# 2. RELEVANCE TO PUBLIC HEALTH

## 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO IODINE IN THE UNITED STATES

Iodine is an essential nutrient. An adequate intake of iodine is required for the production of thyroid hormones. The term *iodine excess* is used in this profile to refer to increases in intake relative to estimated physiological requirements. As a reference point, the chronic dietary intake of iodine in U.S. populations has been estimated to range from approximately 150 to 950 µg/day. Estimates for various populations have ranged from <50 µg/day in iodine-deficient regions to >10 mg/day in populations that regularly ingest seaweeds containing a high iodine content. The National Research Council (NRC) Recommended Dietary Allowance (RDA) for iodine is 150 µg/day (2.1 µg/kg/day for a 70-kg adult), with additional allowances of 25 and 50 µg/day during pregnancy and lactation, respectively.

The diet is the major source of iodine intake in the U.S. population. Iodine enters the human diet from a variety of natural sources, including mineral dissolution and atmospheric transport and deposition of seawater aerosols to surface water, vegetation, and soil. Major food categories that contribute to dietary iodine include marine produce (e.g., fish and shellfish) and milk. Cows and goats absorb iodine from ingested vegetation and water, when iodine is either deposited on the vegetation or in water or when the iodine is taken up by vegetation grown in soils containing iodine. The absorbed iodine is excreted into their milk; goat milk typically has higher concentrations of iodine than cow milk for equal deposition on feed. Additional sources of iodine in milk derive from the use of iodine disinfectants on cows, milking machines, and other milk processing equipment, as well as from supplementation of dairy feed with iodine-containing compounds. Breast milk is the primary source of iodine intake in nursing infants. Commercial infant formula preparations are fortified with sufficient iodine to support infant health, growth, and development. Cow milk is a significant source of iodine intake in children. Iodine is also intentionally added to the U.S. diet as iodized table salt and as iodine-containing bread dough oxidizers. Other sources of intake derive from the use of iodine-containing topical disinfectants (e.g., povidone-iodine), iodine-containing diagnostic and therapeutic agents, dietary supplements, and water purifiers containing iodine.

Thirty-five isotopes of iodine are recognized ($^{108}$I through $^{142}$I). Only one isotope is stable ($^{127}$I); the remaining are radioactive. Most of these have radioactive half-lives of minutes or less. Twelve have

half-lives that exceed 1 hour, and six have half-lives that exceed 12 hours ($^{123}$I, $^{124}$I, $^{125}$I, $^{126}$I, $^{129}$I, and $^{131}$I). Four isotopes ($^{123}$I, $^{125}$I, $^{129}$I, and $^{131}$I) are of particular interest with respect to human exposures because $^{123}$I and $^{131}$I are used medically and all four are sufficiently long-lived to be transported to human receptors after their release into the environment. The U.S. population has been exposed to radioiodine in the general environment as a result of atmospheric fallout of radioiodine released from uncontained and/or uncontrolled nuclear reactions. Historically, this has resulted from surface or atmospheric detonation of nuclear bombs, from routine and accidental releases from nuclear power plants and nuclear fuel reprocessing facilities, and from hospitals and medical research facilities. Estimates have been made of radiation doses to the U.S. population attributable to nuclear bomb tests conducted during the 1950s and 1960s at the Nevada Test Site; however, dose estimates for global fallout have not been completed. Geographic-specific geometric mean lifetime doses are estimated to have ranged from 0.19 to 43 cGy (rad) for a hypothetical individual born on January 1, 1952 who consumed milk only from commercial retail sources, 0.7–55 cGy (rad) for people who consumed milk only from home-reared cows, and 6.4–330 cGy (rad) for people who consumed milk only from home-reared goats. Additional information is available on global doses from nuclear bomb tests and doses from nuclear fuel processing and medical uses can be found in United Nations Scientific Committee on the Effects of Atomic Radiations.

Individuals in the United States can also be exposed to radioiodine, primarily $^{123}$I and $^{131}$I, as a result of clinical procedures in which radioiodine compounds are administered to detect abnormalities of the thyroid gland or to destroy the thyroid gland to treat thyrotoxicosis or thyroid gland tumors. Diagnostic uses of radioiodine typically involve administration, by the oral or intravenous routes, of 0.1–0.4 mCi (4–15 MBq) of $^{123}$I or 0.005–0.01 mCi (0.2–0.4 MBq) of $^{131}$I. These correspond to approximate thyroid radiation doses of 1–5 rad (cGy) and 6–13 rad (cGy) for $^{123}$I and $^{131}$I, respectively. Cytotoxic doses of $^{131}$I are delivered for ablative treatment of hyperthyroidism or thyrotoxicosis; administered activities typically range from 10 to 30 mCi (370–1,110 MBq). Higher activities are administered if complete ablation of the thyroid is the objective; this usually requires 100–250 mCi (3,700-9,250 MBq). Thyroid gland doses of approximately 10,000–30,000 rad (300 Gy) can completely ablate the thyroid gland. An administered activity of 5–15 mCi (185–555 MBq) yields a radiation dose to the thyroid gland of approximately 5,000–10,000 rad (50–100 Gy).

## 2.2 SUMMARY OF HEALTH EFFECTS

An extensive amount of literature is available on the effects of iodine on human physiology and health. The intense interest in iodine derives from early recognition of the necessity of appropriate amounts of

iodine for maintenance of normal function of the thyroid gland and of awareness of diseases of the thyroid gland that are caused or affected by iodine intake. The prevalence of thyrotoxicosis (the clinical outcome of uncontrolled hyperthyroidism) has been estimated to be approximately 0.5%, and that of hypothyroidism is of a greater magnitude. Research directed at understanding the epidemiology, pathophysiology, and therapeutic strategies for these relatively common diseases have given way to a fairly comprehensive, although not complete, understanding of the role of iodine in thyroid gland physiology and the related health consequences and risks associated with excessive or inadequate iodine intake. The use of radioactive iodine ($^{131}I$) for treating thyrotoxicosis, as well as studies of the thyroid gland as a target for internal exposures to atmospheric $^{131}I$ fallout, have further complemented our understanding of iodine toxicity as it relates to exposures to radioactive isotopes of iodine.

This profile does not attempt to summarize in detail all of the studies relevant to the adverse effects of iodine on the thyroid, as to do so would require several volumes. Instead, the focus is on literature that identifies the lowest observable iodine exposure levels associated with adverse effects in humans. Where applicable, relevant studies in animals are summarized, particularly when such studies have identified potential targets of toxicity not already documented in humans or for which adequate dose-response information does not exist for humans. This strategy leads to a focus on the thyroid gland as the primary and most sensitive target of iodine for both chemical and radiologic toxicity. This is not surprising given that avid uptake of absorbed iodine by the thyroid gland results in approximately 90% of the body iodine content residing in the thyroid gland (see Section 3.4, Toxicokinetics). Adverse effects on a wide variety of other organ systems can result from disorders of the thyroid gland, including disturbances of the skin, cardiovascular system, pulmonary system, kidneys, gastrointestinal tract, liver, blood, neuromuscular system, central nervous system, skeleton, male and female reproductive systems, and numerous endocrine organs, including the pituitary and adrenal glands. Although these secondary effects are noted in the profile, they are not discussed in detail and the reader is referred to authoritative references on these subjects for further information.

An important consideration in interpreting the iodine toxicology literature is that the effect of an increase in iodine intake will depend, in part, on the preexisting background dietary intake and the associated physiological adaptations to background intake. The response to an upward increase in intake may be quite different in individuals who have adapted to either low dietary or high dietary intake. Examples of this are described in appropriate sections of this report (e.g., Section 3.2.2.2). In this profile, the term molecular iodine is used to refer to $I_2$; the term *iodide* is used to refer to the anion, $I^-$, the term iodate is used to refer to the anion $IO_3^-$, and the term *iodine* is used to refer to the element in any form, usually

when the form was not specified in the literature being summarized or when the form is not relevant to the discussion. From a physiological perspective, regardless of the form of iodine that is absorbed after exposure, iodide is the form of iodine that is taken up into the thyroid gland, and effects from exposures to iodine ultimately derive from exposure of the thyroid gland to iodide. A more important toxicological distinction is that, unlike iodide, molecular iodine ($I_2$) is a relatively strong oxidizing agent and has the potential to produce injuries related to redox reactions with proteins. This is the primary basis for the use of $I_2$ as a topical antiseptic and antimicrobial disinfectant for drinking water.

The health effects of exposure to radioiodine derive from the emission of beta and gamma radiation. Radioiodine that is absorbed into the body quickly distributes to the thyroid gland and, as a result, the tissues that receive the highest radiation doses are the thyroid gland and surrounding tissues (e.g., parathyroid gland). Tissues other than the thyroid gland can accumulate radioiodine, including salivary glands, gastric mucosa, choroid plexus, mammary glands, placenta, and sweat gland. Although these tissues may also receive a radiation dose from internal radioiodine, the thyroid gland receives a far higher radiation dose. The radiation dose to the thyroid gland from absorbed radioiodine varies with isotope and its radiation emission properties (e.g., type of radiation, energy of emission, effective radioactive half-life). A comparison of the doses delivered to the thyroid gland from a few of the isotopes of iodine is in Table 2-1. The highest total doses are achieved with $^{131}I$, whereas the highest dose rates (rad/hour) are delivered from $^{132}I$.

**Endocrine Effects.** The principal direct effects of excessive iodine ingestion on the endocrine system are on the thyroid gland and regulation of thyroid hormone production and secretion. Effects of excess iodine on the thyroid gland can be classified into three types: hypothyroidism, hyperthyroidism, and thyroiditis. Hypothyroidism refers to the diminished production of thyroid hormones leading to clinical manifestations of thyroid hormone insufficiency. This can occur with or without goiter, an enlargement of the gland that occurs in response to elevated circulating levels of the pituitary hormone, thyroid stimulating hormone (TSH), during periods of suppressed thyroid hormone production. A typical biomarker of hypothyroidism is a decrease in the circulating levels of thyroxine ($T_4$) and, when thyroid failure is far advanced, triiodothyronine ($T_3$). This is always accompanied by an elevation of TSH (also known as thyrotropin) above the normal range, unless the cause of the hypothyroidism resides in the pituitary-hypothalmus. Hyperthyroidism is an excessive production and/or secretion of thyroid hormones. The clinical manifestation of abnormally elevated circulating levels of $T_4$ and/or $T_3$ is thyrotoxicosis. Thyroiditis refers to an inflammation of the gland, which is often secondary to thyroid gland autoimmunity. The above three types of adverse effects of excess iodine can occur in children and

## Table 2-1. Thyroid Doses and Dose Rates for Various Isotopes of Iodine[a]

| Isotope | Percent of dose from beta radiation | Effective half-life in the thyroid (hours) | Mean range of beta-radiation in thyroid (mm) | Total dose from 1 mCi in the thyroid (rad) | Average dose rate of 10 rad from 1 mCi in the thyroid (rad/hour) |
|---|---|---|---|---|---|
| $^{123}$I | 77 | 13 | 0.1 | 76 | 3.7 |
| $^{125}$I | 73 | 866 | 0.01 | 3,747 | 3.0 |
| $^{131}$I | 94 | 177 | 0.4 | 5,627 | 22 |
| $^{132}$I | 90 | 2.3 | 1.7 | 199 | 59 |
| $^{133}$I | 96 | 20 | 1.3 | 1,355 | 46 |
| $^{135}$I | 90 | 6.7 | 1.1 | 434 | 45 |

[a]from Maxon and Saenger 2000

adults, in fetuses exposed *in utero*, or in infants exposed during lactation. The primary effect of iodide excess in the fetus is goiter formation secondary to a suppression of thyroid hormone production and an elevation in TSH levels.

Measurements of serum levels of thyroid hormones and TSH are often used as biomarkers of hypothyroidism and hyperthyroidism in toxicology and epidemiology studies. In interpreting this literature in terms of human health risks, a distinction must be made between outcomes that have a high potential for producing clinical manifestations and outcomes that may not be clinically significant. In this profile, an observed decrease in circulating $T_4$ and/or $T_3$ levels within the normal range and an increase in serum TSH level above the normal range is referred to as *subclinical hypothyroidism*. Similarly, the term *subclinical hyperthyroidism* refers to a condition in which the circulating levels of $T_4$ or $T_3$ are increased within their normal ranges and the serum TSH level is suppressed below the normal range. Typical normal ranges for these hormone levels are discussed in Section 3.8.2

An acute iodide load can cause a decrease in thyroid hormone production in the thyroid gland; this is referred to as the acute *Wolff-Chaikoff effect*. In most people, this is followed by a return to normal levels of production, referred to as *escape* from the acute Wolff-Chaikoff effect, without a clinically significant change in circulating hormone levels. Escape is thought to be the result of down regulation of the iodine transport mechanism in the thyroid gland (see Section 3.4.3.2 for further details on the Wolff-Chaikoff effect). An acute or chronic excess of iodide can also decrease circulating $T_4$ and $T_3$ levels and induce a hypothyroid state in people who have an underlying thyroid abnormality. These effects result from a persistent acute Wolff-Chaikoff effect and a continued inhibition of thyroid hormone synthesis and release. Hypothyroidism is thought to occur primarily in *susceptible* individuals who fail to escape from the inhibitory effect of large doses of iodide that produce the Wolff-Chaikoff effect. Susceptible individuals includes fetuses and newborn infants, patients who have autoimmune thyroiditis, patients with Graves' disease (Graves' disease is a hyperthyroid state in which autoantibodies to the TSH receptor are produced and act on the TSH receptor to stimulate the gland to produce thyroid hormones) previously treated with radioactive iodine or antithyroid drugs, women who have had postpartum thyroiditis, or people who have had subacute thyroiditis. A complete list of such susceptible subpopulations is provided in Table 2-2. The hypothyroidism resolves when the excess iodine is discontinued. Spontaneous recovery usually occurs within 2–3 weeks, although some individuals may develop primary hypothyroidism.

## Table 2-2. Risk Groups for Iodine-induced Hypothyroidism

| | |
|---|---|
| **No underlying thyroid disease** | |
| Fetus and neonate, mostly preterm | |
| | Secondary to transplacental passage of iodine or exposure of neonate to topical or parenteral iodine-rich substances |
| Infant | |
| | Occasionally reported in infants drinking iodine-rich water (China) |
| Adult | |
| | In Japanese subjects with high iodine intake where Hashimoto's thyroiditis has been excluded |
| Elderly | |
| | Reported in elderly subjects with and without possible defective organification and autoimmune thyroiditis |
| Chronic nonthyroidal illness | |
| | Cystic fibrosis |
| | Chronic lung disease (including Hashimoto's thyroiditis) |
| | Chronic dialysis treatment |
| | Thalassemia major |
| | Anorexia nervosa |
| | |
| **Underlying thyroid disease** | |
| Hashimoto's thyroiditis | |
| Euthyroid patients previously treated for Graves disease with $^{131}I$, thyroidectomy, or antithyroid drugs | |
| Subclinical hypothyroidism, especially in the elderly | |
| After transient postpartum thyroiditis | |
| After subacute painful thyroiditis | |
| After hemithyroidectomy for benign nodules | |
| | |
| **Euthyroid patients with a previous episode of amiodarone-induced destructive thyrotoxicosis** | |
| **Euthyroid patients with a previous episode of interferon-alpha-induced thyroid disorders** | |
| **Patients receiving lithium therapy** | |

Source: NRC 2004

Several studies have examined the acute and intermediate-duration effects of increased intake of iodine on thyroid hormone status in adults. Acute iodine exposures (1,500 µg/day), in subjects who have no underlying thyroid disease, have been shown to produce small, reversible changes in serum thyroid hormone levels and serum levels of TSH. These effects result from a small iodine-induced decrease in thyroid hormone release, which is accompanied by a commensurate rise in serum TSH concentration, to maintain normal thyroid function. The results of epidemiological studies suggest that chronic exposure to excess iodine can result in or contribute to hypothyroidism in certain susceptible populations of children (1,150 µg/day, 29 µg/kg/day) and elderly adults (160–800 µg/day, 4–12 µg/kg/day). Several studies have found an increased prevalence of hypothyroidism in residents of areas of Japan where dietary iodine intake is extraordinarily high as a result of consumption of seaweeds with a high iodine content (13 mg/day, 0.22 mg/kg/day). Populations that are iodine deficient and, in particular, those that include people who have goiter, appear to be particularly sensitive to an increase in iodine intake. A more complete list of population subgroups at risk to develop iodine-induced hyperthyroidism is provided in Table 2-3.

People who have autoimmune thyroid disease may be at increased risk of developing thyroid dysfunction when exposed to excess iodide. Euthyroid patients, in a mildly iodine-deficient area, who were diagnosed with Hashimoto's thyroiditis and who were positive for antithyroid (thyroid peroxidase) antibodies developed subclinical hypothyroidism after oral doses of 375 µg/day (5.8 µg/kg/day) for 6 months or clinical hypothyroidism after exposures to 180 mg I/day (2.6 mg/kg/day) for 6 weeks, more than 1,000 times the RDA. Autoimmune thyroiditis in autoimmune-prone individuals can be accelerated by iodine excess, whereas thryoiditis can be attenuated by iodine deficiency.

The clinical case literature demonstrates that doses of iodide exceeding 200 mg/day (2.8 mg/kg/day) given to a mother during pregnancy can result in congenital goiter and hypothyroidism in the newborn infant. An iodine-deficient status of the mother can also lead to goiter in the fetus and neurodevelopmental impairment of the fetus. Adequate iodine supplementation early in pregnancy can correct the deficiency and prevent maternal and neonatal goiter formation. Thyroid dysfunction was not detected in newborns of mothers who received oral doses of 3–4 µg/kg/day during pregnancy for the purpose of correcting or preventing potential iodine deficiency and for the management of Graves' disease during pregnancy.

## Table 2-3. Risk Groups for Iodine-induced Hyperthyroidism

| | |
|---|---|
| **Underlying thyroid disease** | |
| | Iodine supplementation for endemic iodine-deficiency goiter |
| | Iodine administration to patients with euthyroid Graves disease, especially those in remission after antithyroid drug therapy |
| | Nontoxic nodular goiter |
| | Autonomous nodules |
| | Nontoxic diffuse goiter |
| **No underlying thyroid disease** | |
| | Iodine administration to patients with no recognized underlying thyroid disease, especially in areas of mild to moderate iodine |

Source: NRC 2004

## 2. RELEVANCE TO PUBLIC HEALTH

Oral exposure to excess iodide can, under certain circumstances, induce hyperthyroidism and thyrotoxicosis. The epidemiological and clinical literature suggest that iodide-induced hyperthyroidism occurs most often in people who have a previous history of iodine deficiency and goiter, or, rarely, Graves' disease previously treated with anti-thyroid medications. What has been referred to as an *epidemic* of hyperthyroidism occurred in iodine-deficient areas in the midwestern United States between the years 1926 and 1928. Clinical records suggest that the incidence of mortality from hyperthyroidism increased in Detroit during this period from approximately 2–4 deaths per 100,000 to approximately 11 deaths per 100,000 at the peak of the epidemic. Although there is considerable debate about the origins of the epidemic, the advent of aggressive supplementation of the diet with iodide in midwestern iodine-deficient, endemic goiter areas has been implicated as a contributing factor. More recent and more rigorous epidemiologic designs have been applied to several populations in which dietary iodide was supplemented as a prophylaxis for iodine deficiency and goiter. These studies confirm that iodide supplementation of iodide-deficient diets, to achieve intakes in the range of 3–7 μg/kg/day, does indeed result in a detectable increase in the incidence of hyperthyroidism. Cases of iodine-induced hyperthyroidism in people who were euthyroid and without apparent thyroid disease have also been reported; however, only a few have provided dose information, suggesting effects after oral doses of 3–1,440 mg/day (0.05–23 mg/kg/day) for 6 months.

Extensive clinical use of radioiodine, principally $^{123}I$ and $^{131}I$, for diagnostic purposes, and $^{131}I$, and rarely $^{125}I$, for treatment of hyperthyroidism has provided a wealth of information on the effects of relatively high acute exposures on thyroid gland function. Radioiodine is cytotoxic to the thyroid gland at high radiation doses and produces hypothyroidism when doses to the thyroid gland exceed 25 Gy (2,500 rad). Thyroid gland doses of approximately 300 Gy (30,000 rad) can completely ablate the thyroid gland and result in hypothyroidism. This dose is achieved with an acute exposure of approximately 25–250 mCi (0.9–9 GBq). Such high dosages are used to ablate thyroid remnants after surgery for thyroid cancer. Although, a rare outcome, cytotoxic doses of $^{131}I$ can also produce dysfunction of the parathyroid gland, which can receive a radiation dose from β emission of $^{131}I$ in the adjacent thyroid gland.

Clinical cases have been reported in which congenital hypothyroidism occurred in newborn infants after maternal exposures to high doses of $^{131}I$ for treatment of thyroid cancer during pregnancy. Exposure in these cases ranged from 11 to 77 mCi (407–2,850 MBq). Two studies that reviewed the thyroid status of larger sets of infants (37 or 73) born to patients who received $^{131}I$ for ablative treatment of thyroid cancer 2–10 years (mean, 5.3 years) prior to pregnancy (i.e., exposure occurred before conception and fetal

development) found no thyroid gland disorders. The maternal $^{131}I$ exposures ranged from 2 to 17 GBq (50–450 mCi); the mean exposure was 4.4 GBq (120 mCi).

A large amount of epidemiological literature exists on the health outcomes in populations that were exposed to environmental releases of radioiodine. These include (1) releases from explosions of nuclear bombs such as the Marshall Islands BRAVO test, the largest U.S. detonation (15 megatons), and from the Nevada Test Site; (2) releases from nuclear fuel production facilities such as the Hanford Nuclear Site; and (3) accidental releases from nuclear power plants such as the Chernobyl explosion and fire (Table 2-4). In general, releases of these types result in mixed exposures to a variety of radioisotopes and to radiation doses from both external and internal exposure. However, doses from radioiodine that are significant to health derive largely from internal exposure as a result of uptake of relatively short-lived radioiodine isotopes into the thyroid gland (see Section 3.4.2.2). Thus, effects on the thyroid attributable to radioiodine that were subsequently observed, in some cases, years after the event, derived from exposures to the relatively high levels of radioiodine found immediately after the event, rather than from sustained exposures. The relative contribution of the inhalation and oral pathways can be expected to vary depending on the duration of the release and the duration of human contact with the sites of contamination. Epidemiological studies of the Nevada Test Site detonations and releases from the Hanford Nuclear Site have focused on subjects who were potentially exposed through the dietary pathway as a result of repeated releases during periods of 7 or 13 years, respectively.

In the so-called *BRAVO cohort*, which has been studied extensively (see Section 3.2.2 for a more detailed discussion), inhalation may have been a more significant contributor to the internal radioiodine dose because the subjects comprising the cohort were evacuated from the site of major contamination within 2 days after the release of radioiodine to the atmosphere; this would have limited their dietary exposures. Nevertheless, estimates of inhalation intakes of airborne radioactivity amounted to <1% of the total intake estimated based on measurements of $^{131}I$ in urine, suggesting a substantial contribution from other routes. In nursing infants, exposure would have continued from ingestion of contaminated breast milk. Radiation doses to the thyroid gland (external and internal) in the most highly exposed individuals after the Marshall Islands BRAVO test is estimated to have ranged from 0.3 to 20 Gy (30–2,000 rad). External radiation, resulting primarily from exposure to gamma-emitting radioisotopes other than iodine isotopes (e.g., $^{137}Cs$), is estimated to have contributed approximately 4–16% or 10–50% of total thyroid dose, depending on the location of the individual with respect to the blast. Thyroid gland outcomes have been assessed periodically since the BRAVO test in 1954. Cases of thyroid gland disorders began to be detected in the exposed population in 1964, 10 years after the BRAVO test, particularly in exposed children; these

## Table 2-4. Releases from Radioiodine-producing Events

| Source | $^{131}$I Released (PBq)[a] | Reference |
|---|---|---|
| All nuclear bomb tests | 650,000 | Gonzalez 1998 |
| Nevada Test Site nuclear bomb tests | 5,500 | NCI 1997 |
| Chernobyl power plant accident | 3,200 | UNSCEAR 2000 |
| Hanford Nuclear Site nuclear fuel processing-related releases | 27 | CDC 1999 |
| Three Mile Island power plant accident | 0.0004–0.0011 | NRC 1995 |

[a]1 PBq=27,000 Ci

USNRC=U.S. National Regulatory Commission; CDC = Centers for Disease Control; NCI = National Cancer Institute; UNSCEAR=United Nations Scientific Committee on the Effects of Atomic Radiations

included cases of apparent growth retardation, myxedema (typical of hypothyroidism), and thyroid gland neoplasms. Collectively, the various health assessments and studies of the so-called *BRAVO cohort* have revealed dose-related abnormally high elevations in serum concentrations of TSH, characteristic of hypothyroidism. Among exposed children who were 1 year old at the time of the BRAVO test and who received an estimated thyroid radiation dose exceeding 1,500 rad (or 15 Gy), 83% had serum concentrations of TSH >5 mU/L; thyroid nodularity was found in 77% of the most highly exposed group, and thyroid cancer was discovered in 6% of the most highly exposed group.

The 1986 explosion and fire at the nuclear power plant at Chernobyl in Ukraine resulted in the release of airborne radionuclides to the surrounding regions and contamination of soil, food, and surface water. Several populations have been characterized that vary considerably in radiation doses received. These include emergency response workers who received the highest acute radiation doses, early evacuees from areas near the reactor (generally within 30 km of the reactor), and people who continued to inhabit contaminated areas outside the evacuation zone. People living in the vicinity of the Chernobyl accident had contact with contaminated areas and contaminated foods (e.g., goat and cow milk, and locally harvested produce) for weeks to months after the accident. The thyroid radiation doses in this population are thought to have been dominated by the oral exposure pathway. The radiation exposures to the general population (i.e., evacuees and people who continued to inhabit contaminated areas) were attributed largely to isotopes of cesium (e.g., $^{137}Cs$), which accounted for approximately 90–98% of the external radiation dose. However, radioiodine is estimated to have contributed approximately 50% of the total lifetime committed effective radiation dose for children born in the region in 1986, and approximately 80% of the radiation dose received during the first year after the release. Estimates of thyroid radiation doses to the general population are highly uncertain; however, these estimates suggest that doses were highest in children who were younger than 1 year of age at the time of the release. The highest estimated doses were received within the 30-km evacuation zone; median doses ranged from 2.3 Gy (230 rad) at age <1 year to 0.4 Gy (40 rad) in adolescents and adults. Estimated median doses received in populations residing 100–200 km from the plant (e.g., Mogilev region) were <0.3 Gy (30 rad) for all age groups. Thyroid screening programs, cancer registries, and epidemiological studies conducted after the Chernobyl accident have revealed a dose-related elevated prevalence of thyroid nodules and thyroid cancer in children of the Belarus and Ukraine regions, apparent approximately 4 years after the Chernobyl accident. These effects have been associated with thyroid radiation doses of 0.3–1 Gy (30–100 rad). In both Belarus and the Ukraine, the highest rates of childhood thyroid cancer have occurred in areas where exposure to other industrial contaminants is likely to have occurred and where there is evidence for widespread iodine deficiency. These factors may have affected the early appearance of thyroid cancer

after the accident, when vigorous public health screening programs for thyroid abnormalities were initiated. The incidence of thyroid cancer prior to the accident in these areas was poorly documented.

**Immunological and Lymphoreticular Effects.** Excess iodide intake may be a contributing factor in the development of autoimmune thyroid disease in susceptible individuals, which can result in hypothyroidism or hyperthyroidism (associated with Graves' disease). Autoimmune thyroiditis is an inflammation of the thyroid gland that can lead to fibrosis of the gland, follicular degeneration, follicular hyperplasia, and hypothyroidism. IgG autoantibodies to thyroglobulin and, more frequently, thyroid peroxidase are a consistent feature of the disorder. Iodine appears to play an important role in the autoimmune response, as human lymphocytes recognize and proliferate in response to iodinated human thyroglobulin, but not iodine-free thyroglobulin. In general, iodine excess accelerates autoimmune thyroiditis in autoimmune-prone individuals, whereas iodine deficiency attenuates thyroiditis. Several studies have been conducted in people who reside in endemic goiter areas and who received iodide supplementation. These studies suggest that iodine intakes of 230–420 μg I/day (3.3–6.0 μg/kg/day total intake) for 12 months can induce thyroid autoimmunity. However, other studies have not found increases in autoimmunity associated with iodine supplementation at doses of 1,150 μg/day (29 μg/kg/day). Studies using rats have shown that doses of 70–95 mg I/kg/day (in drinking water) for 8–12 weeks may increase the incidence of autoimmune thyroiditis in inbred strains of rats that develop spontaneous thyroid autoimmunity.

Larger scale assessments of thyroid autoimmunity have been conducted in the Marshall Islands, where exposures to $^{131}$I occurred as a result of fallout and contamination from test detonations of thermonuclear devices during the period 1946–1958. These studies have not revealed an elevated prevalence of thyroid autoimmunity relative to other populations. Studies of populations in Belarus and Ukraine suggest a possible contribution of radioiodine exposure to an increased prevalence of thyroid autoimmunity following the Chernobyl accident. Cases of autoimmune hyperthyroidism, with serum antibodies to the TSH receptor, have occurred after exposures to higher levels of $^{131}$I for ablative treatment of non-toxic nodular goiter. No relationship was found between the prevalence or incidence of autoimmune thyroiditis and exposure to lower thyroid doses of radioiodine associated with bomb tests at the Nevada Test Site.

Oral exposure to excess iodide can produce allergic reactions in sensitive individuals. The reactions include urticaria (hives), acneiform skin lesions (ioderma), and fevers. Cases of more serious reactions involve angioedema (localized edema), vasculitis, peritonitis and pneumonitis, and complement activation. Both humoral and cell-mediated immune responses are thought to contribute to these

reactions. In general, reactions to iodide have occurred in association with repeated oral doses of iodide 300–1,600 mg I/day (5–23 mg/kg/day). However, in many of these cases, preexisting disease and related drug therapy may have contributed to the reaction to the iodine; thus, the dose-response relationship for ioderma in healthy people remains highly uncertain.

**Gastrointestinal Effects.** Ablative treatment of thyroid cancers with $^{131}$I has been associated with inflammation of the salivary glands (sialadentitis) in humans. Salivary glands express a transport protein, the sodium-iodine symport (NIS), which is present in high concentrations in the thyroid gland, where it functions to transport iodide into the gland for hormone synthesis. Salivary glands can accumulate iodide in saliva at concentrations considerably above that in serum (see Sections 3.4.2.2 and 3.5.1). Exposures in reported cases of $^{131}$I-induced sialadentitis ranged from 100 to 300 mCi (3.7–11 GBq). Sialadentitis usually occurred within a few days or weeks of exposure and had a duration of several weeks to 2–3 years.

**Neurological Effects.** Exposure to excess iodine has been shown to produce hypothyroidism in certain sensitive individuals. Sensitive populations include fetuses, newborn infants, and euthyroid individuals who have thyroiditis or a history of treated Graves' disease, many of whom have abnormal autoimmune disorders (see Section 3.2.2.2, Endocrine Effects). Of these iodine-induced forms of hypothyroidism, those occurring in the fetus or newborn infant have the greatest potential for producing neurological effects. This is because thyroid hormones are essential to the development of the neuromuscular system and brain. An iodine-induced hypothyroid state can result in delayed or deficient brain and neuromuscular development of the newborn. Iodine-induced hypothyroidism in an older child or adult would be expected to have little or no deleterious effects on the neuromuscular system. Exposure of a fetus to large amounts of radioiodine would result in thyroid tissue ablation and in similar delayed brain and neuromuscular development, if the hypothyroid state was not corrected (e.g., with hormone replacement therapy) after birth.

Exposure to excess iodine can also produce hyperthyroidism in sensitive individuals (see Section 3.2.2.2, Endocrine Effects). These include people who are iodine deficient with goiter, those who have thyroid disease previously, including Graves' disease previously treated with antithyroid drugs, and those who have developed thyrotoxicosis from amiodarone or interferon-alpha treatments. Patients who develop thyrotoxicosis may experience neuromuscular disorders, including myopathy, periodic paralysis, myasthenia gravis, peripheral neuropathy, tremor, and chorea; however, these are not likely to occur in iodine-induced hyperthyroidism, except in sensitive groups, already at risk for neurologic problems.

**Developmental Effects.** Although iodine excess may result in hypothyroidism, iodine deficiency is far more likely to cause prenatal and postnatal hypothyroidism and be associated with neurologic injury leading to cretinism, a developmental effect (see Section 3.2.2.2, Endocrine Effects). Thyroid hormone deficiency from any cause at critical times of development may result in severe mental retardation, neurologic abnormalities, growth retardation, or abnormal pubertal development.

Congenital hypothyroidism secondary to thyroid ablation has been reported subsequent to maternal exposure to ablative doses of $^{131}$I. In one case, an infant became hypothyroid after his mother received 99 mCi (3.7 GBq) of $^{131}$I during her sixth week of pregnancy. Growth retardation was also observed in some children who were exposed to radioiodine in the Marshall Island BRAVO cohort, early after the bomb test. Studies are suggestive of possible extra-thyroidal developmental effects of radioiodine following maternal exposures to ablative doses of $^{131}$I received 2–10 years prior to pregnancy. Dose-response relationships for these effects were not established in these studies; therefore, the observed outcomes may not have been related to the $^{131}$I exposures, The observed outcomes include low birth weights with subsequent normal growth patterns, tetrology of Fallot (pulmonic stenosis, atrial septal defect, and right ventricular hypertrophy), hypoparathyroidism, Down's syndrome, and cardiac anomalies. The maternal $^{131}$I exposures ranged from 1 to 17 GBq (27–460 mCi). Studies of pregnancy outcomes in Belarus and Ukraine populations after the Chernobyl accident are suggestive of possible developmental effects related to radiation exposures. However, interpretation of these results is highly uncertain, as factors other than radioiodine could have affected the outcomes, including exposure to other forms of radiation, nutrition, or other chemical exposures.

Exposure to excess iodine can also produce hyperthyroidism in sensitive individuals (see Section 3.2.2.2, Endocrine Effects). Growth acceleration occurs in childhood hyperthyroidism, from any cause, which is thought to be related to changes in pituitary regulation of growth.

**Reproductive Effects.** Exposure to excess iodine may produce hypothyroidism or hyperthyroidism (see Section 3.2.2.2, Endocrine Effects) and could cause disruption of reproductive function, secondary to thyroid gland dysfunction. Hypothyroidism can produce changes in the menstrual cycle in humans, including menorrhagia (excessive uterine bleeding) and anovulation (no ovulation). Spontaneous abortions, stillbirths, and premature births have also been associated with hypothyroidism. Reproductive impairments associated with hyperthyroidism include amenorrhea and alterations in gonadotropin release

and sex hormone-binding globulin (SHBG), and associated changes in the levels and metabolism of steroid hormones in both females and males.

Clinical follow-up studies of pregnancies in patients who received $^{131}$I (1–17 GBq, 27–460 mCi) for ablative treatment of thyroid cancer 2–10 years (mean, 5.3 years) prior to pregnancy have not shown evidence of effects on reproductive success. However, clinical cases of transient impaired testicular function following exposures to $^{131}$I for ablative treatment of thyroid cancer in men have been reported. Observed effects included low sperm counts, azospermia (absence of spermatozoa), and elevated serum concentrations of follicle stimulating hormone (FSH), which persisted for more than 2 years, but were usually of much shorter duration. Exposures to radioiodine ranged from 30 to 1,335 mCi (1.1–49.5 GBq). In Belarus and Ukraine populations after the Chernobyl accident, pregnant women who resided in heavily exposed areas (including exposures to other industrial contaminants) appeared to be at risk for development of toxemia, renal insufficiency, and anemia.

**Cancer.** The relationship between iodide intake and thyroid cancer has been examined in several large-scale epidemiology studies. The results of these studies suggest that increased iodide intake may be a risk factor for thyroid cancer in certain populations, particularly in populations in iodine-deficient, endemic goiter regions; however, because not all studies have found an increased risk of cancer, the relationship between iodine intake and thyroid cancer remains unclear. A recurrent observation is an apparent shift in the histopathology toward a higher prevalence of papillary cancer after increased iodine intake in otherwise iodine-deficient populations. Two studies found a significant excess of thyroid gland cancer in populations from endemic goiter regions whose diets were supplemented to achieve approximate iodine intakes of 3.5 μg/kg/day.

The thyroid gland receives the highest radiation dose of any organ or tissue following internal exposure to radioiodine (see Section 3.4.2.2, Toxicokinetics), and therefore, cancer of the thyroid gland is a major cancer concern associated with radioiodine exposures. Children are especially vulnerable to radioiodine toxicity and related thyroid cancers (see Section 3.7). Cancer morbidity and mortality among populations who received exposures to radioiodine have been examined in several epidemiology studies. In general, these studies fall into several categories that can be distinguished by the sources of exposure and estimated radiation doses to the thyroid gland and include (see Table 3-3): (1) relatively high exposures and doses (10–20 mCi, 370–740 MBq; >10,000 rad, >100 Gy) achieved when $^{131}$I is administered to treat hyperthyroidism (higher exposures are used in treatment of thyroid cancer); (2) moderate exposures and doses (40–70 μCi, 1.5–2.6 MBq; 80–130 rad, cGy) associated with clinical administration of $^{131}$I for

diagnosis of thyroid gland disorders; (3) low to moderate doses from exposures to fallout from nuclear bomb tests (BRAVO test, 300–2,000 rad, cGy; Nevada Test Site, 1–40 rad, cGy); (4) low to moderate high doses from exposures to releases from nuclear power plant accidents (Chernobyl, 1–200 rad, cGy); and (5) low doses from exposures from operational releases from nuclear fuel processing plants (Hanford Nuclear Site, 0.0001–284 rad, cGy).

The relatively high and acutely cytotoxic radiation doses to the thyroid gland that are achieved in the treatment of thyroid gland disorders, and the related outcomes on the thyroid, are virtually irrelevant to predicting outcomes from the much lower environmental exposures that occur in most U.S. populations. Nevertheless, these studies have revealed that, even at high exposures (3–27 mCi, 111–999 MBq) and thyroid gland doses (60 Gy, 6,000 rad), significant risks for cancers in organs other than the thyroid gland have not been consistently detected when the study designs control for other treatments administered to the patients. However, the data suggest a small increased thyroid cancer risk following $^{131}$I treatment for hyperthyroidism. Studies of diagnostic doses of radioiodine have not consistently revealed significant risks of thyroid or other cancers; those that have, however, found significantly elevated risks only in patients who were administered the radioiodine for diagnosing a suspected thyroid gland tumor and the cancer may have predated the administration of $^{131}$I or the patients may have had previous external radiation exposure. However, in general, studies of the outcomes of medical uses of radioiodine involve subjects who were exposed as adults. Studies of thyroid cancers and external radiation exposure have found a strong age dependence between thyroid radiation dose and thyroid cancer. Risk is substantially greater for radiation doses received prior to age 15 years when compared to risks for doses received at older ages, although the excess thyroid cancer risk is not limited to that age group. This same general trend in age-dependence would be expected for internal exposures to radioiodine; thus, studies of adult exposures to radioiodine may not be directly applicable to predicting outcomes from exposures to children. Studies of populations potentially exposed to radioiodine (0.09–3.2 Gy, 9–325 rad) as a result of nuclear bomb tests at the Nevada Test Site are suggestive, but not conclusive, of a possible association between radioiodine exposures and thyroid cancer. The National Research Council concluded that, because of uncertainties related to dose reconstruction and epidemiological analyses of the outcomes possibly associated with the Nevada Test Site bomb tests, the currently available information is not adequate to determine the extent to which the bomb tests in Nevada increased the incidence of thyroid cancer. A study of cancer in populations that resided near the Hanford Nuclear Site in southeastern Washington during the period 1944–1957 found that incidences of thyroid carcinoma or nodules were found to be unrelated to thyroid radioiodine dose. Although numerous studies have attempted to examine possible associations between the Chernobyl accident and thyroid cancers in the region, the strongest

evidence for an association comes from a case-control study of thyroid cancers among children in Belarus; this study provides reasonably strong evidence for the contribution of higher-level radioiodine exposure and the etiology of thyroid cancers diagnosed after the Chernobyl accident. Ecological studies have provided additional evidence for an association between thyroid cancer and exposures to radioiodine in the region, during childhood. More data and epidemiological analyses of these data, in the future, should improve the estimate of risks related to radioiodine intake.

Breast cancer is also a concern with exposures to high levels of radioiodine after ablative therapy for hyperthyroidism because the breast expresses the sodium-iodide symport (NIS) and can transport and accumulate iodide (see Sections 3.5.4.2 and 3.6.1, Distribution). However, the radiation dose to the breast following exposure to radioiodine is much lower than that of the thyroid gland. Consistent with this, the epidemiological literature to date has not implicated such exposures as a significant risk factor for breast cancer.

## 2.3 MINIMAL RISK LEVELS

Minimal Risk Levels (MRLs) described in this section are for stable iodine ($^{127}I$) and are based on an assessment of dose-response relationships for the chemical toxicity of stable iodine. A discussion of MRLs for ionizing radiation can be found in the ATSDR Toxicological Profile for Ionizing Radiation (1999). The MRL for acute-duration (14 days or less) exposures to ionizing radiation is 0.004 Sv (0.4 rem), and for chronic-duration exposures, is 1 mSv/year (100 mrem/year).

### *Inhalation MRLs*

An MRL could not be derived for inhalation exposure to iodine because of a lack of information on dose-response relationships for the inhalation pathway.

### *Oral MRLs*

- An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure (1–14 days) to iodine.

The acute-duration MRL is based on a no-observed-adverse-effect-level (NOAEL) of 0.01 mg/kg/day in healthy adult humans (Gardner et al. 1988; Paul et al. 1988). Although the NOAEL is derived from acute studies of healthy adults, supporting studies indicate that the NOAEL would also be applicable to children

and elderly adults (Boyages et al. 1989; Chow et al. 1991). On this basis, an uncertainty factor is not needed adjust the NOAEL to account for human variability in sensitivity.

Although there were small increases in the serum concentrations of TSH, as a compensatory response to small decreases in the serum concentrations of thyroid hormone ($T_4$ and $T_3$), in healthy adults who had no history of thyroid disease or detectable antithyroid antibodies, hormone levels were within the normal range for healthy adults. These changes were almost certainly the result of a small decrease in the secretion of T4 and T3 from the thyroid as a result of the excess iodine. Furthermore, the hormone levels reverted to pretreatment levels when the iodine dosage was withdrawn.

Healthy euthyroid adults (nine males, nine females) who had no history of thyroid disease or detectable antithyroid antibodies received daily oral doses of 250, 500, or 1,500 µg I/day as sodium iodide for 14 days (Paul et al. 1988). Based on 24-hour urinary excretion of iodide prior to the iodide supplement, the background iodine intake was estimated to be approximately 200 µg/day; thus, the total iodide intake was approximately 450, 700, or 1,700 µg I/day (approximately 0.0064, 0.01, or 0.024 mg/kg/day, respectively, assuming a 70-kg body weight). Subjects who received 1,700 µg/day (0.024 mg/kg/day) had significantly decreased (5–10%) serum concentrations of $TT_4$, $FT_4$, and $TT_3$ compared to pretreatment levels, and serum TSH concentrations were significantly increased (47%) compared to pretreatment values. All hormone levels were within the normal range during treatment. In this same study, the subjects who received daily doses of 250 or 500 µg I/day for 14 days (respective total intakes of approximately 450 or 700 µg/day; 0.0064 or 0.010 mg/kg/day) had no significant changes in serum hormone concentrations. A limitation of this study is that it included a relatively small number of subjects, although the exposures to these subjects were controlled and quantified with high certainty.

In similar type of study, healthy, euthyroid, adult males (n=10) received daily oral doses of 500, 1,500, or 4,500 µg I/day (as sodium iodide) for 14 days (Gardner et al. 1988). Based on 24-hour urinary excretion of iodide prior to the iodide supplement of 250–320 µg/day, the total estimated intakes were 300, 800, 1,800, or 4,800 µg/day or approximately 0.004, 0.011, 0.026, or 0.069 mg/kg/day. There were no effects on serum thyroid hormone or TSH concentrations at the 800 µg/day intake (0.011 mg/kg/day); however, intakes of 1,800 or 4,800 µg I/day (0.026 or 0.069 mg/kg/day) produced small (10%) but significant, transient decreases in serum $TT_4$ and $FT_4$ concentrations and an increase (48%) in serum TSH concentration, relative to the pretreatment values. Similar to the Paul et al. (1988) study, the Gardener et al. 1988) study included a relatively small number of subjects, whose exposures were controlled and quantified with high certainty.

Although the acute NOAEL is derived from acute studies of healthy adults, supporting studies indicate that the NOAEL would also be applicable to children and elderly adults (Boyages et al. 1989; Chow et al. 1991; see discussion of chronic-duration MRL for a description of these studies.). On this basis, an uncertainty factor is not needed to adjust the NOAEL to account for human variability in sensitivity. In one study (Chow et al. 1991), 30 healthy elderly adult females, without evidence of thyroid peroxidase antibodies (TPA), received daily doses of 500 µg I/day (as potassium iodide) for 14 or 28 days. Serum concentrations of $FT_4$ were significantly decreased and serum TSH concentrations were significantly increased in the women who received the iodide supplements, relative to a placebo control group. On average, the magnitude of the changes did not produce clinically significant depression in thyroid hormone levels; however, five subjects had serum TSH concentrations that exceeded 5 mU/L. The subjects had a lower dietary iodine intake than those in the Gardner et al. (1988) study, approximately 72–100 µg/day, based on urinary iodide measurements. Therefore, the total iodide intake was approximately 600 µg/day or 0.0086 mg/kg/day, essentially the same as the acute NOAEL in healthy adults. The second study, Boyages et al. (1989), is the primary basis for the chronic-duration MRL (see discussion of chronic-duration MRL).

The acute-duration MRL is higher than the National Research Council RDA of 150 µg/day (0.0021 mg/kg/day for a 70-kg adult), 220 µg/day (0.0031 mg/kg/day), and 290 µg/day (0.0041 mg/kg/day) during pregnancy and lactation, respectively (NRC 2001).

- An MRL of 0.01 mg/kg/day has been derived for chronic-duration (>365 days) oral exposure to iodine.

The chronic-duration MRL is based on a NOAEL of 0.01 mg/kg/day and a lowest-observed-adverse-effect level (LOAEL) of 0.029 mg/kg/day for subclinical hypothyroidism in healthy human children (Boyages et al. 1989; Li et al. 1987). An uncertainty factor is not needed to adjust the NOAEL to account for human variability in sensitivity because the NOAEL is based on a sensitive end point in children, a sensitive subpopulation. Supporting studies indicate that the NOAEL would be applicable to elderly adults who may represent another sensitive subpopulation (Chow et al. 1991; Szabolcs et al. 1997). The chronic MRL was based on a chronic human study; however, since the chronic MRL is the same as the acute MRL (0.01 mg/kg/day), it is also applicable to intermediate-duration exposures.

In the studies that form the primary bases for the chronic-duration MRL (Boyages et al. 1989; Li et al. 1987), although serum concentrations of TSH were elevated, they remained within the normal range for

children. Thyroid gland enlargement, however, was observed in children who had no history of thyroid disease or detectable antithyroid antibodies. Hormone levels were within the normal range for healthy children; therefore, these dosages did not induce clinical hypothyroidism. The slight thyroid enlargement can be considered a less-serious LOAEL, not indicative of functional impairment. Thyroid status was compared in groups of children, ages 7–15 years, who resided in two areas of China where iodide concentrations in drinking water were either 462 µg/L (n=120) or 54 µg/L (n=51) (Boyages et al. 1989; Li et al. 1987). Urinary iodine was 1,236 µg I/g creatinine in the high iodine group and 428 µg I/g creatinine in the low iodine group. Assuming a body weight of 40 kg and lean body mass of 85% of body weight, the above urinary iodine/creatinine ratios are approximately equivalent to iodine excretion rates, or steady state ingestion rates of 1,150 (0.029 mg/kg/day) and 400 µg/day (0.010 mg/kg/day) in the high and low iodide groups, respectively. Although the subjects were all euthyroid with normal values for serum thyroid hormones and TSH concentrations, TSH concentrations were significantly higher (33%) in the high iodine group. The high iodide group had a 65% prevalence of goiter and a 15% prevalence of Grade 2 goiter compared to 15% for goiter and 0% for Grade 2 goiter in the low iodine group.

Although the acute NOAEL is derived from studies of children, supporting studies indicate that the NOAEL would be applicable to elderly adults (Chow et al. 1991; Szabolcs et al. 1997). On this basis, an uncertainty factor is not needed to adjust the NOAEL to account for human variability in sensitivity. The Chow et al. (1991) is described in the discussion of the basis for the acute-duration MRL. Szabolcs et al. (1997) studied elderly nursing home residents in the Carpathian Basin and revealed a prevalence of hypothyroidism that increased with increasing iodine intake. Subjects were from one of three regions where, based on reported urinary iodine levels of 72, 100, or 513 µg I/g creatinine, the iodine intakes were approximately 117, 163, or 834 µg/day (0.0017, 0.0023, or 0.012 mg/kg/day for low, n=119; moderate, n=135; or high intake, n=92, respectively). The prevalence of elevated serum TSH concentrations, together with serum $FT_4$ concentrations below the normal range, was 0.95, 1.5, and 7.6% in the low, moderate, and high iodine groups, respectively. If a prevalence of abnormal thyroid hormone levels of <5% is considered a NOAEL, then this study supports a NOAEL in elderly adults that is slightly below 0.012 mg/kg/day. Linear interpolation of the dose-prevalence data reported above yields an estimate of a 5% prevalence at an iodine intake of approximately 0.008 mg/kg/day.

The chronic-duration MRL is higher than the National Research Council RDA of iodine of 150 µg/day (0.0021 mg/kg/day for a 70-kg adult), 220 µg/day (0.0031 mg/kg/day), and 290 µg/day (0.0041 mg/kg/day) during pregnancy and lactation, respectively (NRC 2001).