MINIREVIEW

Iodine Toxicity and Its Amelioration

DAVID H. BAKER[1]

Department of Animal Sciences and Division of Nutritional Sciences, 290 Animal Sciences Laboratory, University of Illinois, 1207 West Gregory Drive, Urbana, Illinois 61801

Iodine (I) toxicity is rare in animals and humans, but nuclear explosions that give off radioactive I and excessive stable I ingestion in parts of the world where seaweed is consumed represent specialized I toxicity concerns. Chronic overconsumption of I reduces organic binding of I by the thyroid gland, which results in hypothyroidism and goiter. Bromine can replace I on position 5 of both T_3 and T_4 with no loss of thyroid hormone activity. Avian work has also demonstrated that oral bromide salts can reverse the malaise and growth depressions caused by high doses of I (as KI) added as supplements to the diet. Newborn infants by virtue of having immature thyroid glands are most susceptible to I toxicity, whether of stable or radioactive origin. For the latter, the 1986 Chernobyl nuclear accident in Belarus has provided evidence that KI blockage therapy for exposed individuals 18 years of age and younger is effective in minimizing the development of thyroid cancer. Whether bromide therapy has a place in I toxicity situations remains to be determined. Exp Biol Med 229:473–478, 2004

Key words: iodine; toxicity; thyroid; goiter; bromine; chick; human

Iodine (I) was first discovered (by accident) as an element by French chemists during the period 1811–1813 (1). Seven years later, a Swiss physician identified I as the active component in the ash of sponges that had been used for centuries to treat goiter (2). Today, I is known to be an essential trace element that is required for synthesis of the thyroid hormones, 3,5,3′-triiodothyronine and thyroxin (i.e., T_3 and T_4). The Food and Nutrition Board of the Institute of Medicine has estimated a daily I requirement for adults of 150 μg/day and a tolerable upper intake level (UL) of 1100 μg/day (3). The UL is defined as the highest level of daily I intake that is likely to pose no risk of adverse health effects in almost all individuals. However, intake levels considerably above the UL are well tolerated by most individuals.

The adult human body contains 15 to 20 mg of I, and roughly 80% is located in the thyroid gland, most in the form of the glycoprotein thyroglobulin, the principal storage form of the thyroid hormones (4). The I present in foods is primarily iodide, but whether the source is iodide (I^-) or iodate (IO_3^-), that is, in iodized salt or as a dough conditioner in bread making, I absorption from the gut (near 100%) is largely in the form of iodide (4, 5). Urine is the main route of I excretion, although smaller amounts of I are also excreted in feces and sweat (4).

Under normal circumstances, I toxicity is not considered a great problem, except in cases of nuclear fallout radiation exposure and in certain parts of the world where seaweed or kelp is consumed. Seaweed may contain up to 4.5 g I/kg and contribute to daily I intakes as high as 200 mg (6). With I toxicosis following a nuclear accident such as the 1986 Chernobyl accident in Belarus (7–9), the principal danger is thyroid cancer in children following inhalation or ingestion of radioactive isotopes of I (e.g., ^{131}I). With chronic overconsumption of "cold" (i.e., nonradioactive) I, the main concern is goiter (6, 10–12).

The review that follows will provide background information on I toxicity in animals and humans. Also, our own recent work on amelioration of I toxicity, using an avian model, will be discussed.

Iodine Toxicity in Animals

Naturally occurring I toxicity in domestic animals is rare, and supplemental I is added to virtually all animal diets to assure I adequacy. Iodine compounds also are used for nonnutritional purposes in animal production: to treat foot rot in cattle, as teat dips and udder washes in dairy cattle, and as sanitizing agents for cleaning of equipment.

[1]To whom request for reprints should be addressed at Department of Animal Sciences, 290 ASL, 1207 West Gregory Drive, University of Illinois, Urbana, IL 61801. E-mail: dhbaker@uiuc.edu

1535-3702/04/2295-0001$15.00

All animal species appear to have a wide margin of safety for excess I consumption. Dietary I levels of 500 to 1000 times the minimal dietary required level are generally well tolerated in rats, pigs, chickens, and ruminant animals (10). Among the species studied, horses seem to be most susceptible to I toxicity. Chronic consumption of diets with high levels of I, for example, kelp consumption by horses, markedly reduces organic binding of I by the thyroid gland, resulting in goiter in the offspring of mares (10).

Studies by Arrington *et al.* (13, 14), Ammerman *et al.* (15), Wilgus *et al.* (16), and Newton and Clawson (17) in rabbits, hamsters, rats, pigs, and chickens suggest that rats, hamsters, pigs, and chickens can tolerate dietary I levels up to 500 mg/kg, but rabbits experience serious mortality in offspring when 250 mg/kg is fed to the dam in late gestation. In 100-kg calves, however, I toxicity signs (coughing, nasal discharge) occurred when supplemented I from calcium iodate reached a dietary level of 50 mg/kg (18). Perdomo *et al.* (19) fed laying hens I levels ranging from 312 to 5000 mg/kg diet and found that egg laying ceased within a week in hens fed the highest I level; at 312 mg I/kg, egg production was reduced. Within 7 days of discontinuing I feeding, egg production returned to normal, even in hens that had been fed 5000 mg I/kg.

Our recent work in young chicks (20) showed that 600 mg I/kg diet (12 mg/day) was very growth depressing when the I supplement (KI) was provided in a methionine-deficient diet (Fig. 1). This same level of I, however, was only marginally growth depressing when added to a methionine-adequate diet (Figs. 1 and 2). Moreover, after 5 to 7 days of *ad libitum* feeding of these diets, chicks fed dietary I doses at or above 900 mg/kg (600 mg/kg in the methionine-deficient diet) displayed bizarre symptoms. They were observed to fall over and lie relatively motionless for several minutes, after which they seemed to recover and resume their normal standing position, only to fall over once again. Unlike findings in pigs and calves (17, 18), our chicks fed supplemental I levels up to and including 1200 mg I/kg showed no evidence of depressed hemoglobin or hematocrit. The growth depression due to I supplementation resulted in all cases from reduced voluntary food intake. Thus, food efficiency for weight gain (i.e., ratio of gain to food) was not decreased in birds fed supplemental I.

The 600 mg I/kg dose in chicks fed the nutritionally adequate corn–soybean meal diet (Fig. 2) resulted in an average daily I intake of about 18 mg (53 mg I/kg body weight). Yet in acute toxicity studies involving single crop intubations of KI solution, 18 mg of I given in a single dose produced no toxicity symptoms whatever. In fact, single-dose crop intubations up to 300 mg I (900 mg I/kg body weight) also produced no symptoms in chicks weighing 300 g. This suggests that rather massive I doses given in a single dose may be quickly cleared and excreted in the urine, whereas consumption of 300 mg over a 10-day period (in many small meals) produces severe anorexia and malaise.

The I content of both milk and eggs can vary greatly depending on the I content of diets consumed by cows and hens (4, 10). This subject will be addressed later in dealing with both stable and radioactive I ingestion by humans.

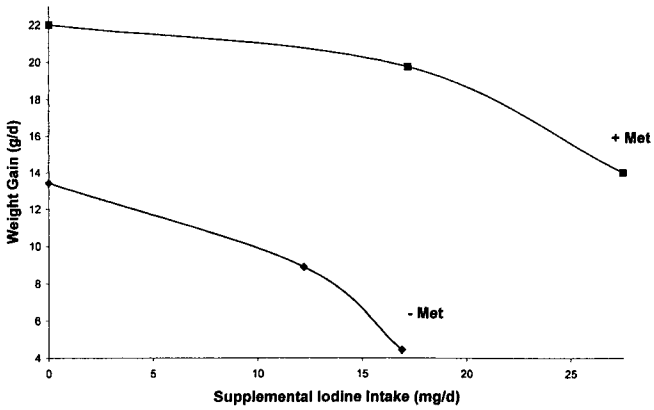

Figure 1. Weight gain as a function of supplemental I intake in young chicks fed 0, 600, or 1200 mg I/kg (from KI) in soybean meal semipurified diets that were either deficient (–Met) or adequate (+Met) in methionine. Data points represent mean values per chick of four pens of four chicks during a 9-day feeding period (Day 8 to Day 17 posthatch); pooled SEM = 0.44 g/day, from Baker *et al.* (20).

Reversal of Oral Iodine Toxicity in Chicks

Some reviews of I toxicity have suggested that oral I toxicity may be ameliorated by oral ingestion of Br, As, F, Co, Mn, or NO_3 (10, 12). Because we had previously studied pharmacologic dietary levels of most of these elements, we decided to evaluate some of them for their potential to ameliorate I toxicity in young chicks (20). Therefore, young chicks were fed corn–soybean meal diets containing 1000 mg I/kg (from KI) in the absence and presence of supplemental NaBr (50 or 100 mg Br/kg), $MnSO_4 \cdot H_2O$ (1000 mg Mn/kg), $CoCl_2 \cdot 6H_2O$ (100 mg Co/kg), or 3-nitro-4-hydroxyphenylarsonic acid (28.5 mg As/kg). We had previously worked with all of these supplements and knew that the dietary levels employed would not be anorexic or toxic (20). Chicks fed the negative-control diet (1000 mg I/kg) exhibited neurological symptoms as well as a 17% reduction in voluntary food intake. When the Mn, Co, and As supplements were added to the high-I diet, no ameliorative activity was evident, but supplemental Br at either 50 or 100 mg/kg prevented the roll-over syndrome and restored both food intake and growth to that observed with birds fed the positive-control diet (no supplemental I).

The apparent reversal of all I toxicity symptoms in this 13-day experiment was so dramatic that we decided to do a follow-up study with an even higher level of supplemental I, that is, 1500 mg I/kg (20). This level of dietary I resulted in a severe 35% reduction in growth, and the neurological roll-over syndrome was also severe. Remarkably, 100 mg Br/kg from supplemental NaBr restored both voluntary food intake and growth to normal, and it also prevented the roll-over symptoms (Fig. 3).

We believe that the positive effect of Br on I toxicity

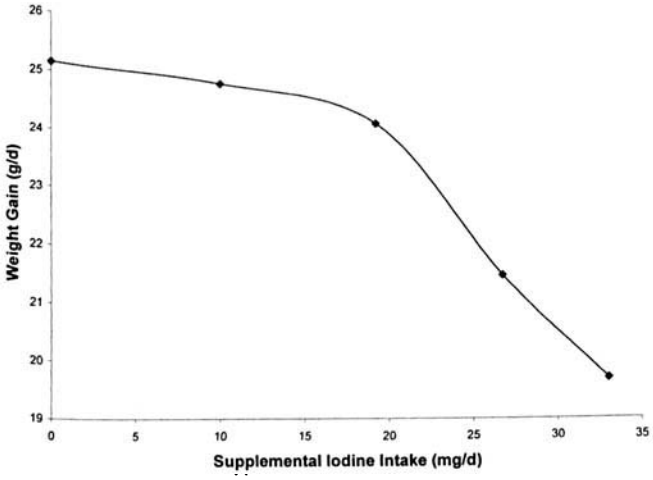

Figure 2. Weight gain as a function of supplemental I intake in young chicks fed graded levels (0, 300, 600, 900, 1200 mg I/kg) of I (from KI) in a corn–soybean meal diet. Data points represent mean values per chick of four pens of four chicks during a 13-day feeding period (Day 8 to Day 21 posthatch); pooled SEM = 0.54 g/day, from Baker *et al.* (20).

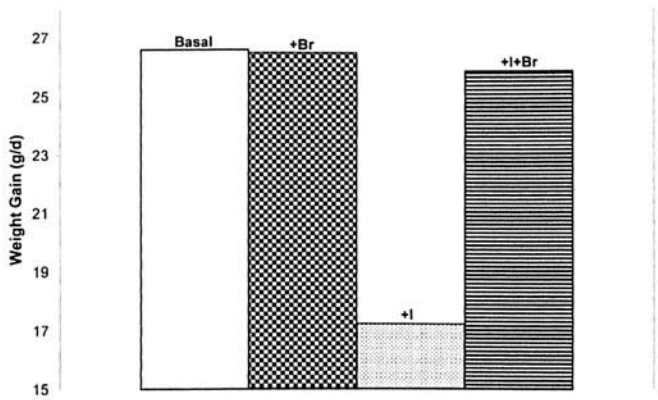

Figure 3. Weight gain of young chicks after feeding a toxic I level (1500 mg I/kg from KI) in corn–soybean meal diets that contained either no added Br or 100 mg Br/kg (from NaBr). Data are mean values per chick of four pens of four chicks during a 13-day feeding period (Day 8 to Day 21 posthatch); pooled SEM = 0.62 g/day, from Baker *et al.* (20).

results primarily from Br somehow reducing thyroidal uptake of I. Vobecky and coworkers (21, 22) have shown in rats that Br supplements similar to those used in our work (i.e., 50 to 100 mg/kg) markedly decrease I uptake by the thyroid gland—at least in rats fed normal (i.e., low, 0.8 mg I/kg) levels of I. Unfortunately, thyroid tissue in 21-day-old chicks is very diffuse, and we were thus unable to evaluate I or Br levels in the thyroid glands of our chicks. Huff *et al.* (23) produced modest growth depressions in mice by feeding iodinated casein (I level or intake not given), and they observed amelioration of the growth depression when 15 mg Br/kg was added to the diet. Because the voluntary food intake depression in our chicks fed high levels of supplemental I was totally corrected by dietary addition of 50 or 100 mg Br/kg, it is unlikely that palatability (i.e., taste) of the high-I diets had anything to do with the anorexia observed when high levels of I were fed. Moreover, chicks have only a limited capacity for taste.

There is some evidence that Br may be an essential (ultra) trace element (23, 24). Should this be the case, it is interesting to speculate that the growth depression and neurological roll-over symptoms resulting from excess I ingestion may have been due to an antagonistic effect of excess I on body Br. However, a definitive function for Br *per se* in the body has not been firmly established. Nonetheless, animal studies in a purified environment (i.e., filtered air, *etc.*) in which a Br-free purified diet is fed might be fruitful to establish whether Br-deficiency symptoms and Br-supplementation responses would be observed.

It is well established that I in position 5 of the thyronine molecule is required for bioactivity of both T_3 and T_4. It is also well known that Br can replace I on position 5 of T_3 and T_4 with full retention of hormone activity (25). The Wolff-Chaikoff effect (26, 27) occurs when excess I is consumed. Thus, when plasma inorganic I exceeds a certain level, organic binding of I by the thyroid gland is inhibited, and this can result in what is popularly referred to as I goiter, a form of hypothyroidism. Whether Br ingestion would ameliorate I goiter is not known.

Excess Iodine Ingestion by Humans

The dietary I requirement of adult humans is estimated to be 150 μg/day (3). Iodine goiter resulting from excessive I ingestion and thyroid cancer in children resulting from exposure to radioactive I (mainly ^{131}I) through ingestion or inhalation are the primary concerns of overexposure to I.

Excess Iodine Intake. The Life Sciences Research Office (LSRO) of the American Societies for Experimental Biology concluded in a 1976 report prepared by Talbot *et al.* (12) that the incidence of various thyroid disorders, including I goiter, Hashimoto thyroiditis, and Graves disease had increased during the period 1950 to 1976. In 1970, examination of 36,000 Americans showed an overall goiter rate of 3.1%, with a much higher frequency in females than males. Although average I intakes increased during this period (12, 28), the LSRO-commissioned report (12) concluded that a cause-and-effect relationship between thyroid disorders and increased I intake was unwarranted. Whereas Hashimoto thyroiditis and Graves disease are considered autoimmune diseases, I goiter occurs as a direct result of excess I intake. Standard diagnostic tests for I goiter (serum thyroid stimulating hormone [TSH], serum T_3 and T_4, ^{123}I uptake) often are inconclusive. Thus, the most conclusive test to confirm that an enlarged thyroid gland is due, in fact, to excessive I ingestion is to withdraw the food sources of excess I to see whether the thyroid hyperplasia diminishes and a euthyroid status is achieved.

In Wolff's comprehensive review of iodide goiter (6), four categories were identified: (i) adult I goiter, usually in asthmatic subjects; (ii) I goiter of the newborn due to the mothers being treated with I; (iii) endemic I goiter, primarily

observed in Hokkaido, Japan, where large quantities of seaweed are consumed, leading to daily I intakes as high as 200 mg (1300 times the daily I requirement) and a goiter incidence of 6% to 12%; and (iv) Graves disease in patients being treated with KI. The most common form of I goiter is that seen in the north island of Japan, that is, Hokkaido, where seaweed (called kombu) is a dietary staple (11). Plasma inorganic I and urinary I are greatly elevated in this population group.

Well over half of adult I goiter patients have been found to ingest inorganic I for a prolonged period, with daily amounts ranging from 18 mg to 1 g (6). Withdrawal of I in these people usually produces a return to the euthyroid condition, and reintroduction of KI generally causes both goiter and hypothyroidism to reappear within 3 weeks (29, 30). Wolff (6) concluded that the relatively rapid reappearance of goiter after reintroduction of I therapy may be the most conclusive test of whether the goiter was, in fact, caused by excess I ingestion.

A daily I intake of 10 times (i.e., 1.5 mg/day) the minimum daily adult requirement of 0.15 mg/d may cause I goiter in some people (6). Genetic predisposition is likely involved in such cases, but there are also factors other than food I that can influence development of goiter. Some foods contain goitrogenic substances that interfere with thyroid hormone synthesis or release (31). Thus, foods such as cassava (32) and various cruciferous vegetables (e.g., cabbage) contain goitrogens. Also, certain food coloring agents (e.g., erythrosine), medicines (e.g., amiodarone), water purification tablets (33), and cosmetics, as well as skin and dental disinfectants, contain substantial quantities of I (3).

Iodate (IO_3) is the form of I often used in iodized salt and as an oxidizing agent in bread making. When consumed (or injected intravenously [IV]), the body readily reduces iodate to iodide. At very high doses of oral IO_3 given to experimental animals, hemolysis, nephrotoxicity, hepatic injury, and corrosive effects in the gut have occurred (5). With IV injection of high doses of iodate (above 10 mg/kg body weight) in rats, retinal damage has been seen. In humans, retinal toxicity occurred when KIO_3 solution (187 to 470 mg/kg body weight) was ingested by five individuals (34).

Finkelstein and Jacobi (35) studied the suicide records of New York City between 1931 and 1937. They found 18 cases of suicide by I. Although records were incomplete, massive doses of tincture of I were taken orally by all 18 of these suicide victims. Death generally occurred within 48 hrs of I consumption. Prior to coma and eventual death, the patients exhibited vomiting, diarrhea, weakened pulse, and urinary retention.

Radioactive Iodine Exposure. Radiation exposure above a threshold level can cause either death or modification of living cells. Radiation-induced cancer can occur decades after exposure. Although everyone is exposed to natural radiation from cosmic rays, radon gas in the earth, burning of coal, diagnostic radiology, radiotherapy, and nuclear medicine, the principal focus here is isotopes of I such as ^{131}I, ^{132}I, and ^{133}I (arising from decay of ^{132}Te) resulting from nuclear weapons testing, nuclear accidents (e.g., Chernobyl), and nuclear bombings (Hiroshima and Nagasaki).

Among the 86,572 individuals in the life span study of survivors of the atomic bombings in Japan, 7578 people died of solid tumors during 1950 to 1990, but only 334 of these deaths occurred as a result of radiation exposure (36). As of 1991, about 48,000 persons (56%) in this group were still living, and it was projected that 44% of this population would still be living in 2000.

The 1979 accident at the Three Mile Island reactor in the United States caused serious damage to the reactor core, but a steam explosion did not occur. Moreover, the containment building surrounding the reactor prevented release of all but trace amounts of radioactive gases. The 1986 Chernobyl accident in Belarus lacked the containment feature. Following the 1986 Chernobyl explosion (7, 8, 36–40), an intense graphite fire burned for 10 days, and large releases of radioactive materials occurred. Of 600 workers present at the site, 134 received high doses (0.7 to 13.4 Gy) and suffered from radiation sickness; 30 died within the first 3 months. About 200,000 other people received lower doses (0.01 to 0.05 Gy), and their health has been (and continues to be) monitored closely.

Thyroid cancer incidence due to childhood exposure to radioactive I in Belarus and surrounding areas (i.e., up to 500 km from the Chernobyl site) has been estimated at 100-fold compared with the incidence before the Chernobyl accident (9). Both inhalation and consumption of radioactive I in food and beverages have been implicated as causative. Experts have concluded that ^{131}I is the main culprit, but I isotopes with shorter half-lives, as well as ^{132}Te, may have contributed as well (9). Remarkably, apart from thyroid cancer, no increases in other forms of cancer, including leukemia, have occurred in those exposed to ionizing radiation, including the recovery operation workers (9).

The World Health Organization (WHO) expert committee suggested that stable I (as KI) prophylaxis be used to treat neonates and children up to 18 years of age (9). Newborn infants represent a critical risk group. After birth, there is a marked increase in thyroid activity that lasts for only a few days. Thus, radioactive I uptake by the thyroid during this neonatal period is greatly elevated. Also, infants have small thyroid glands, and this means that a higher radiation dose is taken up by the gland per unit dose of radioactive I. A single KI dose providing 12.5 mg I is recommended for infants. Iodine is also actively transported into milk, with as much as 25% of I intake by the mother being secreted into milk (41). Thus, KI prophylaxis for lactating mothers who have been exposed to radioactive I is generally recommended. If known exposure has occurred, however, it would be prudent for the mother to discontinue

breast feeding and switch to bottle feeding of uncontaminated milk. The latter, however, is problematic in that much of the thyroid cancer resulting from the Chernobyl accident was thought to have occurred from dairy cows grazing on pasture that was contaminated with radioactive I. Thus, young children received considerable doses of radioactive I from the milk produced by these cows. Howard *et al.* (42) suggested countermeasures to reduce radioiodine levels in milk from exposed dairy cows.

To receive maximal benefit from stable I for thyroidal blocking, it is important that KI be administered shortly before or as soon after radioactive I exposure as possible (43). The passing radioactive cloud may last for a day, and during this period, a single KI dose should protect the exposed person from inhaled radioactive I (9). Recommended single I dosages (from KI) are 12.5 mg (birth to 1 month), 25 mg (1 month to 3 years), 50 mg (3 to 12 years), and 100 mg (over 12 years of age).

In pregnancy the maternal thyroid gland is stimulated in the first trimester. Hence, women in early pregnancy would take up more radioactive I than nonpregnant women. During later pregnancy, the developing fetus takes up and stores I *via* placental transfer, which means the fetus could be exposed to considerable radioactive I because of the mother's exposure. Stable I, if carefully administered, can thus protect both the mother and her fetus. In such cases, however, the newborn infant should be carefully monitored for thyroid function.

Remarkably, the risk of radioactive I–induced thyroid cancer in adults over 40 years of age is extremely low, perhaps approaching zero (9). Stable I prophylaxis is thus not recommended for persons in this age group, unless very high doses of I radiation (5 Gy or higher) are experienced. The low probability of radioactive I–induced thyroid cancer in adults likely explains why physicians often use ^{131}I therapy to ablate the thyroid gland in patients with Graves disease.

Bromine Use for Radioactive Iodine Exposure. Because oral Br administration as NaBr was so effective in reversing I toxicity in growing chickens and because efficacy was likely due to blockage of I uptake by the thyroid, one could speculate that bromide administration might be effective in blocking thyroidal uptake of radioactive I in humans. Clearly, more animal research is needed to evaluate this possible therapy. Moreover, the longer term effects of Br on the thyroid and other body tissues would need thorough evaluation.

The author wishes to express appreciation to Dr. Terri Parr, Dr. Nathan Augspurger, Ms. Pamela Utterback, Ms. Colleen Scherer, and Ms. Nancy David for technical assistance.

1. Roberts RM. Serendipity: Accidental discoveries in science. New York: John Wiley and Sons, pp31–32, 1989.

2. Harington CR. The Thyroid Gland. Oxford: Oxford University Press, 1933.
3. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press, pp258, 2001.
4. Underwood EJ. Trace Elements in Human and Animal Nutrition. New York: Academic Press, pp271, 1977.
5. Bürgi H, Schafner TH, Seiler JP. The toxicity of iodate: a review of the literature. Thyroid 11:449–455, 2001.
6. Wolff J. Iodide goiter and the pharmacologic effects of excess iodide. Am J Med 47:101–124, 1969.
7. Kazakov VS, Demidchik EP, Astakhova LN. Thyroid cancer after Chernobyl. Nature 359:21–22, 1992.
8. Heidenreich WF, Kenigsberg J, Jacob P, Buglova E, Goulko G, Paretzke HG, Demidchick, EP, Golovneva A. Time trends of thyroid cancer incidence in Belarus after the Chernobyl accident. Radiat Res 151:617–625, 1999.
9. World Health Organization. Guidelines for iodine phrophylaxis following nuclear accidents (update 1999). Geneva: WHO/SDE/PHE/99.6, 1999.
10. National Research Council. Mineral Tolerance of Domestic Animals. Washington, DC: National Academy Press, pp227, 1980.
11. Suzuki H, Higuchi T, Sawa K, Ohtaki S, Horiuchi Y. Endemic coast goitre in Hokkaido, Japan. Acta Endocrinol 50:161–176, 1965.
12. Talbot JM, Fisher KD, Carr CJ. A review of the effects of dietary iodine on certain thyroid disorders. Bethesda, MD: Life Sciences Research Office, FASEB, 1976.
13. Arrington LR, Taylor RN Jr, Ammerman CB, Shirley RL. Effects of excess dietary iodine upon rabbits, hamsters, rats and swine. J Nutr 87:394–398, 1965.
14. Arrington LR, Santa Cruz RA, Harms RH, Wilson HR. Effects of excess dietary iodine upon pullets and laying hens. J Nutr 92:325–330, 1967.
15. Ammerman CB, Arrington LR, Warnick AC, Edwards JL, Shirley RL, Davis GK. Reproduction and lactation in rats fed excessive iodine. J Nutr 84:108–112, 1964.
16. Wilgus HR, Gassner FX, Patton AP, Harshfield GS. The Iodine Requirements of Chickens. Colo Agric Exp Stn Tech Bull 49, 1953.
17. Newton GL, Clawson AJ. Iodine toxicity: physiological effects of elevated dietary iodine on pigs. J Anim Sci 39:879–884, 1974.
18. Newton GL, Barrick ER, Harvey RW, Wise MB. Iodine toxicity. Physiological effects of elevated dietary iodine on calves. J Anim Sci 38:449–455, 1974.
19. Perdomo JT, Harms RH, Arrington LR. Effect of dietary iodine upon egg production, fertility and hatchability. Proc Soc Exp Biol Med 122:758–760, 1966.
20. Baker DH, Parr TM, Augspurger NR. Oral iodine toxicity in chicks can be reversed by supplemental bromine. J Nutr 133:2309–2312, 2003.
21. Vobecky M, Babicky A. Effect of enhanced bromide intake on the concentration ratio I/Br in the rat thyroid gland. Biol Trace Elem Res 43–45:509–516, 1994.
22. Vobecky M, Babicky A, Lener J, Svandova E. Interaction of bromine with iodine in the rat thyroid gland at enhanced bromide intake. Biol Trace Elem Res 54:207–212, 1996.
23. Huff JW, Bosshardt DK, Miller OP, Barnes RH. A nutritional requirement of bromine. Proc Soc Exp Biol Med 92:216–219, 1956.
24. Bosshardt DK, Huff JW, Barnes RH. Effect of bromine on chick growth. Proc Soc Exp Biol Med 92:219–221, 1956.
25. White A, Handler P, Smith EL, Stetten D. The thyroid gland. In: Principles of Biochemistry. New York: McGraw-Hill Book Co, pp861–879, 1959.
26. Wolff J, Chaikoff IL. The inhibitory action of iodide upon organic

binding of iodine by the normal thyroid gland. J Biol Chem 172:855–856, 1948.
27. Wolff J, Chaikoff IL. Plasma inorganic iodide as a homeostatic regulator of thyroid function. J Biol Chem 174:555–564, 1948.
28. Fisher KD, Carr CJ. Iodine in Foods: Chemical methodology and sources of iodine in the human diet. Bethesda, MD: Life Sciences Research Office, FASEB, 1974.
29. Nixon PGF. Recurrent myxoedema and goitre attributed to KI. Br Med J 1:748–749, 1957.
30. Frey H. Hypofunction of the thyroid gland due to prolonged excessive intake of KI. Acta Endocrinol 47:105–120, 1964.
31. Gaitan E. Environmental Goitrogenesis. Boca Raton: CRC Press.
32. Abuye C, Kelbessa U, Wolde-Gebriel S. Health effects of cassava consumption in south Ethiopia. East Afr Med J 75:166–170, 1998.
33. Backer H, Hollowell J. Use of iodine for water disinfection: iodine toxicity and maximum recommended dose. Environ Health Perspect 108:679–684, 2000.
34. Singalavanija A, Ruangvaravate N, Dulayajinda D. Potassium iodate toxic retinopathy: a report of five cases. Retina 20:378–383, 2000.
35. Finkelstein R, Jacobi M. Fatal iodine poisoning: a clinicopathologic and experimental study. Ann Intern Med 10:1283–1296, 1937.
36. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Report to the General Assembly (Vol II), 2000.
37. Robbins J, Schneider AB. Thyroid cancer following exposure to radioactive iodine. Rev Endocr Metab Disord 1:197–203, 2000.
38. Likhtarev IA, Sobolev BG, Kairo IA, Tronko ND, Bogdanova TI, Oleinic VA, Epshteim EV, Beral V. Thyroid cancer in the Ukraine. Nature 375:365, 1995.
39. Astakhova LN, Anspaugh LR, Beebe GW, Bouville A, Drozdovitch VV, Garber V, Gavrilin YI, Khrouch VT, Kuvshinnikov AV, Kuzmenkov YN, Minenko VP, Moschik KV, Nalivko AS, Robbins J, Shemiakina EV, Shinkarev S, Tochitskaya SI, Waclawiw MA. Chernobyl-related thyroid cancer in children of Belarus: a case control study. Radiat Res 150:349–356, 1998.
40. Nauman J, Wolff J. Iodine prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks. Am J Med 94:524–532, 1993.
41. Weaver JC. Excretion of radioiodine in human milk. JAMA 173:872–875, 1960.
42. Howard BJ, Voigt G, Segal MG, Ward GM. A review of countermeasures to reduce radioiodine in milk of dairy animals. Health Phys 71:661–673, 1996.
43. Zanzonico PB, Becker DV. Effects of time of administration and dietary iodine levels on potassium iodide (KI) blockade of thyroid irradiation by ^{131}I from radioactive fallout. Health Phys 78:660–667, 2000.