammation of the thyroid gland); goiter, the enlargement of the thyroid gland; abnormal increases or decreases in thyroid hormone levels; sensitivity reactions; or acute toxicity. Absorption of high levels of iodine (particularly from medications such as Lugol's solution or asthma medications) by the mother during pregnancy or breastfeeding may harm the health of the infant; such cases are reviewed. The inability to tolerate excess iodine, and the relationship between dose of iodine and response are discussed. Although some persons can tolerate very high levels of iodine without developing toxic effects, some individuals develop problems when absorbing only 1 milligram per day or less. This is the exception, however, and 1 milligram/day is probably safe for most individuals. The maximum tolerable dose of iodine can be determined by assessing the effects of iodine doses between 0.150 and 1.000 milligrams per day; human studies that do so are needed. (Consumer Summary produced by Reliance Medical Information, Inc.)

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The Recommended Dietary Allowance (RDA) for iodine for adolescents and adults in the United States is 0.150 mg/day (1). Similar recommendations for iodine intake have been made in other countries and by international organizations (2). With few exceptions, reported average daily intakes of iodine in the United States, Australia, New Zealand, Japan, Canada, and several European countries generally meet or exceed these recommendations (3-28). Deficiency of dietary iodine may result in decreased synthesis of the iodine-containing thyroid hormones, thyroxine and triiodothyronine. Iodine intake consistently lower than 0.050 mg/day usually leads to thyroid hypertrophy (i.e., endemic goiter), whereas severe and prolonged iodine deficiency may result in hypothyroidism (which may lead to myxedema in children or adults or cretinism in infants or very young children). On a population basis, iodization programs have been most beneficial in curing or preventing the consequences of iodine deficiency in endemic areas. Iodine deficiency is infrequently observed in the United States and other developed countries, but affects approximately 600 million people in developing countries (29). In addition, epidemiological and experimental studies suggest that endemic goiter predisposes to cancer of the thyroid (30-40). Most people are unaffected by excess exposure to iodine; for those who are affected, the amount of iodine required to cause adverse effects is highly individual. Case reports, population studies, and experimental studies from the mid-1880s to 1988 concerning adverse effects of iodine from foods and dietary supplements, oral drugs, topical medications, and iodinated contrast media (ICM) and other injected solutions have been gathered, organized, and summarized (41). This article reviews these iodine toxicity reports and studies. Six types of responses to excess

iodine have been identified, although they are not always clearly distinguished in the reports and studies. These responses include thyroiditis, goiter, hypothyroidism, hyperthyroidism, sensitivity reactions, and acute responses. Thyroiditis (inflammation of the thyroid gland) is characterized by a painful enlargement or distension of the gland. Other symptoms may include fever, malaise, anorexia, dysphagia, palpitations, weight loss, and tremors (42). Hyperthyroidism (or thyrotoxicosis) resulting from over stimulation of thyroid hormone production attributable to excess iodine is sometimes referred to as *jodbasedow*. Goiter and/or hypothyroidism may result if excess iodine inhibits organic iodine formation (i.e., prevents the binding of iodine to tyrosine in the thyroid). Inhibition of the synthesis of thyroid hormone resulting from excess iodine is often referred to as the Wolff-Chaikoff effect. This inhibitory effect of iodine on thyroid hormone formation explains the beneficial use of iodine in the treatment of hyperthyroidism (43). Excessive iodine exposure during pregnancy is especially dangerous because the fetal thyroid is less able to escape the inhibitory effects of iodine on thyroid hormone formation. In infants, goiters resulting from maternal iodine exposure have resulted in death from respiratory problems. Sensitivity includes allergic and anaphylactic responses cited by various investigators (41). Individuals who are sensitive to iodine may react to excessive exposure with fever, salivary gland enlargement, iododerma, visual problems, and/or other symptoms. The dermatoses resulting from sensitivity to iodine (called iododermas) vary from acneiform eruptions, pruritic red rashes, and urticaria to bullous vesicular, purpuric hemorrhagic, pustular, or tuberculous fungating eruptions (44). Death from these more severe forms of iododerma has been reported (41). Acute responses to the ingestion or injection of a large dose of an iodine-containing solution include cardiovascular collapse, convulsions, and asthma attacks (45). Iodine from foods Food sources of iodine that have caused adverse effects (7-10,14,19,25,28,46-86) include water, seaweed, ground beef containing thyroid tissue, foods to which iodine was added in a supplementation program (e.g., iodized water, bread, or salt), and milk containing iodine originating from feed supplements and iodophor disinfectants. Adverse effects of excess iodine from food sources include thyroiditis, goiter, hypothyroidism, hyperthyroidism, and acneiform or other cutaneous eruptions. Several epidemiological studies associated thyroiditis with the ingestion of seaweed (49) or iodized salt (64,71). Results of a histological study of 2,642 thyroid glands in Michigan between 1915 and 1963 incriminated iodine as partially responsible for the increased incidence of thyroiditis following the introduction of iodized salt (71). A review article by Beierwaltes (87) concluded that the incidence of lymphocytic thyroiditis and Hashimoto's struma (both of which are referred to as lymphocytic goiter) has increased with increasing iodine intake and age. Bagchi et al. (88) reported that excess dietary iodine-induced autoimmune thyroiditis in genetically susceptible chickens and iodine depletion had an ameliorative effect. They concluded that excessive consumption of iodine in the United States may be responsible for the increased incidence of autoimmune thyroiditis in this country. As indicated in Table 2, the incidence of thyrotoxicosis increased in endemic goiter areas when residents increased intake of iodine through supplementation programs or milk contamination. This occurred in the midwestern United States between 1926 and 1928 after the ionization of table salt in 1924, in Tasmania between 1967 and 1969 after the ionization of bread in 1966 and an increase in the iodine content of milk, in The Netherlands after a program of bread ionization, and in England and Wales as a result of increased iodine in milk from iodophors and winter feed supplements. Factors common to these reports of increased thyrotoxicosis from increased dietary iodine are the previous iodine deficiency of the area, the older age of the people who succumbed, and the presence of autonomous thyroid tissue (nodular goiter) in the subjects. Thyroid tissue may develop or increase its autonomous tissue during iodine deficiency (89), and autonomous thyroid function is common in euthyroid goitrous subjects (90). In endemic areas, autonomous tissue is the most common precondition of uncontrolled hormone production, the extent of which is determined by the level and duration of iodine administration and by the mass of autonomous tissue (91). Autonomous thyroid tissue

(which is not regulated by thyroid-stimulating hormone) produces thyroid hormones in direct response to dietary iodine. Thus, excess iodine may precipitate or aggravate hyperthyroidism in people with autonomous thyroid tissue. An increase in the availability of dietary iodine for a population may also cause difficulty in controlling Graves' disease with antithyroid drugs, decrease remission rates for those on antithyroid medication, and increase the dose of radioiodine required to induce euthyroidism (92,93). Persons with undiagnosed Graves' disease who live in endemic areas may become hyperthyroid when more iodine becomes available through supplementation or milk supplies. Stewart (9) noted that the small but real increase in the incidence of hyperthyroidism in persons under 40 years old in Tasmania after bread ionization was usually attributable to Graves' disease. Emrich et al. (94) demonstrated that additional iodine significantly worsens hyperthyroid conditions, especially in areas of iodine deficiency. Another potential dietary source of iodine is the food additive erythrosine (tetraiodofluorescein; FD&C Red No. 3), although there have been no publications of adverse effects of iodine from this source. Except for a transient rise in protein-bound iodine, no changes in thyroid function or thyroregulatory mechanisms were noted in human studies of erythrosine administration (95-98).

Apparently, only a small amount of erythrosine is absorbed from the human intestine (98,99), and the bioavailability of iodine from erythrosine may only be 2% to 5% (100,101). Iodine from dietary supplements Adverse effects of iodine have also been reported from dietary supplements, including seaweed extracts, vitamin/ mineral preparations, and a proprietary blood mixture (80-86). The effects included goiter, hyperthyroidism, hypothyroidism, and one case of sensitivity. One case of infant transient hypothyroidism resulted from maternal ingestion of iodine in a prenatal supplement (102). Iodine from oral drugs Iodine-containing drugs most commonly potassium iodide solutions) have been prescribed for their purported expectorant action for respiratory problems such as asthma, bronchitis, cystic fibrosis, and chronic obstructive pulmonary disease. Iodine-containing drugs have also been prescribed for the treatment of goiter and hyperthyroidism and even for rheumatism and syphilis. Amiodarone is prescribed for cardiac problems such as arrhythmias. Reports of the adverse effects of excess iodine from iodine-containing oral drugs are listed chronologically in reference 41 according to the symptoms that developed-goiter, hypothyroidism with or without goiter, hyperthyroidism with or without goiter, and sensitivity. More than 1,000 cases of adverse response to iodine-containing oral drugs were reported among approximately 200

references. At least 11 deaths resulted from excess iodine in hyperthyroid individuals, and 20 deaths resulted in iodine-sensitive individuals. The side effects of iodine-containing medications have long been known, and most of these drugs are no longer commonly prescribed. The Committee on Drugs of the American Academy of Pediatrics (103) recommends that iodides should be used as expectorants only in patients with chronic disease who cannot obtain amelioration with less toxic agents and that iodides should not be used as expectorants during pregnancy, lactation, or adolescence or by patients with goiter. Hendeles and Weinberger (104) concluded that iodides should not be prescribed for obstructive pulmonary diseases because of the current availability of more effective and safer pharmacologic agents and the absence of a clinically notable expectorant action for iodides. Iodine from topical medications Iodine-containing solutions are well-known antiseptics and have been used in topical medications, vaginal solutions, and mouthwashes. In some cases, wounds or burns have been packed with dressings soaked in povidone-iodine, a topical antimicrobial agent. Adverse responses to iodine in these topical medications include iododerma, metabolic acidosis, goiter, hypothyroidism, and hyperthyroidism. Approximately 80 cases from 44 references are cited in reference 41. At least 10 deaths have been reported after iodine application(41). Metabolic acidosis usually results from the application of iodine to burns. Iodine is more easily absorbed into the body from burns and other wounds than from

intact skin. Iodine from ICM and other injected solutions ICMs (which may be ingested or injected into the body) are commonly used as diagnostic tools to determine structure and function of various body tissues. Iodized oil may be injected as a contrast medium or as an iodine supplement. Twenty-seven articles from reference 41 cited one or more cases in which administration of ICM or iodized oil resulted in hypothyroidism, hyperthyroidism, or other thyroid response. In all cases, the response was indicated to be the result of excess iodine. Seven articles from reference 41 presented evidence of swollen salivary glands as the major or solitary response to injected ICM and, again, in all cases the authors attributed the response to excess iodine. Rose(*) (105) and Nothnagel and Rossbach' (106) reported sensitivity and acute responses attributable to the injection of alcoholic iodine solutions into cysts. (*) Because references 105, 106, and 132 were so old, they were not available through library search mechanisms. They are cross-referenced to other citations in the reference list. Other sensitivity and acute responses attributable to the ingestion or injection of iodine compounds for radiographic studies were reported in 111 articles cited in reference 41. Some investigators described these responses to ICM as allergic, anaphylactic, or systemic and several separated the symptoms into minor and major or severe. Some of these symptoms (e.g., fever, purpura, and urticaria) are similar to the sensitivity symptoms resulting from excess iodine in foods, oral drugs, and topical medications; other symptoms (e.g., cardiovascular collapse, convulsions, respiratory distress, and renal insufficiency or failure) are more severe. Weigen and Thomas (45) described sensitivity and acute reactions to ICM and indicated that the iodine in the compounds was the cause. Hildreth et al. (107) reported that reactions occurring from intravenous urography suggest allergy to iodine as the chief cause. Fifteen of the 111 articles cited in reference 41 reporting sensitivity or acute response to ICM attributed the symptoms specifically to the iodine in the ICM. The other articles indicated only that the ICM was responsible. Although the iodine in the ICM has not been proved to be responsible for all these responses, the symptoms described in both types of articles (those that attribute symptoms to the iodine in the ICM and those that attribute symptoms to ICM) are similar. Excess iodine during pregnancy and lactation

Adverse effects of excessive exposure of a fetus to iodine during pregnancy are indicated in Table 3. [TABULAR DATA OMITTED] Of the case reports cited (102, 108-131), the major sources of excess iodine were iodine solutions prescribed for maternal asthma, other respiratory problems, hyperthyroidism, hypothyroidism, or tachycardia. In one case (102), the iodine source was a prenatal supplement, and the two reports of infant transient hypothyroidism (130, 131) resulted from topical application of povidone-iodine solutions to the mothers. There are only two reports of adverse effects on infant health from maternal iodine use during lactation. Pusey (132) reported iododerma and death in a 1-week-old infant because of iodine in the mother's milk. The mother had been on iodine medication, and iodine was found in the infant's urine. In another report (133), use of a povidone-iodine vaginal gel (50 mg iodine per day for 6 days) by a lactating mother increased the iodine concentration of her milk (3 to 4 times normal), resulted in increased iodine levels in the infant's serum and urine, and produced an iodine odor on the infant.

Acute response to excess iodine In addition to some of the cases that report more extreme effects of large doses of iodine, there are several reports of accidental or intentional iodine poisoning. Finkelstein and Jacobi (134) reviewed 6-year records of the Medical Examiner's Office of New York City and found 18 instances of suicide by iodine. Death usually occurred within 48 hours after taking the solution. The amount taken, recorded in only nine cases, ranged from 1 to 8 oz tincture (approximately 1,184 to 9,472 mg iodine). Finkelstein and Jacobi (134) also reported a case of a 29-year-old man who ingested an unknown amount of tincture of iodine and experienced vomiting, abdominal cramps, anuria, fever, irrational behavior, coma, and cyanosis. He died on the sixth day after ingesting the iodine. Tresch et al. (135) reported the case of a 54-year-old man who mistakenly ingested a potassium iodide solution that contained 15,000 mg iodine. The subject survived the poisoning, but experienced ventricular irritability, swelling of face, neck, and mouth, periorbital edema, serous conjunctivitis, edematous nasal mucosa, and

enlarged and tender salivary glands. A 56-year-old woman who attempted suicide with an unknown quantity of Lugol's solution showed gastrointestinal irritation and ulceration, chemical pneumonitis, hyperthyroidism, hemolytic anemia, acute renal failure (attributable to tubular necrosis), and metabolic acidosis (136). A fatal case of iodine poisoning was reported in a 57-year-old man who exhibited weak pulse, urinary retention, delirium, stupor, and collapse (137). The amount of iodine consumed was not determined. Susceptibility to excess iodine The case reports and studies summarized in reference 41 provide some insight into the percent of the population and the segments of the population who respond adversely to excess iodine. It should be noted that these reports generally reflect persons with diseases or disorders and may not be representative of normal populations. The incidence of iodine-induced goiter ranged from 0.2% to 33.3% in nine studies (41). The incidence of hypothyroidism with or without goiter ranged from 0.5% to 90.0% in 12 studies; however, omitting the studies that concerned patients with Hashimoto's disease and Graves' disease, the range was 0.5% to 33.3% (41). The incidence of hyperthyroidism ranged from 0.01% to 21.3% in 10 studies (excluding a study with goitrous subjects, which reported an incidence of 50.0%) (41). The incidence of sensitivity or acute reactions ranged from 0.00% to 60.0% in 85 studies; however, 78 (91.8%) of these studies had an incidence less than 30%, and 58 (68.2%) had an incidence less than 10% (41).

Relationship between dose and response The relationship between dose of iodine and response (for those who do respond) is affected by a number of factors. One is the route of intake. Doses given intravenously or intramuscularly may be more potent than those given orally or topically. The effectiveness of oral and topical doses depends upon percent absorption from the gastrointestinal tract or skin/mucosal surfaces, respectively. A second factor is the bioavailability of iodine from the various iodine compounds. A third factor is the duration of intake. Some people respond to a single dose, whereas other individuals develop symptoms only after years of intake. A fourth variable is the physiological status of the subject, including age, sex, body size, previous iodine intake, thyroid health, and general health. For example, older adults who have lived many years in an endemic (iodine-deficient) area and those with underlying thyroid disease are more likely to respond to increased iodine intake than are those who live in iodine-sufficient areas or who have normal thyroids. Females are apparently more apt to respond to excess iodine than are males. The information available in the literature comprises primarily case histories and epidemiological studies; few controlled experimental iodine toxicity studies have been conducted. Criteria for thyroiditis, goiter, hypothyroidism, hyperthyroidism, iodine sensitivity, and acute response were not always indicated or clearly indicated in the studies. Diagnoses were usually based on clinical findings, laboratory values, or both. The dose of iodine reported in the studies generally referred to that from the major source (e.g., seaweed, supplement, or drug) and not to the total daily intake, which would have included the rest of the food supply. Information on iodine in the food supply was generally not available in these studies. An evaluation of the oral doses at which adverse effects of iodine were reported (41) indicates that dose is not specifically related to response except that acute response is usually the result of larger doses. Of 1,256 cases (of which 616 were from one reference) there were only 21 (1.7%) cases, reported in six articles, of response to iodine at levels [less than] 1.0 mg/day in 15 papers, 49 (3.9%) individuals had adverse effects from iodine intakes [less than or equal to] 10 mg/day. The adverse effects included hyperthyroidism in 28 cases; goiter in one case; hypothyroidism in 19 cases; and sensitivity reactions in one case. Sources of iodine included prescribed medications, seaweed, seaweed powder, and dietary supplements. Some of the 49 individuals had underlying thyroid disease, which may have affected their response to extra iodine. Exposure to iodine Information on the iodine content of iodine-containing oral drugs, ICM, and topical medications is available (3,5,138-140). Of various pharmaceuticals purchased and analyzed by Vought et al. (138), eight contained between 0.251 and 0.375 mg iodine per dose, and one contained 1.447 mg/dose. Cooper

and Hokin (141) reported finding a mineral supplement in a New Zealand health food store containing 191.1 mg iodine per dose according to the label (167.4 mg/dose by actual analysis). Analysis of 16 seaweed-based supplements produced in the United Kingdom revealed iodine levels of 0.045 to 5.0 mg/dose (142); 13 provided at least 0.5 mg/dose, and 5 at least 1.7 mg/dose. A kelp tablet made in Australia, but available in the United Kingdom, contained 57.0 mg/dose. Information on the iodine content of various foods is available (13,16,22,143-147). The iodine content of seaweed depends upon species and stage of preparation; average levels may range from 1 to 260 mg/100 gm (148,149). Summarized data from various investigators on the iodine content of cow's milk indicate mean values of 0.100 to 0.770 mg iodine per liter and some extreme values [greater than] 4,000 mg/L (150). Levels of salt ionization vary among countries. In the United States, iodized salt provides 0.076 mg iodine/gm (0.418 mg/tsp). Safe upper limits of iodine intake Joseph et al. (91) reported that iodine intakes [less than] 0.100 mg/day pose no risk for patients with autonomous tissue, but that critical amounts are probably between 0.100 and 0.200 mg/day. Thyrotoxicosis induced by iodine supplementation/contamination of the food supply occurred in some individuals at levels of intake [less than or equal to] 0.300 mg/day. The ionization of bread in Tasmania resulted in thyrotoxicosis for some individuals at levels of iodine intake of about 0.200 mg/day (8,9). Iodized bread in The Netherlands (adding 0.120 to 0.160 mg iodine per day) increased the incidence of thyrotoxicosis (10). The spring-summer peak of thyrotoxicosis (related to winter milk) in England occurred with average iodine intakes of 0.236 mg/day for women and 0.306 mg/day for men (14). Side effects have not been reported from the levels of iodine (0.21 to 0.95 mg/day for teenagers and adults) in the U.S. Total Diet Study (21-23). Wolff (151) stated that iodine in amounts 10 or more times the daily requirements (which would be about 1.80 mg/day, as he assumed that 0.180 mg/day was the dietary requirement) would lead to goiter and hypothyroidism. The 10th edition of the Recommended Dietary Allowances (1) indicates that levels of iodine up to 1.000 mg/day for children and up to 2.000 mg/day for adults have no adverse effects. The 9th edition (published in 1980) had indicated that iodine intakes of 0.050 to 1.000 mg/day were safe for adults, and this source is often cited as establishing 1.000 mg iodine per day as the safe upper limit for this element. In a summary report of a workshop on exposure to iodine sponsored by the American Medical Association (152), it was concluded that an iodine level [less than or equal to] 1.000 mg per day was nonhazardous. The basis for this conclusion rested on work from two studies, one that reported few ill effects from an iodinated water supply at a prison (53,153-156) and one concerning iodine levels to suppress uptake of radioactive iodine by the thyroid (157). As of the latest reports in 1978, the study concerning the iodinated water supply at a prison (53,153-156) had been ongoing for 15 years. During this time, 750 men and women had ingested approximately 1 to 2 mg iodine per day from the water supply for various periods with no change in serum thyroxine and few side effects (156). One hundred seventy-seven women who were incarcerated at this prison had given birth to 181 infants without evidence of adverse effects in the infants (155). It was, however, noted that four women who were hyperthyroid before entering became more symptomatic while consuming the iodinated water supply, and that of 15 inmates tested, two had impaired organic formation of thyroidal iodine (53). This study of the iodinated water supply at a prison is probably the best to date in establishing an upper limit of safety for iodine intake. Its strong point is the large number of subjects; its weak points are the imprecise estimates of iodine intake and the variable duration of intake attributable to different sentence lengths. Saxena et al. (157) conducted an experimental study to determine the minimal effective dose of iodine that would be necessary to suppress uptake by the normal thyroid of radioactive iodine. During the course of this study, 1.000 mg iodine per day was administered to 14 children 1 to 11 years old for approximately 3 months without encountering any toxic effects. Because only certain segments of the population are affected by excess iodine, studies with few subjects may not include susceptible individuals and may thus overestimate the maximum safe level of intake of this

substance. Studies in which varying doses of iodine are administered to small numbers of subjects for short periods (usually to estimate minimal doses of oral iodide required to inhibit thyroidal uptake of radioactive iodine) without side effects should not be used to verify the safety

of these iodine levels or to establish safe upper limits of iodine intake. Implications The response to excess iodine is variable. Some individuals tolerate large intakes without side effects, whereas others may respond adversely to levels close to recommended intakes. On the basis of studies reviewed here, it appears that an iodine intake [less than or equal to] 1.000 mg/day is probably safe for the majority of a population, but may cause adverse effects in some individuals. Those who are most likely to respond adversely are those who have lived in endemic goiter areas or who for other reasons have a habitually low intake of iodine, those with other thyroid disorders (e.g., Hashimoto's disease or Graves' disease), and those who are sensitive to iodine. The maximum tolerable level of iodine appears to range from somewhat above the RDA (i.e., about 0.200 mg/day) to 1.000 mg/day These levels of intake are possible from diets that include milk, iodized salt, and/or seaweed. (Products containing the red food coloring erythrosine also have high levels of iodine, but because of poor absorption and limited bioavailability, this compound is probably not of concern with regard to iodine toxicity) To define the maximum tolerable levels of iodine more precisely, human experimental studies should determine the effects and safety of levels between 0.150 and 1.000 mg per day in normal subjects, subjects with autonomous thyroid tissue, and iodine-sensitive subjects. When iodine supplementation for endemic areas is considered, some attempt should be made to estimate the current and proposed daily iodine intake of various age-sex groups in the population and to determine the consequences of the increased iodine. in areas where iodine deficiency is not so widespread, it may be more advantageous to direct ionization programs to those who will benefit from them most (e.g., infants, young children, teenagers, and women of childbearing age) rather than to the entire population. Iodine-containing drugs, topical medications, and ICM should be prescribed and used with caution; physicians should monitor their patients carefully for adverse response to such products. Commercially available products that contain iodine should be clearly labeled as to the iodine level per dose.

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