TOXICOLOGICAL PROFILE FOR IODINE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

April 2004

DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Iodine, Draft for Public Comment was released in September 2001. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE,
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Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

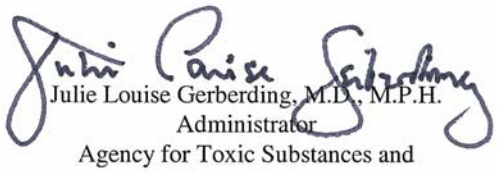
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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Background Information

The toxicological profiles are developed by ATSDR pursuant to Section 104(i) (3) and (5) of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund) for hazardous substances found at Department of Energy (DOE) waste sites. CERCLA directs ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. ATSDR and DOE entered into a Memorandum of Understanding on November 4, 1992 which provided that ATSDR would prepare toxicological profiles for hazardous substances based upon ATSDR's or DOE's identification of need. The current ATSDR priority list of hazardous substances at DOE NPL sites was announced in the Federal Register on July 24, 1996 (61 FR 38451).

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 **How Can (Chemical X) Affect Children?**
Section 1.7 **How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.8 **Children's Susceptibility**
Section 6.6 **Exposures of Children**

Other Sections of Interest:

Section 3.9 **Biomarkers of Exposure and Effect**
Section 3.12 **Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 *Fax*: (770) 488-4178
E-mail: atsdric@cdc.gov *Internet*: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History — The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III *Medical Management Guidelines for Acute Chemical Exposures* is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact*: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 Phone: 770-488-7000 FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 Phone: 919-541-3212.

Radiation Emergency Assistance Center/Training Site (REAC/TS) provides support to the U.S. Department of Energy, the World Health Organization, and the International Atomic Energy Agency in the medical management of radiation accidents. A 24-hour emergency response program at the Oak Ridge Institute for Science and Education (ORISE), REAC/TS trains, consults, or assists in the response to all kinds of radiation accidents. Contact: Oak Ridge Institute for Science and Education, REAC/TS, PO Box 117, MS 39, Oak Ridge, TN 37831-0117 • Phone 865-576-3131 • FAX 865-576-9522 • 24-Hour Emergency Phone 865-576-1005 (ask for REAC/TS) • e-mail: cooleyp@orau.gov • website (including emergency medical guidance): http://www.orau.gov/reacts/default.htm

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Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 Phone: 202-347-4976 FAX: 202-347-4950 e-mail: AOEC@AOEC.ORG Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 Phone: 847-818-1800 FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for iodine. The panel consisted of the following members:

1. Dr. Lewis E. Braverman, Section Chief, Endocrinology, Diabetes, and Nutrition, Boston Medical Center, 88 East Newton Street, Evans 201, Boston, MA 02118;

2. Dr. Richard Leggett, Life Sciences Division, Oak Ridge National Laboratory, 11401 Glen Iris Lane, Knoxville, TN 37922-1744;

3. Dr. Ray Lloyd, Research Professor of Radiobiology, University of Utah School of Medicine, 6588 South Gold Medal Drive, Taylorsville, UT 84084-6964;

4. Dr. Marvin Rallison, Professor Emeritus of Pediatric Endocrinology and Metabolism, University of Utah School of Medicine, 1706 Oakridge Dr., Salt Lake City, UT 84106;

5. Dr. Elaine Ron, Senior Investigator, National Cancer Institute, Division of Cancer Epidemiology and Genetics, Radiation Epidemiology Branch, 6120 Executive Boulevard, EPS/7084, Rockville, MD 20852;

6. Dr. Kiyohiko Mabichi, National Cancer Institute, 6120 Executive Boulevard, Rockville, MD 20852;

7. Dr. Noel R. Rose, Professor of Molecular Medicine, Johns Hopkins University, 615 North Wolfe St., Baltimore, MD 21205; and

8. Dr. Roy E. Shore, Professor and Director, Division of Epidemiology and Biostatistics, New York University School of Medicine, 650 First Ave., New York, NY 10016-3240.

These experts collectively have knowledge of iodine's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about iodine and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Iodine has been found in at least 8 sites. Radioactive iodine has been found at 9 sites, including iodine-129 (^{129}I) in at least 3 sites, and iodine-131 (^{131}I) in at least 6 sites of the 1,636 current or former NPL sites. However, the total number of NPL sites evaluated for iodine is not known. As more sites are evaluated, the sites at which iodine is found may increase. This information is important because exposure to iodine may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact. External exposure to radiation may occur from natural or man-made sources. Naturally occurring sources of radiation are cosmic radiation from space or radioactive materials in soil or building materials. Man-made sources of radioactive materials are found in consumer products, industrial equipment, atom bomb fallout, and to a smaller extent from hospital waste and nuclear reactors.

If you are exposed to either radioactive or stable iodine, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS IODINE?

Iodine is a naturally occurring element that is essential for the good health of people and animals. Iodine is found in small amounts in sea water and in certain rocks and sediments. Iodine occurs in many different forms that can be blue, brown, yellow, red, white, or colorless. Most forms of iodine easily dissolve in water or alcohol. Iodine has many uses. Its most important use is as a disinfectant for cleaning surfaces and storage containers. Iodine is also used in skin soaps and bandages, and for purifying water. Iodine is used in medicines. Iodine is added to food, such as table salt, to ensure that all people in the United States have enough iodine in their bodies to form essential thyroid hormones. Iodine is put into animal feeds for the same reason. Iodine is used in the chemical industry for making inks and coloring agents, chemicals used in photography, and in making batteries, fuels, and lubricants. Radioactive iodine also occurs naturally. Radioactive iodine is used in medical tests and to treat certain diseases, such as over-activity or cancer of the thyroid gland.

1.2 WHAT HAPPENS TO IODINE WHEN IT ENTERS THE ENVIRONMENT?

The oceans are the most important source of natural iodine in the air, water, and soil. Iodine in the oceans enters the air from sea spray or as iodine gases. Once in the air, iodine can combine with water or with particles in the air and can enter the soil and surface water, or land on vegetation when these particles fall to the ground or when it rains. Iodine can remain in soil for a long time because it combines with organic material in the soil. It can also be taken up by plants that grow in the soil. Cows or other animals that eat these plants will take up the iodine in the plants. Iodine that enters surface water can reenter the air as iodine gases. Iodine can enter the air when coal or fuel oil is burned for energy; however, the amount of iodine that enters the air from these activities is very small compared to the amount that comes from the oceans.

Radioactive iodine also forms naturally from chemical reactions high in the atmosphere. Most radioactive forms of iodine change very quickly (seconds to days) to stable elements that are not radioactive. However, one form, ^{129}I, changes very slowly (millions of years), and its levels build up in the environment. Small amounts of radioactive iodine, including ^{129}I and ^{131}I, can

also enter the air from nuclear power plants, which form radioiodine from uranium and plutonium. Larger amounts of radioactive iodine have been released to the air from accidents at nuclear power plants and from explosions of nuclear bombs.

1.3 HOW MIGHT I BE EXPOSED TO IODINE?

Iodine is a natural and necessary part of the food that you eat and the water that you drink. In the United States, most table salt contains iodine. Iodine is put into table salt to make sure that everyone has enough iodine in their bodies to form essential thyroid hormones. In the past, people in some areas of the United States did not get enough iodine in their diets. Iodine is in some breads because it is added to flour to condition bread dough for baking. Iodine is also in cow and goat milk. Iodine gets into milk when cows or goats eat iodine that is in their food and water. Iodine can also get into milk when iodine is used to clean milking machines and milk storage containers, and to clean the animals' udders at dairy farms and dairies. Iodine is in ocean fish, shellfish, and certain plants that grow in the ocean (kelp). This is because there is iodine in sea water, and some sea plants and animals concentrate iodine in their tissues. Iodine can also be in the air. Iodine is in sea spray and mist, which are tiny drops of sea water. Iodine is in cleansers and medicines that are used to clean and bandage skin wounds (tincture of iodine). You can be exposed to these if they are placed on your skin. Some medicines have iodine in them. Iodine is used to treat water to make it safe for drinking. You can buy iodine water purifying tablets that you add directly to water. You can also buy water treatment cartridges for your home that have iodine in them. Some iodine will get into the water that you drink if you use these tablets or cartridges.

People are almost never exposed to radioactive iodine, unless they work in a place where radioactive iodine is used or if they are given radioactive iodine by their doctors. Radioactive iodine is used in certain medical tests and treatments. You might have these tests if your doctor needs to look for problems in your thyroid gland or if your doctor needs to treat you for a problem with your thyroid gland. In the past, people were exposed to radioactive iodine released from nuclear bomb tests, after accidental explosions and fires at nuclear power plants, or from facilities that processed or used nuclear fuel for power plants.

1.4 HOW CAN IODINE ENTER AND LEAVE MY BODY?

Most of the iodine that enters your body comes from the food that you eat. A smaller amount comes from the water that you drink. Iodine will enter your body if it is in the air that you breathe. Some forms of iodine can enter your body when placed on the skin. Iodine can also be injected into your blood by your doctor for special medical tests or treatments. Iodine that enters your body quickly goes into your thyroid gland, a small important organ in your neck. Iodine is used in the thyroid gland to make hormones that are needed for growth and health. Almost all of the iodine in your body is in your thyroid gland. Iodine that does not go into your thyroid gland leaves the body in your urine in a few weeks to months. Small amounts of iodine can also leave your body in sweat or in breast milk. Iodine that leaves your body each day is usually replaced by the iodine that you eat in your food, so that the amount of iodine in your body is just enough to keep you healthy.

1.5 HOW CAN IODINE AFFECT MY HEALTH?

Iodine is needed for your thyroid gland to produce thyroid hormones. You and your thyroid gland are healthy when there is just enough iodine in your body, about 10–15 milligrams, so that just the right amount of thyroid hormones are produced. This amount would look like much less than a pinch of table salt if placed in your hand. This amount of iodine is in most people when they eat the foods that people normally eat in the United States. Your thyroid gland can become unhealthy if more or less than this amount of iodine is in your body. An unhealthy thyroid gland can affect your entire body. If the thyroid gland cannot make enough hormone, then you would have to be given thyroid hormone in pills. If your thyroid gland makes too much hormone, then you would have to be given drugs to make your thyroid make less hormone. Radioactive iodine can also be unhealthy for your thyroid gland. If too much radioactive iodine enters your body, the radioactive iodine will destroy your thyroid gland so that the gland will stop making hormones. Too much radioactive iodine in your body can also cause thyroid nodules or cancer.

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will harm people is to learn how the chemical is absorbed, used, and released by the body. In the case of a radioactive chemical, it is also important to gather information concerning the radiation dose and the dose rate to the body. For some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

1.6 HOW CAN IODINE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

Babies and children need iodine to form thyroid hormones, which are important for growth and health. If infants and children do not have enough iodine in their bodies, their thyroid glands will not produce enough thyroid hormone and they will not grow normally. If they have too much iodine in their bodies, they may develop an enlarged thyroid gland (goiter), which may not produce enough thyroid hormone for normal growth. We also need just the right amount of iodine from our mothers before we are born. Too much iodine from the mother can cause a baby's thyroid gland to be so large that it makes breathing difficult or impossible. Not enough iodine from the mother can cause a baby to not produce enough thyroid hormone, which can affect growth and mental development of the baby. Radioactive iodine in food can be more harmful to babies and children than to adults. When radioactive iodine is in the air, it can get onto the grass and water that the cows eat and drink. Infants and children drink a lot more milk than most adults. If there is radioactive iodine in the milk that a child or infant drinks, more iodine will enter the thyroid gland of the child than of an adult who drinks less milk. In addition, because the thyroid gland of a child or infant is smaller than that of an adult, a child's thyroid

gland will receive a higher radiation dose than the an adult. Children are more sensitive to the harmful toxic effects of iodine and radioactive iodine than adults because their thyroid glands are still growing and the thyroid gland tissues are more easily harmed by radioactive iodine, and because children need a healthy thyroid gland for normal growth.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO IODINE?

We all are exposed to iodine in the food that we eat and in the water that we drink. Iodine is needed for your good health. We do not want to prevent exposure to iodine, but we do want to try to prevent exposure to too much iodine. This is not likely to happen from eating a normal diet in the United States or from drinking water or breathing air. It could happen if you were careless about storing soaps or cleansers or medicines that have iodine in them. For example, a child could swallow medicines that contain iodine. People are rarely exposed to radioactive iodine, unless they work in a place where radioactive iodine is used or if they are given radioactive iodine by their doctors for certain medical tests or treatments.

If your doctor finds that you have been exposed to significant amounts of iodine, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO IODINE?

Most physicians do not test for iodine in their offices, but can collect samples and send them to special laboratories. They can also feel the thyroid for lumps that may have been caused by disease or past exposure to radioactive iodine, but the results do not tell the cause. Every person's body contains a small amount of iodine, but normally not radioactive iodine (such as ^{131}I). Iodine can be measured in the blood, urine, and saliva. The amount is normally measured by its mass (in grams). If the iodine is radioactive, it can be measured by its mass or by its radiation emissions. These emissions are used to tell the amount of radioactive iodine (in curies or becquerels) and the radiation dose it gives to your body (in sieverts or rem).

Radiation detectors can measure radioactive iodine inside your body using the radiation coming from the thyroid gland in your neck. This is useful only if you recently inhaled or ingested some, or if your physician recently gave you some for medical purposes. Your body quickly eliminates iodine and radioactive iodine, so tests should be done shortly after exposure.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), the Food and Drug Administration (FDA), the Department of Energy (DOE), and the U.S. Nuclear Regulatory Commission (USNRC).

Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR), the National Institute for Occupational Safety and Health (NIOSH), and the FDA.

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for iodine include the following:

The National Research Council has established a Recommended Dietary Allowance for iodine of 150 micrograms per day (μg/day), with additional allowances of 25 μg/day during pregnancy and

50 µg/day during nursing. The EPA has established regulations that limit releases of certain forms of radioactive iodine to the environment and require that industries report releases of certain forms of radioactive iodine. NIOSH has established recommendations for limits of worker exposures to iodine and radioactive iodine. The Nuclear Regulatory Commission, the National Council of Radiation Protection and Measurements (NRCP) and the International Commission of Radiological Protection (ICRP) have established recommended limits for worker exposures to radioactive iodine and for releases of radioactive iodine to the environment.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, your regional Nuclear Regulatory Commission office, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles CD-ROM by calling the information and technical assistance toll-free number at 1-888-42ATSDR (1-888-422-8737), by email at atsdric@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

For-profit organizations may request a copy of final profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

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).

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of iodine. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. Section 3.2 contains a discussion of the chemical toxicity of stable iodine; radiation toxicity associated with exposure to radioiodine is discussed in Section 3.3.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Health effects of the element iodine are categorized by the chemical nature of stable iodine (^{127}I) and the radioactive nature of unstable isotopes (e.g., ^{131}I). Four radioactive isotopes (^{123}I, ^{125}I, ^{129}I, and ^{131}I) are of particular interest with respect to human exposures because ^{125}I and ^{131}I are used medically and all four isoptopes are sufficiently long-lived to be transported to human receptors after their release into the environment. These isotopes of iodine emit, primarily, beta radiation (that travel short distances in tissues) and gamma radiation (that can penetrate the entire body). The radiation dose from these radionuclides can be classified as either external (if the source is outside the body) or internal (if the source is inside the body).

The external dose from iodine radionuclides arises primarily from the penetrating gamma radiation that can travel through air. Beta radiation emitted outside the body is normally of little health concern unless the radioactive material contacts the skin. Skin contact can allow the beta radiation to pass through the epidermis to live dermal tissue where it can contribute to the radiation dose to the skin. At very high external doses, beta (and gamma) radiation (e.g., greater than 3 Gy, 300 rad) can cause such adverse effects as skin erythema, ulceration, or necrosis (Agency for Toxic Substances and Disease Registry [ATSDR] 1999).

Once radioactive iodine is internalized, it is absorbed, distributed, and excreted in the same manner as stable iodine. The internal radiation dose from radioactive iodine is actually a measure of the amount of energy that the beta and gamma emissions deposit in tissue. The short-range beta radiation produces a

localized dose while the more penetrating gamma radiation contributes to a whole-body dose. Molecular damage results from the direct ionization of atoms that are encountered by beta and gamma radiation and by interactions of resulting free radicals with nearby atoms. Tissue damage results when the molecular damage is extensive and not sufficiently repaired in a timely manner.

In radiation biology, the term *absorbed dose* is the amount of energy deposited by radiation per unit mass of tissue, expressed in units of gray (Gy) or rad (see Appendix D for a detailed description of principles of ionizing radiation). The term *dose equivalent* refers to the biologically significant dose, which is determined by multiplying the absorbed dose by a quality factor for the type and energy of the radiations involved. Dose equivalent is expressed in units of sievert (Sv) or rem. The quality factor is considered to be unity for the beta and gamma radiation emitted from iodine radionuclides, so for these radionuclides, the absorbed dose (in Gray or rad) is numerically identical to the dose equivalent (in rem or sievert). The absorbed dose from internalized iodine radionuclides is estimated by taking into account the quantity of radionuclides entering the body (via ingestion or inhalation), the biokinetics (retention, distribution, and excretion) of the radionuclides, the rate at which the radionuclides decay to stable forms, the energies and intensities of the beta and gamma radiation emitted, and the characteristics of tissues that result in the energy of the emitted radiation being absorbed by tissues. Each tissue, therefore, can receive a different absorbed dose for a given amount of radioactivity that enters the body. The total absorbed dose to the body will reflect the integration of the absorbed doses for the all tissues. In summaries of the radioiodine toxicology literature provided in this profile, units of activity, absorbed dose, or dose equivalent are cited as reported in the literature and the corresponding conventional or SI units are provided in parentheses.

The EPA has published a set of internal dose conversion factors for standard persons of various ages (newborn; 1, 5, 10, or 15 years of age; and adult) in its Federal Guidance Report No. 13 supplemental CD (EPA 1999). For example, the EPA has estimated that the dose equivalent following ingestion of 1 Bq of ^{131}I is 2.2×10^{-8} Sv (assuming an integration time of 50 years for an adult following the initial exposure). Age-specific dose coefficients for inhalation and ingestion of any of the radioactive isotopes of iodine by the general public can be found in International Commission on Radiological Protection (ICRP) publications 71 (ICRP 1995) and 72 (ICRP 1996), respectively. Dose coefficients for inhalation, ingestion, and submersion in a cloud of iodine radionuclides can be found in U.S. EPA Federal Guidance Report No. 11 (EPA 1988). Dose coefficients for external exposure to radioisotopes of iodine in air, surface water, or soil contaminated to various depths can be found in U.S. EPA Federal Guidance Report No. 12 (EPA 1993).

The ICRP has developed reference values for dose coefficients that relate dose equivalents to a unit of activity to which a person might be exposed. For example, the ICRP (1996, 2001) has estimated that the dose coefficient for an acute exposure of an adult to ^{131}I is $2.2x10^{-8}$ Sv/Bq. Age-specific dose coefficients for inhalation and ingestion of any of the radioactive isotopes of iodine can be found in ICRP publications 71 (ICRP 1995) and 72 (ICRP 1996), respectively.

3.2 DISCUSSION OF HEALTH EFFECTS FOR STABLE IODINE BY ROUTE OF EXPOSURE

Section 3.2 discusses the chemical toxicity of iodine. Radiation toxicity resulting from exposure to radioiodine is discussed in Section 3.3.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of iodine are indicated in Tables 3-1 and 3-2 and Figures 3-1 and 3-2.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for iodine. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Iodine is absorbed in humans when I_2 or methyl iodide vapors are inhaled (Black and Hounam 1968; Morgan and Morgan 1967; Morgan et al. 1967a, 1967b, 1968). Once absorbed, iodide would be expected to exert effects that are similar to that of iodide absorbed after ingestion, including effects on the thyroid gland and thyroid hormone status, sensitivity reactions, and cancer (see Section 3.2.2). Iodine (I_2) is a strong oxidizing agent; therefore, exposure to high air concentrations of I_2 vapor could potentially produce upper respiratory tract irritation and possibly oxidative injury. No studies were located regarding the following health effects in humans or animals after inhalation exposure to stable iodine:

3.2.1.1 Death

3.2.1.2 Systemic Effects

3.2.1.3 Immunological and Lymphoreticular Effects

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

3.2.2 Oral Exposure

The section that follows provides background information relevant to the various study summaries that are presented subsequently. A description of the approaches used to calculate doses of stable iodine is provided. The actual study summaries follow.

A large number of human experimental, clinical, and epidemiological studies on the effects of excess iodine on human health have been reported. The key studies that provide information on exposures associated with effects are summarized in this section of the profile. Oral iodine intakes were not directly assessed in many studies with sufficient accuracy to define dose-response relationships; however, measurements of urinary iodide provide a basis for estimating intakes in some of the studies (Konno et al.

1993b). Rather than describing the basis for estimating intakes from urinary iodine data in each of the study descriptions that follow, the general approach used is described here. If a 24-hour urinary iodide measurement was provided that could be regarded as a steady state value (relatively constant intake for at least 6 months), the intake was assumed to be equivalent to the 24-hour excretion rate. This assumption is consistent with information available on the toxicokinetics of iodide that indicates nearly complete absorption of ingested iodide and that urinary excretion accounts for >97% of the absorbed dose (see Sections 3.5.1.2 and 3.5.4.2). The assumption is also supported by studies in which 24-hour urinary iodide was measured before and after supplementation. For example, 31 patients received oral supplements of 382 µg I/day for 6 months. Prior to the supplementation, the mean 24-hour urinary iodide excretion rate was 36 µg/day (range, 13–69), whereas after 6 months of iodide supplementation, the mean 24-hour urinary iodide excretion rate was 415 µg/day (Kahaly et al. 1998). The difference between these two values, 379 µg/day, is nearly identical to the supplemental dose of 382 µg/day.

If a urine iodide concentration was provided for a morning sample that included overnight bladder urine, the measured concentration was assumed to represent the 24-hour average concentration and iodide intake was calculated as:

$$Intake_I = U_I \cdot 1.4 \qquad \text{Equation (1)}$$

where U_I is the measured urinary iodine concentration and 1.4 is the average volume of urine excreted per day (L/day) for a 70-kg adult (ICRP 1981). Equation 1 is in reasonable agreement with observed relationships between morning bladder urine iodide concentrations and 24-hour iodide excretion rates (Konno et al. 1993b; Nagata et al. 1998). Urine iodide concentration from untimed (spot) samples, other than morning samples that included overnight bladder urine, were considered to be potentially too uncertain to derive intake estimates, unless paired urinary creatinine concentrations or a urinary iodide:creatinine ratio (µg I:g creatinine) was reported. Urinary iodide:creatinine ratios were converted to estimated iodide intake as follows, assuming a constant relationship between urinary creatinine excretion rate and lean body mass. The rate of creatinine excretion (e.g., E_{Cr} , g creatinine/day) was calculated from the relationship between lean body mass (LBM) and E_{Cr}:

$$LBM = 0.0272 \cdot E_{Cr} + 8.58 \qquad \text{Equation (2)}$$

where the constants 0.0272 and 8.58 are the weighted arithmetic mean of estimates of these variables from eight studies reported in Forbes and Bruining (1976). Lean body mass was calculated as follows (ICRP 1981):

$$LBM = BW \cdot 0.88, males \qquad \text{Equation (3)}$$
$$LBM = BW \cdot 0.85, females$$

where BW is the reported or assumed body weight for males (75 kg) and females (65 kg) (EPA 1997f). A mean value of 60 kg (females, 55 kg; males, 65 kg) was assumed for body weights of adult populations of the Asian Pacific countries (e.g., Japan, China, Marshall Islands). Iodide intake was calculated as:

$$Intake_I = U_{I/Cr} \cdot E_{Cr} \qquad \text{Equation (4)}$$

where $U_{I/Cr}$ is the urinary iodide:creatinine ratio (μg I/g creatinine). This approach yields relationships between 24-hour urinary iodide excretion rates and the urinary iodide:creatinine ratios that are in reasonable agreement with observations (Konno et al. 1993b).

3.2.2.1 Death

Two recent reviews of the clinical case literature note that deaths have occurred after ingestion of iodine preparations (FDA 1989b; Pennington 1990b). A review of medical records from the New York City Medical Examiners Office revealed that, in a period of 6 years, there were 18 deaths from attempted suicides in which adults ingested iodine tinctures (Finkelstein and Jacobi 1937). Tinctures of iodine contain a mixture of molecular iodine (I_2) and sodium triiodide (NaI_3) and have iodine concentrations of approximately 40 mg/mL. Doses of iodine from ingestion of the tinctures ranged from 1,200 to 9,500 mg (17–120 mg/kg), and deaths usually occurred within 48 hours of the dose. In one case, an adult male ingested 15 g of iodine as a potassium iodide solution and survived the episode; 18 hours after the dose, his serum iodide concentration was 2.95 mg/mL (Tresch et al. 1974). Symptoms of toxicity that have been observed in lethal or near-lethal poisonings have included abdominal cramps, bloody diarrhea and gastrointestinal ulceration, edema of the face and neck, pneumonitis, hemolytic anemia, metabolic acidosis, fatty degeneration of the liver, and renal failure (Clark 1981; Dyck et al. 1979; Finkelstein and Jacobi 1937; Tresch et al. 1974).

Two cases of infant deaths were reported in which death was from complications related to compression of the trachea by a goiterous thyroid gland; the mothers had ingested potassium iodide during their pregnancies at doses of approximately 850 and 1,180 mg I/day (12 and 17 mg/kg/day) (Galina et al. 1962).

The LOAEL values in humans for exposures by the oral route are presented in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

Systemic effects of oral stable iodine exposure, other than after massive acute iodine overload such as in cases of attempted suicides (see Section 3.2.2.1), are on the thyroid gland and are discussed in the section on Endocrine Effects. As noted in the introduction to this chapter of the profile, adverse effects on a wide variety of other organ systems can result from iodine-induced 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. The reader is referred to authoritative references on these subjects for further information (Braverman and Utiger 2000).

Endocrine Effects. The principal direct effects of excessive stable iodine ingestion on the endocrine system are on the thyroid gland and regulation of thyroid hormone production and secretion. Adverse effects on the pituitary and adrenal glands derive secondarily from disorders of the thyroid gland. Effects on the thyroid gland can be classified into three types: hypothyroidism, hyperthyroidism, and thyroiditis. Hypothyroidism refers to the diminished production of thyroid hormone leading to clinical manifestations of thyroid insufficiency and can occur with or without goiter, a functional hypertrophy of the gland in response to suppressed hormone production and elevated serum thyroid stimulating hormone (TSH, also known as thyrotropin) concentrations. Typical biomarkers of hypothyroidism are a depression in the circulating levels of thyroxine (T_4) and/or triiodothyronine (T_3) below their normal ranges. This is always accompanied by an elevation of the pituitary hormone, TSH, above the normal range. 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 effects can occur in children and adults, in fetuses exposed *in utero*, or in infants during lactation.

Table 3-1 Levels of Significant Exposure to Iodine - Chemical Toxicity - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Human	1 d				17 (death)	Finkelstein and Jacobi 1937 I2, NaI3
	Systemic						
2	Human	14 d (C)	Endocr	0.0086			Chow et al. 1991 KI
3	Human	1 d (C)	Endocr	3.4			Delange 1996 Iodized oil
4	Human	14 d (C)	Endocr	0.069			Gardner et al. 1988 NaI
5	Human	7 d (W)	Endocr	0.46			Georgitis et al. 1993 I2, I-
6	Human	14 d (C)	Endocr	0.024[b]			Paul et al. 1988 NaI

Table 3-1 Levels of Significant Exposure to Iodine - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
7	Human	14 d (C)	Endocr	1				Robison et al. 1998 NaI
8	Human	14 d (C)	Endocr	1				Robison et al. 1998 I2
	Immuno/ Lymphoret							
9	Human	8 d (C)				20	(fever)	Horn and Kabins 1972 KI
10	Human	5 d (C)				4.3	(ioderma)	Soria et al. 1990 KI
	INTERMEDIATE EXPOSURE							
	Death							
11	Human	9 mo (C)				12	(death from tracheal compression by goiter)	Galina et al. 1962 KI
12	Human	9 mo (C)				17	(death from tracheal compression by goiter)	Galina et al. 1962 KI

Table 3-1 Levels of Significant Exposure to Iodine - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
	Systemic								
13	Human	4 mo (C)	Endocr				23	(clinical hyperthyroidism with thyrotoxicosis)	Ahmed et al. 1974 KI
14	Human	2 mo (C)	Endocr				7.3	(goiter in neonate)	Coakley et al. 1989 KI
15	Human	9 mo (C)	Endocr				6.4	(goiter and hypothyroidism in neonate)	Hassan et al. 1968 KI
16	Human	11 wk (W)	Endocr	15					Jubiz et al. 1977 KI
17	Human	90 d (C)	Endocr	0.0039	0.46	(subclinical hypothyroidism with gland enlargement)			LeMar et al. 1995 I2 ,I-
18	Human	9 mo (C)	Endocr	0.0047					Liesenkotter et al. 1996 KI

Table 3-1 Levels of Significant Exposure to Iodine - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
19	Human	9 mo (C)	Endocr				13	(goiter, hypothyroidism in neonate)	Martin and Rento 1992 KI
20	Human	28 d (C)	Endocr		0.39	(subclinical hypothyroidism with gland enlargement)			Namba et al. 1993 I-
21	Human	3 mo (C)	Endocr				5.4	(goiter in neonate)	Penfold et al. 1978 KI
22	Human	4 mo (C)	Endocr				6.6	(goiter in neonate)	Penfold et al. 1978 KI
23	Human	6 mo (C)	Endocr				0.05	(clinical hypothyroidism)	Shilo and Hirsch 1986 sea-kelp
24	Human	7 wk (C)	Endocr				2.6	(clinical hyperthyroidism with thyrotoxicosis)	Vagenakis et al. 1972 KI
25	Human	9 mo (C)	Endocr				4.6	(goiter in fetus)	Vicens-Colvet et al. 1998 ND

Table 3-1 Levels of Significant Exposure to Iodine - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
	Immuno/ Lymphoret								
26	Human	NS (C)					23	(fever)	Horn and Kabins 1972 KI
27	Human	6 mo (C)					11	(ioderma)	Kincaid et al. 1981 KI
28	Human	8 mo (C)					8.6	(ioderma)	Soria et al. 1990 KI
	CHRONIC EXPOSURE								
	Systemic								
29	Human	11 yr (W)	Endocr	0.01[c]	0.029	(subclinical hypothyroidism with gland enlargement)			Boyages et al. 1989 I-
30	Human	2 yr (C)	Endocr				2.9	(clinical hypothyroidism with goiter in neonate)	Iancu et al. 1974 NaI
31	Human	NS (W)	Endocr				1	(goiter with elevated serum TSH)	Khan et al. 1998 ND

Table 3-1 Levels of Significant Exposure to Iodine - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
32	Human	46 yr (F)	Endocr			0.22	(clinical hypothyroidism without autoimmunity)	Konno et al. 1994 I-
33	Human	68 yr (F, W)	Endocr	0.0046				Laurberg et al. 1998 I-
34	Human	16 mo (C)	Endocr	0.0039				Pedersen et al. 1993 KI
35	Human	81 yr (F, W)	Endocr	0.0023		0.012	(clinical hypothyroidism without autoimmunity; elderly adults)	Szablocs et al. 1997 I-
	Immuno/ Lymphoret							
36	Human	15 yr (C)				15	(fever)	Kurtz and Aber 1982 KI
37	Human	1 yr (C)				14	(ioderma)	Rosenberg et al. 1972 KI
	Cancer							
38	Human	NS (F)				0.0035	(thyroid cancer; in endemic goiter area)	Bacher-Stier et al. 1997 I-

Table 3-1 Levels of Significant Exposure to Iodine - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
39	Human	NS (F)				0.0035	(thyroid cancer; in endemic goiter area)	Harach and Williams 1995 I-

a The number corresponds to entries in Figure 3-1.

b Used to derive an acute oral MRL based on a no-observed-effect-level (NOEL) of 0.01mg/kg/day in healthy adult humans, for changes in serum thyroid hormone levels. The no-observed-adverse-effect-level (NOAEL) is 0.024 mg/kg/day.

c Used to derive a chronic oral MRL of 0.005 mg/kg/day; dose divided by an uncertainty factor of 2 for human variability.

(C) = capsule; d = day(s); Endocr = endocrine; (F) = feed; kg = kilogram(s); LOAEL = lowest-observed-adverse-effect level; mg = milligram(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NA = not specified; TSH = thyroid-stimulating hormone; (W) = drinking water; wk = week(s); yr = year(s)

Figure 3-1. Levels of Significant Exposure to Iodine - Chemical Toxicity - Oral

Acute (≤14 days)

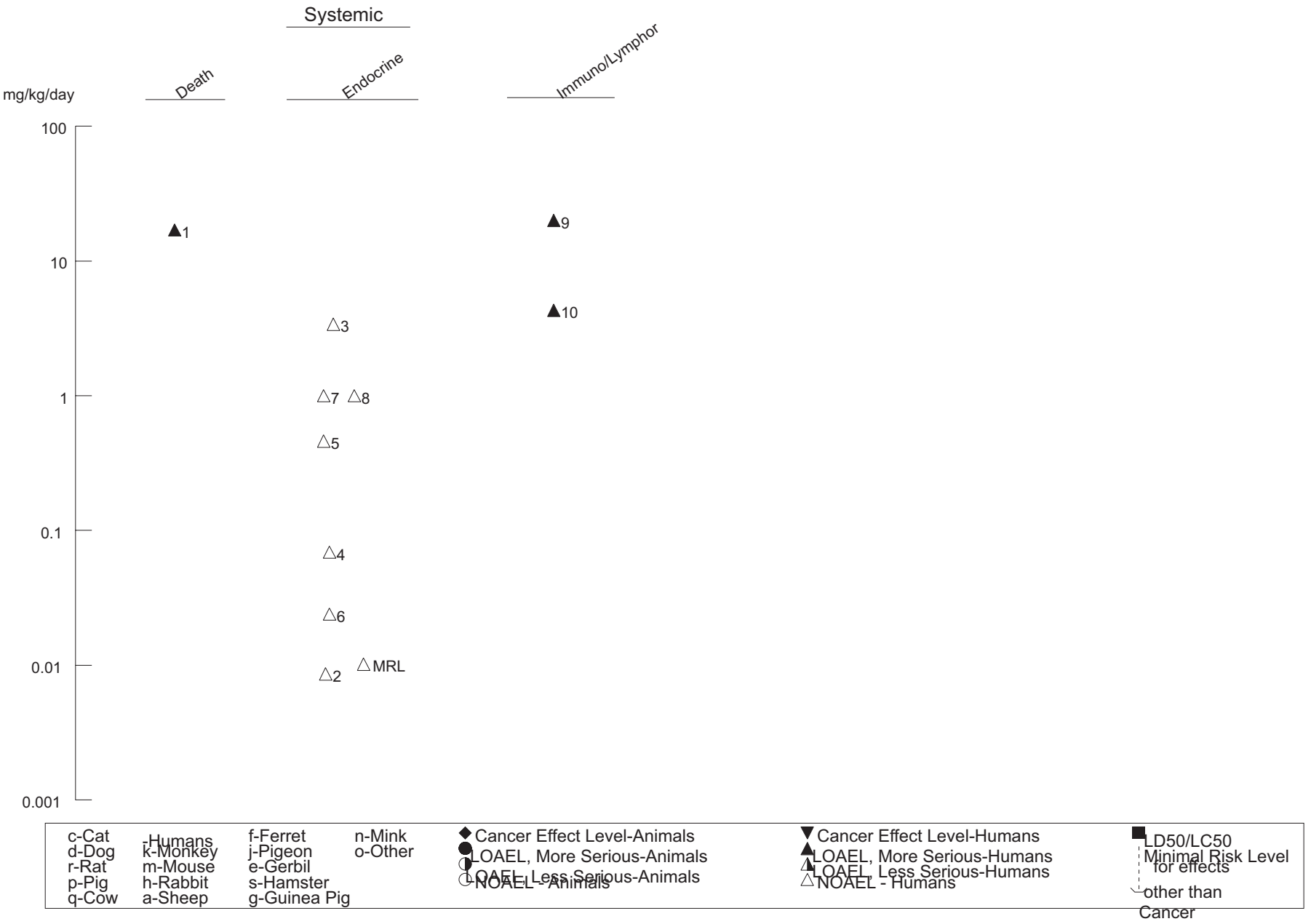


Figure 3-1. Levels of Significant Exposure to Iodine - Chemical Toxicity - Oral (*Continued*)

Intermediate (15-364 days)

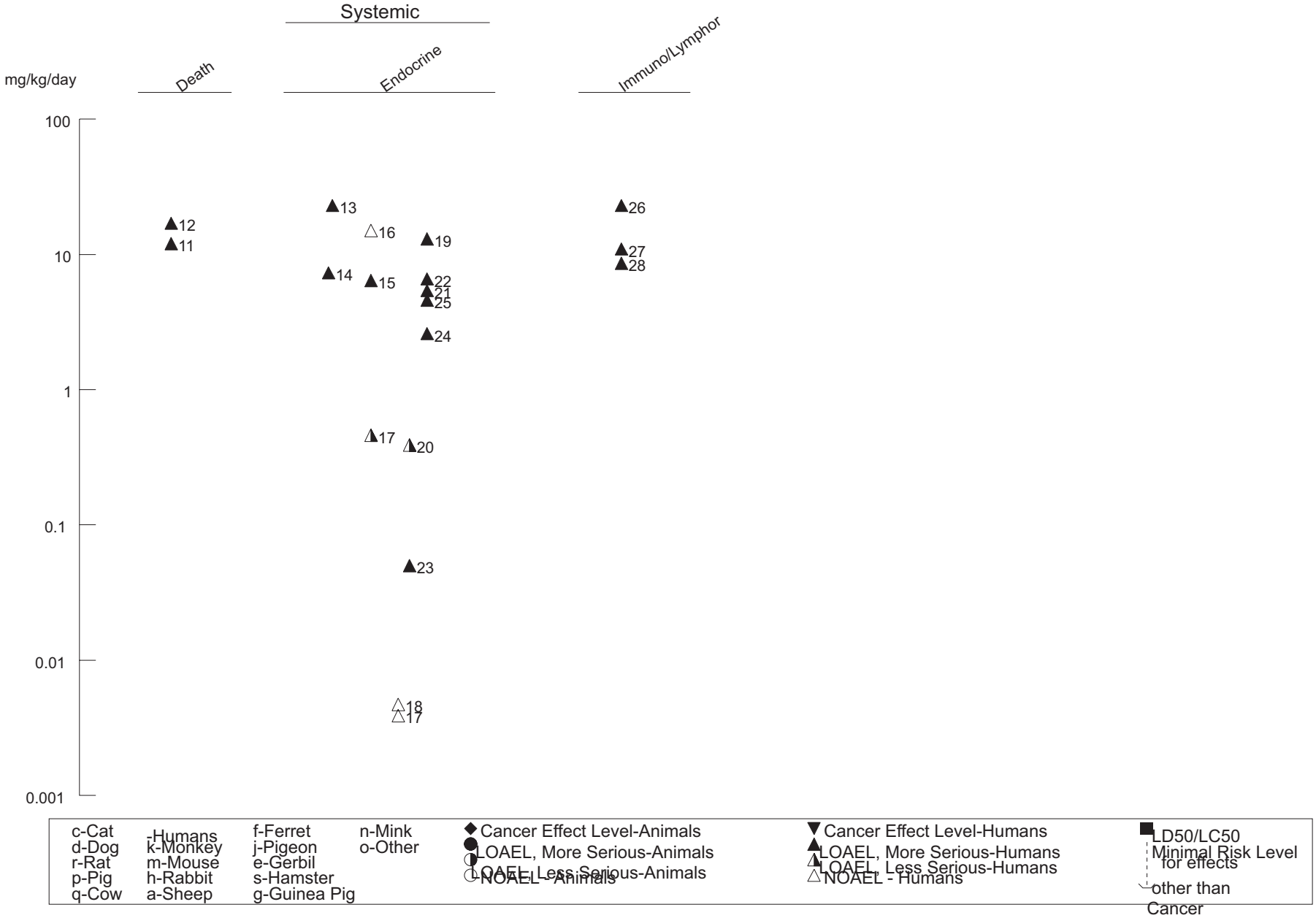
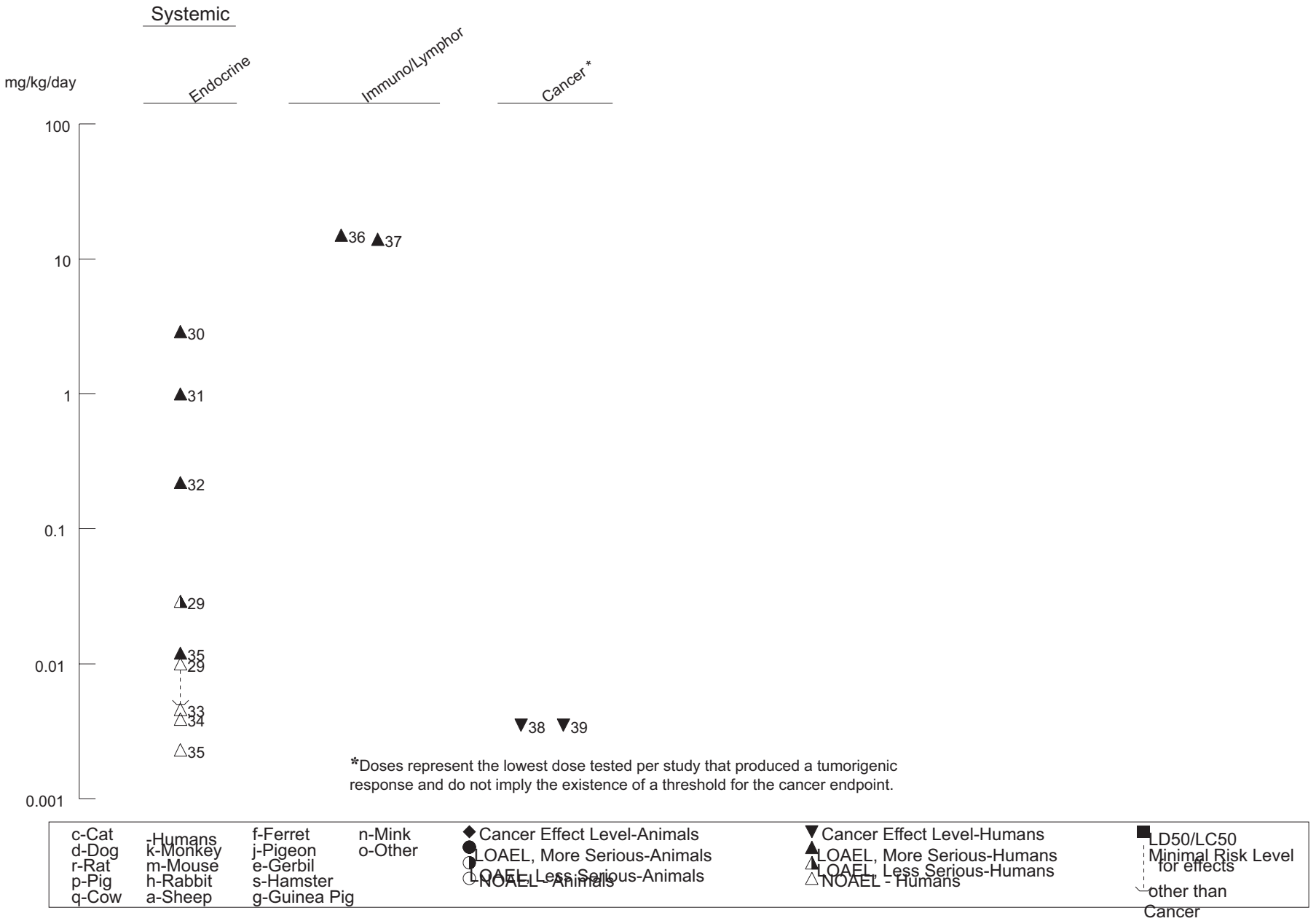


Figure 3-1. Levels of Significant Exposure to Iodine - Chemical Toxicity - Oral (*Continued*)

Chronic (≥365 days)



Measurements of serum levels of thyroid hormones and TSH are often used as biomarkers of hypothyroidism and thyrotoxicosis 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 are not clinically significant. In this profile, an observed increase in serum TSH level and normal T_4 and T_3 levels 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 normal and the serum TSH concentration is suppressed. Typical normal ranges for these hormone levels are discussed in Section 3.9.2

Hypothyroidism

An acute iodide excess (above the preexisting dietary intake) transiently decreases the production of thyroid hormones in the thyroid gland; this is referred to as the acute *Wolff-Chaikoff effect* (Wolff et al. 1949). In normal people, this is followed by a return to normal levels of hormone synthesis, referred to as *escape* from the acute Wolff-Chaikoff effect, without a significant change in circulating hormone levels. Escape is thought to be the result of down regulation of the sodium-iodide symport (NIS), the iodide transporter in the thyroid gland, resulting in a decrease in the intrathyroidal iodine and the resumption of normoral hormone synthesis (see Section 3.5.3.2 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 some people who have underlying thyroid disorders. These effects are the result of a failure to escape from the acute Wolff-Chaikoff effect. Most people who experience iodine-induced hypothyroidism recover when the excess iodine intake is discontinued. Susceptible individuals include fetuses and newborn infants, elderly, patients who have underlying thyroid disease, and patients who have received treatment with antithyroid medications. A complete list of susceptible groups is presented in Table 2-2, recovery occurs when the excess iodine is discontinued.

Several studies have examined the acute effects of increased intake of iodine on thyroid hormone status in adults (Chow et al. 1991; Gardner et al. 1988; Georgitis et al. 1993; Namba et al. 1993; Paul et al. 1988; Robison et al. 1998). These effects, in subjects who have no underlying thyroid disease, result from a small iodine-induced decrease in thyroid hormone release, which is accompanied by a rise in serum TSH concentration, to maintain normal thyroid function. The studies included relatively small numbers of subjects (<30) and, therefore, had low statistical power; this complicates the generalization of findings to large populations (in particular, findings of no significant effect). However, an important attribute of these studies is that iodine intakes were controlled and quantified with high certainty. The results of these studies suggest that acute (14 days) increases in iodine intake of 1,500 µg/day (21 µg/kg/day) above the

preexisting dietary intake can be tolerated without producing a clinically adverse change in thyroid hormone levels, although such doses may produce a small reversible depression in serum T_4 concentrations and a small rise in serum TSH concentrations, both within the normal range of values for healthy individuals. Changes in thyroid hormone levels within normal ranges are not considered to be clinically adverse; however, they are indicative of a subtle suppression of thyroid hormone release. The above conclusions apply to healthy adults who have no prior history of thyroid disease, no detectable antithyroid antibodies, and no prior history of chronic deficiency or excessive iodine intakes (Gardner et al. 1988; Paul et al. 1988). One study found that subclinical hypothyroidism was induced by an acute increase of 500 µg/day (7 µg/kg/day) in elderly adults (Chow et al. 1991), suggesting the possibility that elderly adults may be less tolerant of an iodide excess than younger adults. Based on estimates of the background dietary intakes of the subjects in these studies, in most cases estimated from measurements of urinary iodide excretion, the total iodide intakes (including background dietary intake) that could produce subclinical hypothyroidism were approximately 1,700 µg/day or approximately 24 µg/kg/day (Gardner et al. 1988; Paul et al. 1988). Acute intakes of approximately 700 µg/day or approximately 10 µg/kg/day had no detectable effect on thyroid status in healthy individuals (Gardner et al. 1988; Paul et al. 1988). One study found no evidence for disturbances in thyroid hormone status in healthy adults who received doses of 300 µg/kg/day (approximately 20 mg/day) for 14 days (Robison et al. 1998). This suggests that, at least under certain conditions, exposure levels >10–24 µg/kg/day may be tolerated in some people. Brief summaries of the relevant studies that provide information on oral exposures to iodine that suppress the thyroid gland are provided below.

Healthy euthyroid adults (nine males, nine females) who had no history of thyroid disease or detectable antithyroid antibodies received daily oral doses of 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 1,700 µg I/day (approximately 24 µg/kg/day, assuming a 70-kg body weight). Serum concentrations of TT_4, FT_4, and TT_3 were significantly depressed (5–10%) compared to pretreatment levels and serum TSH concentrations were significantly elevated (47%) compared to pretreatment values. Hormone levels were within the normal range during treatment and, therefore, the subjects were not hypothyroid. In this same study, nine females received daily doses of 250 or 500 µg I/day for 14 days and there were no significant changes in serum hormone concentrations. Total intake was approximately 450 or 700 µg/day (6 or 10 µg/kg/day). Some of these women participated in the higher dose study 1 year earlier.

In a similar type of study, healthy, euthyroid, adult males (n=10) received daily oral doses of 500 μg I/day (as sodium iodide) for 14 days; there were no effects on serum thyroid hormone or TSH concentrations; however, dosages of 1,500 or 4,500 μg I/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 (Gardner et al. 1988). Urinary iodide excretion prior to the dose ranged from 250 to 320 μg/day, suggesting that the background dietary intake was approximately in this same range (see Sections 3.5.1.2 and 3.5.4.2). The magnitude of the changes at the higher iodide dosages yielded hormone concentrations that were within the normal range and, thus, would not represent a significant thyroid suppression. This suggests that an acute oral intake of 500 μg/day above a preexisting dietary intake, or approximately 800 μg I/day total (11 μg/kg/day), is tolerated without thyroid gland suppression in healthy adult males, and intakes as high as 4,800 μg I/day (69 μg/kg/day) may be tolerated in some people without clinically adverse effects.

Another similar experimental study has been reported in which 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 (Chow et al. 1991). Serum concentrations of FT_4 were significantly decreased (change from pretreatment level, approximately -1 pmol/L) and serum TSH concentrations were significantly increased (change from pretreatment level approximately +0.6 mU/L) in the women who received the iodide supplements, relative to a placebo control group. On average, the magnitude of the changes did not produce depression in thyroid hormone levels below the normal range; however, five subjects had serum TSH concentrations that exceeded 5 mU/L, considered mildly elevated. 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 (9 μg/kg/day).

Higher acute iodine exposures have been shown to produce reversible thyroid gland hypertrophy, in addition to hormone suppression. The effects of tetraglycine hydroperiodide, an iodine compound used to purify drinking water, were examined in an acute experimental study (Georgitis et al. 1993). When dissolved in water, tetraglycine hydroperiodide releases I_2 and iodide (as a reduction product). Seven healthy adults, who had no history of thyroid disease, ingested 227 mL (8 ounces) of a flavored drink into which tetraglycine hydroperiodide had been dissolved; the dosage was 32 mg/day of iodine for 7 consecutive days (460 μg/kg/day). Seven age-, weight-, and height-matched controls received water without added iodine. A statistically significant decrease in serum concentration of T_4 and T_3 (14–15%) and a significant increase in TSH concentration (50%) occurred in the treatment group during the

treatment, relative to their pretreatment values, whereas no change occurred in the control subjects. Two subjects in the treatment group had T_4 concentrations below approximately 60 nmol/L, which is slightly below normal, and two subjects had TSH concentrations that were between 4.5 and 6 mU/L, which were slightly elevated and suggestive of mild thyroid impairment (it is not clear from the report if these were the same two subjects). In a more extensive study of similar design, eight healthy euthyroid adults (seven males, one female), who were negative for thyroid antimicrosomal antibody, ingested approximately 32 mg iodine/day (460 µg/kg/day) as tetraglycine hydroperoxide dissolved in juice or water, for 90 days (LeMar et al. 1995). The mean pretreatment 24-hour urinary iodide excretion rate was 276 µg/day. Thyroid gland volumes, as determined from ultrasound measurements, increased significantly during the treatment, with a peak volume 37% above the pretreatment volume and reverted to pretreatment volumes 7 months after the iodine dosing was discontinued. Serum TSH concentrations increased significantly during treatment, with only one subject having a 3-fold increase to a value above normal, 6.1 mU/L; this subject also had the highest thyroid volume during the treatment period. None of the subjects developed clinical hypothyroidism.

Daily doses of 27 mg I/day (390 µg/kg/day), as licorice lecithin-bound iodide, given for 28 days to 10 healthy, euthyroid adult males who were TPA negative resulted in a statistically significant, 15% increase in thyroid gland volume, as determined from ultrasound measurements, compared to pretreatment values (Namba et al. 1993). Serum concentrations of FT_4 and T_3 were decreased, and serum TSH and thyroglobulin (T_g) concentrations were significantly elevated, although the values were all within the normal ranges. All values, including thyroid gland volume returned to normal within 28 days after the last iodide supplement. In a clinical study of 22 hypothyroid adults from Japan who consumed an estimated 1–43 mg I/day (17–720 µg/kg/day, from consumption of seaweed), 12 patients reverted to a euthyroid state after 3 weeks of voluntary dietary iodine restriction (Tajiri et al. 1986). When seven of these patients who converted to a euthyroid state after dietary restriction received supplements of 25 mg I/day (420 µg/kg/day) as Lugol's solution (a mixture of 50 mg/mL I_2 and 100 mg/mL potassium iodide KI) for 2–4 weeks, all reverted to a hypothyroid state (serum TSH concentrations >5 mU/L). In this same study, 11 healthy euthyroid adults (8 females, 3 males) received 25 mg I/day for 14 days (420 µg/kg/day). The mean serum TSH concentrations significantly increased (40%) during the treatment compared to their pretreatment values; however, their TSH concentrations during treatment (3.9 mU/L) did not exceed the normal range (<5 mM/L).

In contrast to the results of the above studies, no clinical abnormalities in thyroid hormone status occurred when healthy, euthyroid, adult males (n=6 or 7), who had no history of thyroid-related illness, ingested

daily oral doses of 300 or 1,000 µg I/kg/day as either I_2 or sodium iodide for 14 days (Robison et al. 1998). Based on measurements of urinary iodide excretion rates, the pretreatment iodide intakes were approximately 100 µg/day. The high dosage (1,000 µg I/kg/day) produced a small but statistically significant increase in serum TSH concentrations compared to a sodium chloride control group; the TSH concentrations in the control group did not exceed the normal range (<5 mU/L) and reverted to control levels within 10 days after the iodine supplementation was ended. Serum TT_4 and TT_3 were not significantly different in the treatment groups, compared to the control group. As noted previously, studies of this size have low statistical power, which complicates the interpretation of findings of no significant effect.

In a more remarkable, intermediate-duration experimental study, four healthy adults (three males, one female) received a daily oral dose of approximately 1,000 mg I/day as a saturated solution of potassium iodide (30 drops/day, approximately 36 mg I/drop, 15 mg I/kg/day) for 11 weeks (Jubiz et al. 1977). A small, statistically significant decrease in the mean serum concentration of T_4 occurred (pretreatment, 8.8 µg/dL; treatment minimum 7.6 g/dL) and an increase in TSH concentration (pretreatment, 7.3 mU/L; treatment maximum, 13.5 mU/L). The above changes were no longer evident within 1 week after the treatment was discontinued. In a similar study, eight euthyroid adults (seven male, one female), who were hepatitis patients, received daily oral doses of approximately 360 mg I/day (5 mg/kg/day) as a saturated solution of potassium iodide (10 drops/day, approximately 36 mg I/drop) for 60 days (Minelli et al. 1999). A small statistically significant decrease in the mean serum concentration of T_4 (pretreatment, 13.8 pmol/L; treatment minimum 13.2 pmol/L) and an increase in TSH concentration (pretreatment, 0.6 mU/L; treatment maximum, 1.7 mU/L) occurred. Two patients were reported to have developed transient elevated serum TSH concentrations during the iodide treatment, with normal concentrations of FT_4 and FT_3. There were no incidences of clinical hypothyroidism or hyperthyroidism. A nearly identical result was reported for eight euthyroid hepatitis patients who had previously received recombinant interferon-alpha therapy (but who did not develop thyroid dysfunction during therapy) and who subsequently received daily doses of approximately 360 mg I/day (5 mg/kg/day) as a saturated solution of potassium iodide for 60 days (Minelli et al. 1997). As part of the study reported by Jubiz et al. (1977), 13 patients with obstructive pulmonary disease who were receiving 1,000–2,000 mg I/day (14–28 mg/kg/day) as a saturated potassium iodide solution for periods of 1 month to 8 years exhibited unambiguous symptoms of hypothyroidism, including thyroid gland enlargement, depressed serum concentrations of T_4 (mean 2–2.7 µg/dL), and elevated serum TSH concentrations (20–35 mU/L). Serum T_4 and TSH levels returned to normal in all but one of the patients within 1 month after the iodide dosage

was discontinued. However, in the Jubiz et al. (1977) study, the presence of chronic thyroiditis was not determined.

The results of several epidemiological studies suggest that chronic exposure to excess iodine can result in or contribute to hypothyroidism. Thyroid status was compared in groups of children, ages 7–15 years, who resided in two areas of China where drinking water iodide concentrations were either 462 µg/L (n=120) or 54 µg/L (n=51) (Boyages et al. 1989; Li et al. 1987). Although the subjects were all euthyroid with normal values for serum thyroid hormones and TSH concentrations, TSH concentrations were significantly higher in the high iodine group. The prevalence and severity of goiter in the population were evaluated, the latter based on a goiter severity classification scale (Grade 0, no visible goiter; Grade 1, palpable goiter that is not visible when the neck is not extended; Grade 2, palpable and visible goiter when the neck is not extended). The high iodide group had a 65% prevalence of goiter compared to 15% in the low iodine group. The prevalence of more severe, Grade 2 goiter, was also higher in the high iodide group (15%) compared to the low iodide group (0%). 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 µg/day (29 µg/kg/day) and 400 µg/day (10 µg/kg/day) in the high and low iodide groups, respectively.

Zhao et al. (2000) compared the prevalence of thyroid enlargement among children 5–15 years of age to drinking water and urinary iodine levels in residents of 65 townships in Jiangsu Province, China. This area had a high prevalence of childhood goiter, although urinary iodide measurements suggested dietary iodine sufficiency. Urinary iodine measurements were obtained for adults who resided in the same townships as the children. The prevalences of goiter and abnormal thyroid volume (not defined in the report) increased with increasing urine iodine concentration. The prevalences of goiter increased from 15% (802 µg I/L urine) to 38% (1,961 µg I/L urine). The prevalences of abnormal thyroid volume increased from 5 to 17% over this same range of urinary iodine concentrations. Assuming an adult urine volume of 1.4 L/day and an adult body weight of 60 kg, the observed range of urinary iodide concentrations in adults (520–1,961 µg I/L) corresponded to approximate intakes of 730–2,750 µg/day (12–46 µg/kg/day).

A survey of a group of Peace Corps volunteers revealed a high prevalence of goiter among volunteers who drank water from iodine filters (Khan et al. 1998). Of 96 volunteers surveyed, 44 (46%) had enlarged thyroid glands, 33 (34%) had elevated serum TSH concentrations ($4.2 mU/L), and 4 (4%) had

depressed serum TSH concentrations (#0.4 mU/L). The mean iodide concentration in filtered drinking water was 10 mg I/L, which corresponded to a daily intake of iodide from drinking water of 50–90 mg I/day (0.7–1.3 mg/kg/day, based on a reported daily water consumption of 5–9 L/day). This estimate was consistent with measured mean urinary iodide concentration of 11 mg/L, which corresponds to approximately 55–99 mg I/day excreted or ingested, assuming daily urine volumes similar to water consumption. When the excess iodine was removed from the drinking water, all measures of thyroid function returned to normal (Pearce et al. 2002).

In a study of elderly adults, thyroid status was compared in 423 residents (ages 66–70 years) of Jutland, Denmark who had iodine intakes of 40–60 µg/day (0.7 µg/kg/day) and 100 residents of Iceland who had intakes of 300–350 µg/day (5 µg/kg/day) (Laurberg et al. 1998). Subjects from the high iodine intake region had a significantly higher prevalence (18%) of serum TSH levels above the high end of the normal range (>4 mU/L) compared to subjects from the low iodine region (3.8%). The prevalence of serum TSH concentrations above 10 mU/L was 4.0% in the high iodine region and 0.9% in the low iodine region. Females in both regions had a significantly higher prevalence of elevated TSH concentrations than males. Serum concentrations of T_4 were not depressed, even in subjects with TSH concentrations that exceeded 10 mU/L. Thus, although the subjects appeared to be euthyroid, the higher iodine intakes were associated with a subclinical suppression of the thyroid gland as indicated by a high prevalence of elevated serum TSH concentrations. A study of elderly nursing home residents in the Carpathian Basin also revealed a prevalence of hypothyroidism that increased with increasing iodine intake (Szabolcs et al. 1997). 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 (1.7, 2.3, or 12 µg/kg/day for low, n=119; moderate, n=135; or high intake, n=92, respectively). The prevalence of serum TSH concentrations above the normal range was 4.2, 10.4, and 23.9% in the low, moderate, and high iodine groups, 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.

Several studies have found increased prevalence of hypothyroidism in residents of areas of Japan where dietary iodine intake is high as a result of consumption of seaweeds containing a high iodine concentration. In one study, urinary iodide and serum TSH concentrations were measured in a group of 1,061 adult residents of five coastal areas of Japan and in 4,100 residents of two inland areas (Konno et al. 1993a, 1994). The subjects were classified as having high or normal iodine intakes based on whether their urinary iodide concentrations were less than or greater than the high end of the *normal range*,

75 µmol/L (9,500 µg/L). The urine samples were not timed and urinary creatinine concentrations were not reported; therefore, only rough estimates of the rate of urinary excretion of iodide (µg/day) and iodide intake can be made. The report indicates that the urine samples were collected in the morning and included night urine (i.e., urine voided on awakening). If it is assumed that the concentrations of iodide in the morning urine samples reflect the concentration for a 24-hour sample and that the 24-hour urine volume is approximately 1.4 L (ICRP 1981), then the 24-hour excretion and intake rates in the high iodine group may have been approximately 13.3 mg/day (0.22 mg/kg/day, assuming a body weight of 60 kg). Even if the morning urine samples were relatively concentrated compared to the 24-hour average, the above urine iodide concentrations suggest an iodide intake of several mg/day. This is consistent with other reported estimates that range from 1 to 5 mg/day in Japan among consumers of seaweed (Pennington 1990b). Examples of much higher intakes (25–40 mg/day, 0.4–0.7 mg/kg/day) have been reported in hypothyroid patients who consume seaweed (Tajiri et al. 1986). The prevalences of elevated serum TSH concentrations (>5 mU/L) and urine iodide concentrations (>9,500 µg/L) were both significantly higher in the costal regions compared to the inland regions (Konno et al. 1994). Serum TSH concentrations were positively correlated with the urine iodide concentrations, and the prevalence of elevated serum TSH concentrations in the seven areas correlated positively with the prevalence of high urinary iodide concentrations. There were no significant correlations or associations with urine iodide and suppressed concentrations of serum TSH (<0.15 mU/L) or with the presence of thyroid antibodies.

A study of iodine supplementation for treatment of endemic goiter related to iodine deficiency provides additional evidence that increases in iodine intake can induce thyroid dysfunction, including thyroid autoimmunity. Otherwise healthy adults who had goiter but no evidence of clinical hypothyroidism or hyperthyroidism or antithyroid antibodies received either a placebo (16 females, 15 males) or 200 µg I/day (3 µg/kg/day total intake) (16 females, 15 males) as potassium iodide for 12 months (Kahaly et al. 1997). A significant decrease in thyroid volume occurred in the treated group relative to the control group. Three subjects in the treatment group (9.7%, two females and one male) developed elevated levels of thyroglobulin and thyroid microsomal antibodies compared to none in the control group. Two of these subjects developed hypothyroidism and one subject developed hyperthyroidism; all three subjects reverted to normal thyroid hormone status when the iodide supplementation was discontinued. In a similar study, 31 adult euthyroid patients from an endemic goiter region who had goiter received 500 µg/day potassium iodide (382 µg I/day, 5 mg I/kg/ day based on reported median body weight of 75 kg) for 6 months, and 31 patients received 0.125 µg T_4/day (Kahaly et al. 1998). Based on reported measurements of 24-hour urine iodide excretion, the preexisting iodide intake was approximately 40 µg/day (range, 13–77, 0.6 µg/kg/day); thus, the total intake during treatment was approximately

420 µg I/day (6 µg/kg/day). After 6 months of iodide supplementation, the mean 24-hour urinary iodide excretion rate was 415 µg/day, which is consistent with the estimate of a total iodide intake of approximately 420 µg/day. Six of the patients who received iodide (19%) developed high titres of thyroglobulin and thyroid microsomal antibodies, compared to none in the T_4 group. Four of the high antibody patients became hypothyroid and two patients became hyperthyroid. The thyroid hormone status reverted to normal and antibody titres decreased during a 6-month period following the treatment in which the patients received a placebo.

People who have autoimmune thyroid disease may be at increased risk of developing thyroid dysfunction when exposed to excess iodide. Euthyroid patients (37 females, 3 males) from an iodine-deficient region, who were diagnosed with Hashimoto's thyroiditis and who were positive for antithyroid (thyroid peroxidase) antibodies, received an oral dose of 250 µg potassium iodide (190 µg I/day) for 4 months; a similar group of thyroiditis patients (41 females, 2 males) served as controls (Reinhardt et al. 1998). Based on urinary iodide measurements of 72 µg I/g creatinine before the iodide supplementation, the preexisting iodide intake was approximately 125 µg/day, for a total iodide dosage of 375 µg/day (5.8. µg/kg/day) in the treatment group. Seven patients in the treatment group developed elevated serum TSH concentrations (>4 mU/L) and one patient developed overt clinical hypothyroidism with a TSH concentration of 43.3 mU/L and a serum FT_4 concentration of 7 pmol/L. One patient in the treatment group became clinically hyperthyroid with a serum FT_4 concentration of 30 pmol/L and TSH concentration of <1 mU/L. One patient in the control group developed mild subclinical hypothyroidism. After the iodine supplementation was discontinued, three of the seven hypothyroid patients in the treatment group reverted to normal thyroid. An additional patient in the treatment group became hypothyroid, requiring T_4 supplements. The patient who became hyperthyroid while in the treatment group reverted to normal thyroid status after the iodide supplements were discontinued. In a smaller clinical study of patients from an iodine-deficient region, four of seven euthyroid patients with Hashimoto's thyroiditis who received 180 mg I/day (2.6 mg/kg/day) as a saturated potassium iodide solution for 6 weeks developed hypothyroidism, which reverted to normal after the iodide supplementation was discontinued (Braverman et al. 1971a). In addition to autoimmune diseases, other thyroid disorders predispose people to iodine-induced hypothyroidism (Table 2-2).

Maternal exposures to excess iodine during pregnancy have been shown to produce goiter and hypothyroidism in neonates. In general, clinical cases have involved maternal exposures to several hundred mg I/day during pregnancy. For example, in one clinical case, hypothyroidism and life-threatening goiter occurred in an infant born to a woman who consumed approximately 200 mg I/day

(2.9 mg/kg/day), as sodium iodide, for 2 years, including during pregnancy (Iancu et al. 1974). The infant was treated with levothyroxine and reverted to a normal gland and hormone status within 3 weeks after birth, without further hormone therapy. In another case, a woman ingested approximately 260–390 mg I/day (4.6 mg/kg/day) during pregnancy and her infant developed goiter *in utero*, which was successfully treated *in utero* with levothyroxine; the thyroid gland and hormone status of the infant was normal at birth (Vicens-Colvet et al. 1998). Coakley et al. (1989) reported, as part of the results of a screening program for congenital hypothyroidism, two cases in which women ingested iodide during pregnancy and gave birth to infants who had a transient goiter. In one case, the estimated total dose iodide dose was approximately 38.3 g I, of which approximately 15.3 g was ingested during the last month of pregnancy. These doses are equivalent to an average daily total dose of approximately 96 mg I/day during the first 8 months and 510 mg I/day (7.3 mg/kg/day) during the last month of pregnancy. Penfold et al. (1978) reported two cases, one of goiter without hypothyroidism in an infant born to a mother who ingested approximately 380 mg I/day (5.4 mg/kg/day) as potassium iodide during the last trimester of pregnancy, and the other case of goiter with hypothyroidism in an infant born to a mother who had ingested approximately 460 mg I/day (6.6 mg/kg/day) as potassium iodide during the last 4 months of pregnancy. In both cases, hypothyroidism and/or goiter were temporary and did not require thyroid hormone therapy. Hassan et al. (1968) reported three cases of neonatal goiter and hypothyroidism. In each case, the mother had ingested daily doses of potassium iodide during pregnancy; approximate doses were 450, 688, and 765 mg I/day (6–11 mg/kg/day). The goiter and hypothyroidism reversed with temporary thyroid hormone therapy. Bostanci et al. (2001) reported a similar outcome in an infant of a mother who ingested 130 mg I/day as potassium iodide during the last 4 months of pregnancy. Martin and Rento (1962) reported two cases of goiter and severe but reversible hypothyroidism in infants born to mothers who ingested potassium iodide during pregnancy; the approximate dosages were 920 and 1,530 mg I/day (13 and 22 mg/kg/day). In two cases, infants died with complications related to a goiterous thyroid gland compression of the trachea; the mothers had ingested potassium iodide during their pregnancies at doses of approximately 850 and 1,180 mg I/day (12 and 17 mg/kg/day) (Galina et al. 1962).

The above clinical cases demonstrate that doses of iodide exceeding 200 mg/day (2.8 mg/kg/day) during pregnancy can result in congenital goiter and hypothyroidism. There is also a large clinical experience with the lower doses of iodide supplementation given during pregnancy for the purpose of correcting or preventing potential iodine deficiency and for the management of Graves' disease during pregnancy. In a study of 35 women with Graves' disease who received 6–40 mg iodide (0.1–0.7 mg/kg/day, assuming a 60-kg body weight) as potassium iodide during pregnancy, 2 of 35 infants had serum TSH concentrations above normal at birth (>20 mU/L) and none had FT_4 concentrations below normal at birth (<10 pmol/L;

7 ng/L), suggesting that this level of iodide supplementation did not induce a hypothyroid state in the newborn, but did produce a subclinical elevation in TSH levels in some infants (Momotani et al. 1992). In a study of iodide supplementation during pregnancy in an iodide-deficient area of Denmark, 28 women received daily doses of 200 µg I/day from the 17th–18th week of pregnancy through the first 12 months after delivery and 26 women received no supplementation (Pedersen et al. 1993). Pretreatment urinary iodide levels were 51 and 55 µg/L, respectively, in the two groups, suggesting a preexisting dietary iodine intake of approximately 75 µg/day (assuming that the urine iodide concentration reflected the 24-hour average and that urine volume was approximately 1.4 L/day) and a total iodide intake of 275 µg/day (4 µg/kg/day). There were no statistically significant differences in serum TT_4, FT_4, T_3, or TSH concentrations in the infants in the two groups at birth, and there were no abnormal values for the hormones in any of the infants. In a similar type of study, 38 pregnant women from a potentially iodine-deficient region of Germany received daily doses of 230 µg I/day as potassium iodide during pregnancy and lactation and 70 women received no supplementation. Pretreatment urinary iodide levels were 53 µg I/g creatinine (median), suggesting a preexisting iodide intake of approximately 90 µg/day (Liesenkötter et al. 1996) and a total intake of 320 µg/day (5 µg/kg/day). Thyroid gland volumes were significantly decreased in infants from the supplemented group, compared to the control group (median control, 1.5 mL; median treated, 0.7 mL). One infant (1/38, 2.6%) from the supplemented group was classified as having an enlarged gland (>1.5 mL) compared to 14 (14/70, 20%) from the control group. The report indicates that *"no hypothyroidism or hyperthyroidism was observed in the mothers or newborns"*, although the end points evaluated, other than serum TSH, were not indicated.

In general, the aforementioned 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 (Coakley et al. 1989; Galina et al. 1962; Hassan et al. 1968; Iancu et al. 1974; Martin and Rento 1962; Penfold et al. 1978; Vicens-Calvet et al. 1998), although this effect has not been observed in all studies (Liesenkötter et al. 1996; Pedersen et al. 1993). 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 (Glinoer et al. 2001).

Iodized oil has been used to supplement intakes in populations that are iodine deficient in areas where supplementation with iodized table salt or drinking water is not practical. Iodized oil (ethiodiol) consists of a mixture of covalently iodinated fatty acids of poppy seed oil; the iodine content is approximately 38% by weight. Iodine in iodized oil is taken up in adipose tissue and has a much longer retention time in

the body than iodide salts; thus, epidemiological studies of iodized oil cannot be directly compared to those of iodide. Nevertheless, the studies provide some useful information on oral exposures to iodine that are tolerated during pregnancy without apparent adverse consequences to the fetal or neonatal thyroid. Delange (1996) reviewed epidemiological studies in which iodized oil was administered just prior to and/or during pregnancy to prevent maternal and neonatal hypothyroidism. A study of an iodine-deficient population in Algeria (with a 53% prevalence of goiter and 1% prevalence of congenital cretinism) compared thyroid status in infants born to mothers who received a placebo or a single oral dose of 240 mg I (3.4 mg/kg), as iodized oil, either 1–3 months prior to conception, during the first month of pregnancy, or during the third month of pregnancy. Neonatal serum concentrations of TSH were significantly lower in the treated groups compared to controls (treated, 4.6–4.9 mU/L; placebo, 12.4 mU/L) and serum T_4 concentrations were significantly higher compared to controls (treated, 10.4–11 µg/dL; placebo, 6.7 µg/dL). The incidence of infant hypothyroidism was 0 in 554 infants; the incidence in the placebo control was 2 in 982 (0.2%). A similar outcome occurred in a population from an iodine-deficient region of Malawi (59% prevalence of goiter, 1% incidence of cretinism), where pregnant women received either a placebo or an oral dose of 240 mg I as iodized oil (Delange 1996).

Hyperthyroidism

Oral exposure to excess iodide can, under certain circumstances, induce hyperthyroidism and thyrotoxicosis. The epidemiological and clinical literature suggests that hyperthyroidism occurs most often in people who have a previous history of iodine deficiency, goiter, or thyroid diseases including nodular goiter or Graves' disease (Braverman and Roti 1996; Fradkin and Wolff 1983; Leger et al. 1984; Paschke et al. 1994). Cases of iodine-induced hyperthyroidism in people who were euthyroid and without apparent thyroid disease have been reported (Rajatanavin et al. 1984; Savoie et al. 1975; Shilo and Hirsch 1986); however, only a few have provided dose information. In one case, a 72-year-old female without apparent preexisting thyroid disease developed clinical hyperthyroidism after ingesting approximately 2.8–4.2 mg I/day (0.05 mg/kg/day) in the form of sea-kelp tablets; her thyroid status reverted to normal within 6 months after she stopped taking the tablets (Shilo and Hirsch 1986). In another case, a 15-year-old male developed hyperthyroidism and thyrotoxicosis after receiving 1,440 mg I/day (23 mg/kg/day) as a saturated solution of potassium iodide for 4 months (Ahmed et al. 1974). The thyroid status reverted to normal within 6 months after the potassium iodide was discontinued.

In a clinical study, eight healthy adult euthyroid females, who had nontoxic goiter, received oral doses of 180 mg I/day (2.6 mg/kg/day) as a saturated potassium iodide solution for 10–18 weeks (Vagenakis et al. 1972). Four of the eight patients developed clinical hyperthyroidism and thyrotoxicosis. Two patients

developed thyrotoxicosis within 7–10 weeks after supplementation began, which became more serious after supplementation was discontinued. One patient developed clinical hyperthyroidism after 10 weeks of supplementation and then became overtly thyrotoxic after the iodide supplementation was stopped. A fourth patient developed subclinical hyperthyroidism during iodide treatment and became clinically hyperthyroid with thyrotoxicosis after supplementation was stopped.

What has been referred to as an *epidemic* of hyperthyroidism occurred in the midwestern United States between the years 1926 and 1928 (Kohn 1975, 1976). 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 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 (Lind et al. 1998; Stanbury et al. 1998). These studies confirm that iodide supplementation of iodide-deficient diets does indeed result in a detectable increase in incidence of hyperthyroidism.

In an epidemiology study conducted in Austria, the annual incidence of hyperthyroidism was evaluated in patients examined at nuclear medicine centers (where all thyroid examinations are conducted in Austria) before and after an upward adjustment was made in the use of iodized table salt in 1991 (Mostbeck et al. 1998). The mean urinary iodide concentration before the adjustment was 42–78 µg I/g creatinine and after the adjustment was 120–140 µg I/g creatinine; these are approximately equivalent to 77–146 µg/day (1.1–2.1 µg/kg/day) and 225–263 µg/day (3.2–3.8 µg/kg/day), respectively. The analysis included 392,820 patients examined between 1987 and 1995 in 19 nuclear medicine centers. A significant relative risk of hyperthyroidism, both for Graves' disease and intrinsic thyroid autonomy, was found when the annual incidences of each in the postadjustment period (1991–1995) were compared to the preadjustment period (1987–1989). The highest relative risks were for Graves' disease, which were 2.19 (2.01–2.38, 95% confidence interval [CI]) for overt clinical disease and 2.47 (2.04–3.00) for subclinical disease. A regression analysis of the pre- and postadjustment incidences found a significant increasing trend for hyperthyroidism of both types in the postadjustment period and no trend in the preadjustment period. When the postadjustment incidence data were stratified by time periods 1990–1992 or 1993–1995, and by sex and age, higher relative risks were evident for intrinsic thyroid autonomy among males compared to females and in subjects older than 50 years compared to younger than 50 years. The incidence for

hyperthyroidism (all forms of overt or subclinical) was 70.1 per 100,000 in the preadjustment period and reached a peak of 108.4 per 100,000 in 1992, after the adjustment.

Data collected on the incidence of hyperthyroidism in Tasmania also show that a 2–4-fold increase in hyperthyroidism cases occurred within a few months after diets were supplemented with iodide for preventing endemic goiter from iodide deficiency (Connolly et al. 1970). The approximate supplemental dose was 80–200 µg/day from the addition to potassium iodide to bread. Mean 24-hour urinary iodide excretion rates suggested a total postsupplementation iodide intake of approximately 230 µg/day (3.3 µg/kg/day); range, 94–398 µg/day (1.3 – 5.7 µg/kg/day), some of which may have came from sources other than supplemented bread (Connolly 1971a, 1971b). The highest incidence of hyperthyroidism after the iodine supplementation began occurred in people over 50 years of age (Stewart 1975; Stewart and Vidor 1976).

A large multinational epidemiological study was conducted in Africa to evaluate the effectiveness and possible adverse consequences of the introduction of iodized salt into diets of populations residing in iodine-deficient and endemic goiter regions of Africa (Delange et al. 1999). In each study area, urine and table salt were collected from a group of 100–400 randomly-selected children, ages 6–14 years. Health care facilities were surveyed for information on thyroid disease in each area. In Zimbabwe, the incidence of hyperthyroidism increased by a factor of 2.6 within 18 months after the widespread introduction of iodized salt into the diet (from 2.8 in 100,000 to 7.4 in 100,000). Females accounted for 90% of the cases, with the highest incidence in the age group 60–69 years. The most common disorders were toxic nodular goiter (58%) and Graves' disease (27%) (Todd et al. 1995). Urinary iodide concentration in children increased by a factor of 5–10 over this time period. Urine samples were reported as "casual samples" and, thus, there is a large uncertainty in translating the concentrations into intakes. Median urine iodide concentrations ranged from 290 to 560 µg/L. Reported estimates of iodide intake from salt and seafood were 500 µg/day (7.1 µg/kg/day) and 15–100 µg/day (0.2-1.4 µg/kg/day), respectively. Increased numbers of cases of thyrotoxicosis along with an increase in urinary iodide levels (from 16 to 240 µg/L) occurred after iodized salt was introduced into the diet of an iodine-deficient population in the Kivu region of Zaire (Bourdoux et al. 1996).

An epidemiological study in Switzerland examined the incidence of hyperthyroidism before and after the iodine content of salt was increased from 7.5 to 15 mg/kg (Baltisberger et al. 1995; Bürgi et al. 1998). The study population included 109,000 people. The mean urinary iodide concentration was 90 µg I/g creatinine before the supplementation and 150 µg I/g creatinine after the supplementation. This is

equivalent to an increase in intake from approximately 170 to 280 µg I/day (4 µg/kg/day), assuming a body weight of 70 kg. During the first year after supplementation began, the combined annual incidence of hyperthyroidism diagnosed as either Graves' disease or toxic nodular goiter increased by 27% (from 62.3/100,000 to approximately 80/100,000). Subsequent to this increase, the incidence of hyperthyroidism steadily declined to 44% of the presupplementation rates, with most of the decrease resulting from a decline in incidence of toxic nodular goiter.

In an experimental study, adults with goiter who lived in an iodine-deficient region of Sudan received a single oral dose of 200, 400, or 800 mg iodine (3–11 mg/kg/day) as iodine oil (37–41 subjects per dose group) and their thyroid status was evaluated for a period of 12 months (Elnagar et al. 1995). Approximately half of the subjects were clinically hypothyroid with serum T_4 concentrations <50 nmol/L and TSH concentrations >4 mU/L. One week after the iodine oil was administered, there was a dose-related increase in the incidence of serum TSH concentrations; 1 in 41 (2.5%) in the low-dose group, 3 in 37 (8.1%) in the middle-dose group, and 10 in 39 (25.6%) in the high-dose group, although the number of subjects exceeding 4 mU/L was not dose-related. One subject in the low-dose group and three subjects in the high-dose group became hyperthyroid during the observation period. One of the high-dose subjects remained hyperthyroid 1 year after the dose of iodine oil.

3.2.2.3 Immunological and Lymphoreticular Effects

Information on immunological effects of oral exposure to stable iodine in humans relates to thyroid gland autoimmunity or immune reactions (e.g., ioderma). The highest NOAEL values and all reliable LOAEL values in each duration category for immunological and lymphoreticular effects from exposures by the oral route are presented in Table 3-1 and plotted in Figure 3-1.

Excess iodide intake may be contributing factor in the development of autoimmune thyroiditis in people who are susceptible (Brown and Bagchi 1992; Foley 1992; Rose et al. 1997, 2002; Safran et al. 1987). Autoimmune thyroiditis is an inflammation of the thyroid gland that can lead to fibrosis of the gland, follicular degeneration, follicular hyperplasia, and hypothyroidism (Weetman 2000). IgG autoantibodies to thyroglobulin and thyroid peroxidase are consistent features of the disorder. Iodine appears to play an important role in autoimmune response as human lymphocytes recognize and proliferate in response to iodinated human thyroglobulin, but not iodine-free thyroglobulin (Rose et al. 1997). Poorly iodinated thyroglobulin is also less antigenic than iodine-rich thyroglobulin (Ebner et al. 1992)

Evidence for iodide inducing autoimmune thyroiditis in humans is incomplete. Autoimmunity, as indicated by IgG autoantibodies to thyroglobulin and thyroid peroxidase, has been observed in some studies in individuals whose iodide intakes were <500 µg/day (Hall et al. 1966; Kahaly et al. 1997, 1998; Koutras et al. 1996), and not in other studies in which intakes were similar or higher (Boyages et al. 1989; Li et al. 1987). This variable dose-response relationship suggests that factors other than iodide intake play a role in the development of thyroid autoimmunity. Several studies have been conducted of people who reside in endemic goiter areas and who received iodide supplementation. In one study, otherwise healthy adults who had goiter, but no evidence of clinical hypothyroidism or hyperthyroidism or antithyroid antibodies, received either an oral placebo (16 females, 15 males) or 200 µg I/day (3 µg/kg/day total intake) (16 females, 15 males) as potassium iodide for 12 months (Kahaly et al. 1997). Three subjects in the treatment group (9.7%, two females and one male) developed elevated levels of thyroglobulin and thyroid microsomal antibodies compared to none in the control group. Two of these subjects developed hypothyroidism and one subject developed hyperthyroidism; all three subjects reverted to normal thyroid hormone status when the iodide supplementation was discontinued. In a similar study, 31 adult euthyroid patients from an endemic goiter region who had goiter received either 500 µg/day potassium iodide (382 µg I/day, 5.1 µg I /kg/day based on reported median body weight of 75 kg) for 6 months, and 31 patients received 0.125 µg T_4/day (Kahaly et al. 1998). Based on reported measurements of 24-hour urine iodide excretion, the preexisting iodide intake was approximately 40 µg/day (range, 13–77, 0.6 µg/kg/day); thus, the total intake during treatment was approximately 420 µg I/day (6 µg/kg/day). After 6 months of iodide supplementation, the mean 24-hour urinary iodide excretion rate was 415 µg/day, which is consistent with the estimate of a total iodide intake of approximately 420 µg/day. Six of the patients who received iodide (19%) developed high titres of thyroglobulin and thyroid microsomal antibodies, compared to none in the T_4 group. Four of the high antibody patients became hypothyroid and two patients became hyperthyroid. The thyroid hormone status reverted to normal and antibody titres decreased during a 6-month period following the treatment in which the patients received a placebo. A comparison of autoantibody titres of 27 adult patients who were diagnosed with iodide-induced goiter and/or hypothyroidism with 55 healthy adults revealed a significantly greater incidence of antibodies to thyroglobulin in the goiter patients (13 of 27, 48%) than in the healthy controls (9 of 55, 16%) (Hall et al. 1966). Iodide doses in the goiter group varied from 24 to 3,728 mg I/day (0.3–53 mg/kg/day). Koutras (1996) reported that 30% of a group of goiter patients developed thyroid autoimmunity several weeks after receiving 150 or 300 µg/day potassium iodide (115 or 130 µg I/day, 1.6–1.9 µg/kg/day); further details of the study were not provided. A small, but significant, rise in thyroid peroxidase antibodies was observed in Peace Corps workers in West Africa

when they were exposed for months to a greatly increased intake of iodine in their drinking water (Pearce et al. 2002).

Other studies have not found increases in autoimmunity associated with iodine supplementation. For example, thyroid status was compared in groups of children, ages 7–15 years, who resided in two areas of China where drinking water iodide concentrations were either 462 µg/L (n=120) or 54 µg/L (n=51) (Boyages et al. 1989; Li et al. 1987). Although the subjects were all euthyroid with normal values for serum thyroid hormones and TSH concentrations, TSH concentrations were significantly higher 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. There were no differences in the serum titres of either thyroglobulin or thyroid peroxidase antibodies between the high and low iodine groups. 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 µg/day (29 µg/kg/day) and 400 µg/day (10 µg/kg/day) in the high and low iodide groups, respectively.

The effects of iodide on the development of autoimmune thyroiditis have been examined in animal models. In general, iodine does not induce autoimmune thyroiditis in outbred strains of rats; however, a susceptible inbred strain, the BB/Wor rat, has a high incidence of spontaneous autoimmune thyroiditis and does respond to iodide with an increased incidence of thyroid autoimmunity (Allen et al. 1986). This can be detected histologically as a lymphocytic infiltration of the gland (lymphocytic thyroiditis) accompanied by increased serum titres of antibodies to thyroglobulin, and increased serum TSH concentrations, indicating thyroid gland suppression (Allen and Braverman 1990). Weanling BB/Wor rats that were exposed to 0.05% iodide in drinking water for 8 weeks (approximately 85 mg/kg/day) had a significantly higher incidence of lymphocytic thyroiditis (27 of 35, 77%) compared to a control group (11 of 36, 30%) that received tap water. Similarly exposed outbred strains did not have an increase in lymphocytic thyroiditis. The spontaneous incidence of lymphocytic thyroiditis in the Buffalo strain rat (a Sprague-Dawley strain) is increased after neonatal thymectomy (Noble et al. 1976). In thymectomized Buffalo rats, 12 weeks of exposure to 0.05% iodide in drinking water (approximately 70 mg/kg/day) resulted in a significant increase in the incidence of lymphocytic thyroiditis (73%) compared to a control group that received tap water (31%) (Allen and Braverman 1990). The treatment group also had significantly higher serum TSH concentrations and significantly higher serum titres of antithyroglobulin antibody. In both of the above two studies, intake from food (Purina chow) was approximately

0.05 mg/kg/day. Obese strains of chickens are also highly susceptible to lymphocytic thyroiditis when exposed to excess iodine (Bagchi et al. 1985a).

Oral exposure to markedly excess iodide can produce allergic reactions in sensitive subjects. The reactions include urticaria, acneiform skin lesions, and fevers (Kubota et al. 2000; Kurtz and Aber 1982; Rosenberg et al. 1972; Stone 1985). There were also cases of more serious reactions involving angioedema (localized edema), vasculitis, peritonitis and pneumonitis, and complement activation (Curd et al. 1979; Eeckhout et al. 1987). Both humoral and cell-mediated immune responses are thought to be involved (Curd et al. 1979; Rosenberg et al. 1972; Stone 1985). In general, reactions to iodide have occurred in association with repeated doses exceeding 300 mg I/day.

Oral exposure to markedly excess iodide can produce skin lesions, referred to as ioderma, which are thought be a form of cell-mediated hypersensitivity and unrelated to thyroid gland function (Rosenberg et al. 1972; Stone 1985). Characteristic symptoms include acneiform pustules, which can coalesce to form vegetative (proliferating) nodular lesions on the face, extremities, trunk, and mucous membranes. The lesions regress and heal when the excess iodide intake is discontinued. The clinical literature includes cases of ioderma that occurred subsequent to oral doses of iodide at 300–1,000 mg I/day (5–14 mg/kg/day) (Baumgartner 1976; Khan et al. 1973; Kincaid et al. 1981; Kint and Van Herpe 1977; PeZa-Penabad et al. 1993; Rosenberg et al. 1972; Shelly 1967; Soria et al. 1990). 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. A typical regimen in the case literature was potassium iodide co-administered with theophylline and phenobarbital for treatment of obstructive lung disease. In at least two cases, transient dermal lesions typical of ioderma were elicited by a single oral dose of 360 or 500 mg iodide (5.1 or 7.1 mg/kg/day), as potassium iodide, and similar lesions were induced in these same patients by oral doses of aspirin, suggesting a possible cross sensitivity (Shelly 1967). In a more typical case, an adult male developed proliferating (vegetative) dermal lesions of the face, scalp, and trunk 5 days after receiving approximately 300 mg I/day (5.1 mg/kg/day) as potassium iodide (390 mg/day), along with penicillin for an acute respiratory tract infection (Soria et al. 1990). The lesions healed within 4 weeks after the potassium iodide was discontinued. Another adult male developed a vegetative dermal lesion of the neck and trunk after receiving approximately 600 mg I/day (10 mg/kg/day) as potassium iodide (720 mg/day) along with theophylline for obstructive pulmonary disease for 8 months (Soria et al. 1990). The lesions regressed within 3 weeks after the potassium iodide was discontinued and returned when an oral provocation dose of potassium iodide was administered. Another case of ioderma occurred in an adult female who received

oral doses of approximately 740 mg I/day (11 mg/kg/day) as potassium iodide (970 mg/day) for 6 months, as part of a treatment for obstructive lung disease (Kincaid et al. 1981). Other drugs included in the patient's treatment were ephedrine, theophylline, and phenobarbital. The lesions occurred on the face and conjunctiva of the eye, and healed several weeks after the potassium iodide was discontinued. A similar case occurred in an adult woman, similarly treated for 1 year with 990 mg I/day (14 mg/kg/day) as potassium iodide (1,300 mg/day) for asthma (along with ephedrine, theophylline, and phenobarbital) (Rosenberg et al. 1972). The vegetative lesions occurred on her face and arms and healed within 3 weeks after the potassium iodide was discontinued. In a more complex case, an adult female who was being treated for a variety of disorders, including polyarteritis nodosa, for which she was receiving cyclophosphamide and prednisone, and pneumonia, for which she was receiving an expectorant containing potassium iodide, developed vegetating dermal lesions on her face (Soria et al. 1990). The lesions healed within 1 month after the iodide expectorant was discontinued. She received vidarabine during this period, as the dermal lesions were, at that time, suspected of being a herpes simplex infection. One week after receiving approximately 400 mg I/day (6 mg/kg/day) as potassium iodide (520 mg/day), similar lesions of the skin and oral mucosa developed. The lesions healed within 3 weeks after the potassium iodide was discontinued.

Oral exposures to markedly excess iodide can induce fevers that are thought to have an immunological basis, and appear to be related to thyroid function (Horn and Kabins 1972; Kurtz and Aber 1982). Reported clinical cases have almost always involved a preexisting disease, usually pneumonia or obstructive lung disease in which potassium iodide was administered along with other drugs, including antibiotics, barbiturates, and methylxanthines; thus, the dose-response relationship for healthy people is highly uncertain. In one case, recurrent fevers occurred in an adult male who was receiving oral doses of approximately 1,080 mg I/day (15 mg/kg/day) as a potassium iodide solution (assumed, but not specified in the case report, to be a saturated solution) for approximately 15 years (Kurtz and Aber 1982). The fevers stopped within 2 weeks after the potassium iodide was discontinued. In another case, an adult male developed a fever 8 days after the start of a daily regimen of approximately 1,440 mg I/day as a saturated solution of potassium iodide for treatment of a respiratory illness; the fever stopped within 3 days after the potassium iodide was discontinued (Horn and Kabins 1972). In another case, an adult female developed a fever after a dosage of approximately 1,620 mg I/day (23 mg/kg/day) as a saturated potassium iodide solution along with ampicillin to treat pneumonia (Horn and Kabins 1972). The fever stopped within 36 hours after the potassium iodide was discontinued; at the same time, a regimen of diazepam, secobarbitol, and glycerol guaiacolate was administered. The fever returned when a challenge dose of potassium iodide was administered. A fourth case involved an adult female diabetic patient who

received 1,080 mg I/day (15 mg/kg/day) as a saturated potassium iodide solution along with antibiotics, cortisone, and aminophylline for pneumonia (Horn and Kabins 1972). Four days after the potassium iodide treatments began, the patient developed a fever, which stopped when the potassium iodide was discontinued.

3.2.2.4 Neurological Effects

Exposure to excess stable iodine has been shown to produce subclinical hypothyroidism, and in sensitive individuals who have underlying thyroid disease, may take the form of hypothyroidism. Sensitive populations include fetuses, newborn infants, and individuals who have thyroiditis or a history of Graves' disease, many of whom have abnormal autoimmune disorders (see Section 3.2.2.2, Endocrine Effects). Of these iodine-induced forms of hypothyroidism, that occurring in the fetus or newborn infant has 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 (Boyages 2000b). Iodine-induced hypothyroidism in an older child or adult would be expected to have little or no deleterious effects on the neuromuscular system.

Exposure to excess stable iodine can also produce hyperthyroidism in sensitive individuals (see Section 3.2.2.2, Endocrine Effects). These include people who are initially iodine deficient, those who have thyroid disease, including nodular goiter, Graves' disease, those who have been previously treated with antithyroid drugs, , and those who have developed thyrotoxicosis from amiodarone or interferon-alpha treatments (Roti and Uberti 2001). Patients who develop thyrotoxicosis may experience neuromuscular disorders, including myopathy, periodic paralysis, myasthenia gravis, peripheral neuropathy, tremor, and chorea (Boyages 2000a); however, these are not likely to occur in iodine-induced hyperthyroidism, except in sensitive groups, already at risk for neurological problems.

3.2.2.5 Reproductive Effects

Oral exposure to excess stable iodine may produce hypothyroidism or hyperthyroidism (see Section 3.2.2.2, Endocrine Effects) and may 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). Abortions, stillbirths, and premature births have also been associated with hypothyroidism (Longcope 2000a). Reproductive

impairments associated with hyperthyroidism include amenorrhea, alterations in gonadotropin release and sex hormone-binding globulin (SHBG), and changes in the levels and metabolism of steroid hormones in both females and males (Longcope 2000b).

The highest NOAEL values and all reliable LOAEL values in each duration category for reproductive effects from exposures by the oral route are presented in Table 3-1 and plotted in Figure 3-1.

3.2.2.6 Developmental Effects

Exposure to excess stable iodine may produce hypothyroidism and hyperthyroidism (see Section 3.2.2.2, Endocrine Effects), which could give rise to developmental defects secondary to thyroid gland dysfunction (Boyages 2000a, 2000b). Hypothyroidism may be associated with impairment in neurological development of the fetus or growth retardation (Boyages 2000a, 2000b; Snyder 2000a). Martin and Rento (1962) reported two cases of goiter and severe transient hypothyroidism, without neurological sequellae in infants born to mothers who ingested potassium iodide during pregnancy; the approximate dosages were 920 and 1,530 mg I/day (13 and 22 mg/kg/day). Growth acceleration may occur in childhood hyperthyroidism, which is thought to be related to accelerated pituitary growth hormone turnover or a direct effect of thyroid hormone on bone maturation and growth (Snyder 2000b).

The highest NOAEL values and all reliable LOAEL values in each duration category for developmental effects from exposures by the oral route are presented in Table 3-1 and plotted in Figure 3-1.

3.2.2.7 Cancer

Cancer effect levels (CELs) for stable iodine exposures by the oral route are presented in Table 3-1 and plotted in Figure 3-1.

The relationship between stable iodine intake and thyroid cancer has been examined in several epidemiology studies. The results of these studies suggest that increased iodide intake may be a risk factor for thyroid cancer in certain populations, in particular, populations residing in iodine-deficient (Bacher-Stier et al. 1997; Harach and Williams 1995; Franceschi 1998; Franceschi and Dal Maso 1999). Studies of populations in which iodine intakes are sufficient have not found significant associations between iodine intake and thyroid cancer (Horn-Ross et al. 2001; Kolonel et al. 1990) however, a recurrent observation is an apparent shift in the histopathology towards a higher prevalence of papillary

cancers, relative to follicular cancers, after increased iodine intake (e.g., dietary supplementation) in otherwise iodine-deficient populations (Bakiri et al. 1998; Belfiore et al. 1987; Feldt-Rasmussen 2001; Kolonel et al. 1990; Pettersson et al. 1991, 1996).

Two case control studies have been conducted on populations whose iodine intakes are sufficient; both found no significant association between iodine intake and thyroid cancer. A case control study of women residents of the San Francisco Bay area of the United States examined dietary habits, including iodine intake and other variables in 608 cases of thyroid cancer and 558 age- and ethnicity-matched controls, diagnosed during the period 1995–1998 (Horn-Ross et al. 2001). Dietary iodine intakes were estimated based on the results of a dietary habits questionnaire and published compilations of the iodine content of various foods. When cases and controls were classified according to dietary iodine intake (quintile), the risk of papillary thyroid cancer was significantly lower in women who consumed >273 µg I/day compared to women who consumed <273 µg I/day (<4.2 µg/kg/day); the odds ratio (OR) for the highest quintile (>537 µg I/day, >8.3 µg/kg/day) was 0.49 (95% confidence interval [CI] 0.29–0.84). When cases and controls were classified according to seafood consumption rates, ORs for papillary thyroid cancers were significantly elevated for consumption of >2.0 g/day of fish sauce/dried salted fish compared to none (limited to Asian women; OR 2.3, 95% CI 1.3–4.0). ORs for other types of seafood consumed were not significant. Other variables for which ORs were statistically significant included medical radiation of head or neck (OR 2.7, 95% CI 1.2–6.2), history benign goiter or thyroid nodules (OR 4.7, 95% CI 3.1–7.2), and family history of thyroid disease (ORs ranged from 1.5 hyper- or hypothyroidism to 6.1 for thyroid cancer).

Another case control study of residents of Hawaii examined dietary habits, including iodine intake and other variables in 191 cases of thyroid cancer and 441 age- and sex-matched controls, diagnosed during the period 1980–1987 (Kolonel et al. 1990). Dietary iodine intakes were estimated based on the results of a dietary habits questionnaire and published compilations of the iodine content of various foods. Female cases had significantly higher dietary iodine intakes than controls, although the group mean differences were not substantial; cases, 394 µg I/day (6.1 µg/kg/day); controls, 326 µg I/day (5.0 µg/kg/day). When cases and controls were classified according to dietary iodine intake (quartile), the ORs for thyroid cancer in females increased with increasing iodine intake; however, ORs were not statistically significant and there were no significant trends in the OR with increasing iodine intake. Other variables for which ORs were statistically significant included miscarriage (2.4), use of fertility drugs (4.2), and the combination of either of the former characteristics with an iodine intake exceeding 300 µg I/day or 4.6 µg/kg/day (4.8 or 7.3, respectively), or seafood intake exceeding 27 g/day (3.0 or 6.9, respectively). A limitation of this

study is that iodine intakes were estimated from dietary surveys and were not verified by measurements of urinary excretion of iodine.

Several cohort studies conducted on populations residing in iodine-deficient regions have found significant associations between thyroid cancer and iodine intake. A cohort study compared thyroid cancer rates in iodine-sufficient and iodine-deficient regions of Sweden during the period 1958–1981 (Pettersson et al. 1991, 1996). Iodine-deficient regions were defined as having had a goiter prevalence that was >33% in females and >15% in males, based on a 1930 survey. In Sweden, dietary iodine intake has increased over the study period as a result of dietary supplementation, which began in 1936 and was subsequently increased in 1966 and 1971 (Pettersson et a. 1996). Thus, iodine deficiency, even in the previously deficient regions has diminished. A multivariate model that included sex, age, dates of diagnosis, and region (i.e., iodine deficient or sufficient) as variables was applied to a sample of 5,838 thyroid cancer cases to estimate adjusted RR for thyroid cancer, where RR was the ratio of the adjusted cancer incidence rates for iodine-deficient:iodine-sufficient regions. The RR for papillary thyroid cancer was 0.8 (95% CI, 0.73–0.88), suggesting lower risk in the iodine-deficient regions, relative to the iodine-sufficient regions. The RR for follicular thyroid cancer was 1.98 (1.60–2.4) in males and 1.17 (1.04–1.32) in females, suggesting a 1.2- to 2-fold higher risk for follicular cancer in populations living in the iodine-deficient regions, relative to iodine-sufficient regions. The prevalence of papillary cancers was significantly higher, and follicular cancers were significantly lower in the iodine sufficient areas. Analysis of incidence of thyroid cancer as a function of dates of diagnosis revealed a significant trend for increasing follicular cancers in the iodine-deficient areas, but not in the iodine-sufficient areas. A significant trend for increasing papillary cancers was evident in both the iodine-sufficient and iodine-deficient regions.

Another cohort study examined the prevalence of thyroid cancer during the period 1979–1985 in populations living in iodine-deficient and iodine-sufficient areas of Sicily (Belfiore et al. 1987). Mean urinary iodine excretion rate in the deficient regions was approximately 19–43 µg I/day (0.3–0.6 µg/kg/day) and, in the iodine-sufficient regions, was approximately 114 µg I/day (1.6 µg/kg/day); the intakes in the two regions would be expected to be similar to urinary excretion rates. Randomly selected subjects from both regions were subjected to radioiodine thyroid scans to determine the presence of cold thyroid gland nodules, indicative of a possible tumor with suppressed iodine uptake. The prevalence of cold nodules in the iodine deficient region was significantly greater (72 of 1,683, 4.3%) than in the iodine-sufficient group (21 of 1,253, 1.7%). In the second phase of this study, all patients who had cold nodules in the two study areas, 911 patients from the iodine-deficient region, and 2,537 patients from the

iodine-sufficient region, were biopsied. The prevalence of thyroid cancer among patients who had one or more cold nodules was higher in the iodine-sufficient region (5.48%) than in the iodine-deficient region (2.96%). The prevalence of papillary tumors, relative to that of follicular tumors, was higher in the iodine-sufficient region (3.8) than in the iodine-deficient region (1.0). When the thyroid cancer prevalence among patients with cold nodules was adjusted for the estimated prevalence of cold nodules in the two regions, the estimated prevalence of thyroid cancer in the iodine-deficient region was significantly higher (127 in 100,000) than in the iodine-sufficient region (93 in 100,000).

The results of several ecological studies suggest that the incidence of thyroid cancer may increase in endemic goiter regions after supplementation of the diet with iodine. In Austria, iodized salt was introduced into the diet in 1963 and then increased further in 1991. The mean urinary iodide concentration before the adjustment was 42–78 µgI/g creatinine and after the adjustment was 120–140 µgI/g creatinine; these are approximately equivalent to 77–146 µg/day (1–2 µg/kg/day) and 225–263 µg/day (3–4 µg/kg/day), respectively (Bacher-Stier et al. 1997; Mostbeck et al. 1998). A retrospective analysis of medical records in the Tyrol region of Austria (1,063,395 inhabitants) concluded that the incidence of thyroid cancer increased from 3.1 per 100,000 year for the period 1960–1970 to 7.8 for the period 1990–1994 (Bacher-Stier et al. 1997). The prevalence of papillary tumors appeared to increase relative to that of follicular tumors after supplementation; the ratio of papillary:follicular tumors was 0.6 before supplementation and 1.5 after supplementation. Improved diagnosis may have contributed to the increased incidence. In support of this, a trend was observed towards increased prevalence of less advanced tumor stages in 439 patients for which complete medical records were available. The authors reported that “no excessive natural radiation has been found in Tyrol”.

A retrospective analysis of 1,000 consecutive patient records from endocrine wards in Algiers, recorded during the period 1967–1991, revealed significantly greater prevalence of differentiated follicular thyroid tumors in patients who resided in an endemic goiter region (53.6%; n=581) than in nonendemic regions (44.0%; n=236) (Bakiri et al. 1998). The prevalence of follicular tumors was significantly greater than that of papillary tumors in the endemic areas, whereas follicular tumors were less prevalent than papillary tumors in the nonendemic region. The ratio of papillary:follicular tumors was 1.2 in the endemic region and 0.8 in the nonendemic region. The mean urinary iodide concentration in the goiter endemic area was <50 µg I/g creatinine and was >80 µg I/g creatinine in the nonendemic region; these are approximately equivalent to <95 µg/day (1.2 µg/kg/day) and >150 µg/day (2.1 µg/kg/day), respectively.

A retrospective analysis of 144 cases of thyroid cancer in the Salta region of Argentina, diagnosed during the period 1960–1980, found that the prevalence of papillary tumors appeared to increase relative to that of follicular tumors after dietary iodine supplementation was initiated as prophylaxis for goiter; the ratio of papillary:follicular tumors was 1.8 before supplementation and 3.0 after supplementation (Harach and Williams 1995; Harach et al. 1985). The mean urinary iodide concentration before the supplementation was 9 µg I/g creatinine and after the supplementation was 110–150 µg I/g creatinine; these are approximately equivalent to 17 µg I/day (0.2 µg/kg/day) and 205–280 µg I/day (3–4 µg/kg/day), respectively.

3.2.3 Dermal Exposure

3.2.3.1 Death

No information was located on deaths associated with dermal exposure to iodine.

3.2.3.2 Systemic Effects

No information was located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, body weight, or other systemic effects of dermal exposure to stable iodine.

Endocrine Effects. Povidone-iodine is a complex of I_2 and polyvinyl pyrrolidone and is widely used as a topical antiseptic for mouth, skin, and vaginal infections, and surgical procedures. Topical preparations of povidone-iodine contain approximately 9–12% iodine, of which a small fraction is in free solution (Lawrence 1998; Rodeheaver et al. 1982). Dermal exposure to povidone-iodine has induced acute toxicity in humans. In one case, hyperthyroidism and thyrotoxicosis developed in an adult male who, for 6 months, received povidone-iodine skin washes to treat dermal ulcers but had no other history of excess iodine intake or treatment with iodine-containing drugs (Shetty and Duthie 1990). The patient had elevated antithyroglobulin and thyroid peroxidase (thyroid microsomal) antibodies. The disorder eventually required therapy with propylthiouracil and radioiodine. It is possible that the povidone-iodine exposure may have aggravated a pre-existing autoimmune disorder in the patient rather than having been the cause of the thyrotoxicosis.

In a study of 27 neurological ward patients who received topical povidone-iodine treatments for various procedures and for periods of 3–133 months, serum iodide, T_4, and FT_4 concentrations were significantly higher than a group of 13 patients who did not receive povidone-iodine treatments (Nobukini et al. 1997). Eight of the 27 patients who received povidone-iodine treatments were clinically hyperthyroid (serum FT_4 concentration above the normal range) and 3 of 27 patients were suspected of having subclinical hypothyroidism (serum TSH concentrations above the normal range). None of these patients had elevated antithyroglobulin or thyroid peroxidase antibodies, suggesting that thyroid autoimmunity was not the cause of the apparent thyroid hormone disturbances. Serum FT_4 concentrations were significantly positively correlated with the duration of povidone-iodine exposure. In a similar study, the thyroid hormone status of 16 healthy nurses who regularly used povidone-iodine formulations, mainly for hand-washing and gargling, was compared to that of 16 hospital workers who had little or no contact with povidone-iodine (Nobukini and Kawahara 2002). Mean serum FT_4 levels were slightly, but significantly, higher in the groups of nurses compared to the comparison group (1.30±0.15 ng/dL, 1.15"0.14, $p<0.01$); however, serum TSH, FT_3, and FT_4 levels were within the normal range for all study participants.

Several cases of hypothyroidism induced by topical applications of povidone-iodine to wounds have been described. In one case, an adult female was exposed to approximately 22 mg iodine as povidone-iodine, 3 days/week for 22 months, when an open fistula was swabbed with povidone-iodine and packed with iodoform impregnated gauze (Prager and Gardner 1979). The patient developed clinical hypothyroidism with thyroid enlargement and became euthyroid within 6 weeks after the iodine treatment of the wound was discontinued. Another patient who had a small nodular goiter developed hyperthyroidism following betadine irrigation of a mediastinal wound, after cardiac bypass surgery (Rajatanavin et al. 1984). In another study, mouth rinsing with iodine-containing mixtures for gingivitis, for 6 months, induced a small decrease in serum T_4 and a compensatory rise in serum TSH; however, all values were well within the normal range (Ader et al. 1988).

Povidone-iodine gels are used for vaginal lubrication during labor checks prior to delivery. Use of povidone-iodine gels has been associated with increased serum iodide concentrations as well as changes in thyroid hormone status, indicative of subclinical thyroid gland suppression. In a study of 18 women who received intravaginal treatments with povidone-iodine gel during labor checks, serum iodide concentrations were significantly higher after the applications than before the applications (Jacobson et al. 1984). Serum TSH concentrations were significantly elevated (5.9 mU/L) in the povidone-iodine group compared to a group of 13 women who received vaginal lubricants that did not contain iodine (1.9 mU/L). There were no differences in the levels of T_4 or T_3 between the iodine and no-iodine groups.

Topical application of povidone-iodine during labor has been found to produce thyroid gland suppression in newborns. In a study of 30 women who received topical povidone-iodine in preparation for a cesarean section, newborn serum TSH concentrations (cord blood) were significantly higher than in newborns from 12 mothers who also underwent a cesarean section, but who were not exposed to povidone-iodine (Novaes et al. 1994); however, the levels were not above the normal range for newborns (>20 mU/L, de Zegher et al. 1994; Momotani et al 1992). Serum concentrations of T_4 and T_3 were not different in the two groups of newborns. In a study of infants delivered by mothers who received intravaginal povidone-iodine during labor checks, serum TSH concentrations were significantly higher and T_4 and T_3 concentrations were significantly lower compared to 18 control infants delivered from mothers who were not exposed to povidone-iodine during labor (l'Allemand et al. 1983). Twenty percent of the infants from the treated mothers had serum TSH concentrations above the normal range for newborn infants (>20 mU/L) and serum T_4 concentrations below the normal range (<7 µg/dL) and, thus, were hypothyroid. All infants were euthyroid at 14 days after birth.

Daily douching with betadine for 14 days was associated with an increase in serum iodide levels, small decreases in T_4, small rises in serum TSD, and a decrease in thyroid iodide uptake, All values returned to baseline within 2 weeks after the exposure (Safran et al. 1982).

Use of povidone-iodine for topical disinfection and surgical wound disinfection in infants has been shown to induce hypothyroidism and hyperthyroidism. In a prospective study, 17 premature infants (#36 weeks gestation), who were euthyroid with no indications of thyroid disorders, received topical povidone-iodine applications for various procedures beginning within 24 hours of birth (Brown et al. 1997). Five of 17 (29%) of the infants had a significant decrease (<50% of pretreatment value) in their serum T_4 concentrations compared to none of 14 control infants who received the same clinical procedures, but with topical application of a noniodine disinfectant (chlorhexidine). These five infants had serum T_4 concentrations that were below 40 nmol/L (3.1 µg/dL) 4–6 days after exposure to povidone-iodine, indicating mild hypothyroidism (60 nmol/L is low end of normal range), although their serum TSH concentrations were not elevated (<20 mU/L, de Zegher et al. 1994; Momotani et al. 1992). Their T_4 status reverted to normal within 10–25 days after treatment. There were no significant differences between the treatment and control group mean values for serum T_4 or TSH. Iodide concentrations in random untimed urine samples were approximately 24 times higher in the treatment group (1,800–3,600 µg/L) than in the control group (90–150 µg/L), indicating absorption of some of the topically applied iodine. In a study of 30 intensive care ward infants who received frequent topical applications of

povidone-iodine for various procedures, five infants (20%) developed clinical hypothyroidism with serum T_4 and T_3 concentrations below the normal range, serum TSH concentrations above the normal range, and thyroid gland enlargement (Chabrolle and Rossier 1978a, 1978b). Urinary iodide excretion at the time of treatment ranged from 2.9 to 4.8 mg I/day in four of the patients and was 0.14 mg I/day in one of the patients, suggesting daily absorbed doses of iodine in this same range. The thyroid hormone status reverted to normal after the povidone-iodine treatments were discontinued. A 30% incidence of hypothyroidism was reported in 10 intensive care ward newborns who received topical povidone-iodine applications for various procedures for >2 days in duration (l'Allemand et al. 1987). A newborn infant who received povidone-iodine irrigations of wound drains became clinically hyperthyroid without elevated serum titres of antithyroglobulin or thyroid peroxidase (thyroid microsomal) antibodies (Bryant and Zimmerman 1995). The patient became euthyroid within 1 month after the povidone-iodine irrigations were discontinued. Thyroid status of four infants with spinal bifida who received daily povidone-iodine antiseptic dressings were followed; two of the four patients became hypothyroid after 4 weeks of exposure and required treatment with T_4 (Barakat et al. 1994). The patients became euthyroid within 9 months after the povidone-iodine applications were discontinued. In a study of 47 neonatal intensive care patients who were exposed to topical povidone-iodine for varying lengths of time, no evidence of hypothyroidism was found (Gordon et al. 1995).

3.2.3.3 Immunological and Lymphoreticular Effects

Dermal exposures to povidone-iodine have produced localized and systemic allergic responses in humans. In one case, an adult male developed a reaction to application of povidone-iodine to an arm wound. The reaction consisted of itching of the extremities, urticaria, and angioedema (of the face), which were ameliorated with antihistamine treatment (López Sáez et al. 1998). A serum specific IgE assay detected reactivity in the patient's serum to various povidone-iodine and various other iodine preparations. Several case reports have been published that describe dermatitis in people who have been exposed to topical applications of povidone-iodine and subsequently reacted to dermal challenge tests to povidone-iodine (Nishioka et al. 2000; Okano 1989; Tosti et al. 1990).

Intravaginal applications of povidone-iodine have also induced allergic reactions in humans. In one case, an adult woman developed a bronchospastic reaction in response to application of povidone-iodine and an iodine-containing contrast medium (Moneret-Vautrin et al. 1989). The patient reacted in a dermal challenge test to povidone-iodine, but not the contrast medium, and the patient's serum tested positive for histamine release and basophil degranulation *in vitro*. In another case, anaphylaxis occurred in a patient

after an intravaginal application of povidone-iodine. The patient reacted to povidone-iodine in a dermal challenge test (Waran and Munsick 1995).

Although the above cases appear to implicate povidone-iodine as the causative agent in the allergic responses reported, povidone itself, without iodine, has also been shown to produce allergic reactions and anaphylaxis in humans and may have contributed to the reactions observed in some of these cases (Garijo et al. 1996).

3.2.3.4 Neurological Effects

No information was located on neurological effects associated with dermal exposure to iodine. Dermal exposure to excess iodine may produce mild transient hypothyroidism and hyperthyroidism (see Section 3.2.3.2, Endocrine Effects), which could give rise to neurological manifestations of thyroid gland dysfunction including impairments in neurological development and myopathies (Boyages 2000a, 2000b). However, based on the mild effects that have been observed in association with dermal exposures, such severe neurological sequellae are not likely.

3.2.3.5 Reproductive Effects

No information was located on reproductive effects associated with dermal exposure to iodine. Dermal exposure to excess iodine may produce mild transient hypothyroidism and hyperthyroidism (see Section 3.2.3.2, Endocrine Effects). Either could give rise to disruption of reproductive systems secondary to thyroid gland dysfunction; however, based on the mild effects that have been observed in association with dermal exposures, significant disruptions of reproductive function are not likely. Hypothyroidism can produce changes in the menstrual cycle in humans, including menorrhagia (excessive uterine bleeding) and anovulation (no ovulation). Abortions, stillbirths, and premature births have also been associated with hypothyroidism (Longcope 2000a). Reproductive impairments associated with hyperthyroidism include amenorrhea, alterations in gonadotropin release, and sex hormone-binding globulin (SHBG), and changes in the levels and metabolism of steroid hormones in both females and males (Longcope 2000b).

3.2.3.6 Developmental Effects

No information was located on developmental effects associated with dermal exposure to iodine. Dermal exposure to excess iodine may produce mild transient hypothyroidism and hyperthyroidism (see Section 3.2.3.2, Endocrine Effects). Use of povidone-iodine for topical disinfection and surgical wound disinfection in infants has been shown to induce hypothyroidism and hyperthyroidism, and topical application of povidone-iodine during labor has been found to produce transient, mild hypothyroidism in newborns (see Section 3.2.3.2, Endocrine Effects). Hypothyroidism or hyperthyroidism could give rise to developmental effects secondary to thyroid gland dysfunction (Boyages 2000a, 2000b). Developmental effects of hypothyroidism include severe impairment in neurological development of the fetus known as cretinism, or growth retardation (Boyages 2000a, 2000b; Snyder 2000a). Severe impairment of neurological development or growth retardation are effects only seen with severe, long-standing thyroid deficiency, not the transient form that has been associated with dermal iodine-induced hypothyroidism. Growth acceleration may occur in childhood hyperthyroidism, which is thought to be related to accelerated pituitary growth hormone turnover or a direct effect of thyroid hormone on bone maturation and growth (Snyder 2000b).

3.2.3.7 Cancer

No information was located on cancer in association with dermal exposure to iodine.

3.2.4 External Exposure

No information was located on health effects associated with external exposure to radioiodine.

3.3 DISCUSSION OF HEALTH EFFECTS FOR RADIOACTIVE IODINE BY ROUTE OF EXPOSURE

Section 3.3 discusses radiation toxicity associated with exposure to radionuclides of iodine and is organized in the same manner as that of Section 3.2, first by route of exposure (inhalation, oral, and external) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing NOAELs or LOAELs reflect the actual dose (levels of exposure) used in the studies. Refer to Section 3.2 for detailed discussion of the classification of endpoints as a NOAEL, less serious LOAEL, or serious LOAEL.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of radioiodine are indicated in Tables 3-1, and 3-2 and Figures 3-1 and 3-2. Because cancer effects could occur at lower exposure levels, Figures 3-1 and 3-2 also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Refer to Appendix B for a User's Guide, which should aid in the interpretation of the tables and figures for Levels of Significant Exposure.

3.3.1 Inhalation Exposure

A large amount of epidemiological literature exists on the heath outcomes in populations exposed to radioiodine as a result of releases from explosions of nuclear bombs (e.g., Marshall Islands, Nevada Test Site), operational releases from nuclear fuel reprocessing facilities (e.g., Hanford Nuclear Site), and accidental releases from nuclear power plants (e.g., Chernobyl). Releases of these types resulted in mixed exposures to a variety of radioisotopes, and radiation doses from both external and internal exposure. However, doses from radioiodine that are significant to health effects derive largely from internal exposure to the thyroid gland as a result of absorption and uptake of radioiodine into the thyroid gland (see Section 3.5.2.2). Inhalation of airborne radioiodine is likely to have occurred after each of these releases and prior to ground deposition of radioiodine. However, the major contributors to thyroid radiation dose in each of these incidents are thought to have been from ingestion of milk, grains, vegetables, and water contaminated from atmospheric deposition of radioiodine. Ingestion of human breast milk is also considered to have been a contributor to doses received in nursing infants. For example, it has been estimated that, in seven Ukraine cities following releases of radioiodine from the Chernobyl nuclear power plant, inhalation of ^{131}I contributed between 2 and 13% of total absorbed radiation dose, whereas the ingestion pathway contributed from 87 to 98% (IAEA 1991). In the Marshall Islands, after the BRAVO bomb test, the inhalation pathway is thought to have contributed <1% of the absorbed radioiodine, with the ingestion pathway contributing 80–99% (Lessard et al. 1985). Because of the more substantial contribution of the oral pathway to the absorbed thyroid radiation doses, health

effects studies related to the Chernobyl accident, the Marshall Islands, the Hanford Nuclear Site, and the Nevada Test Site are discussed in the oral section of this profile (Section 3.3.2). However, the effects observed that have been related to the internal radiation dose to the thyroid gland are also directly relevant to inhalation exposures since inhaled radioiodine absorbed from either the respiratory tract or gastrointestinal tract would be expected to distribute to the thyroid gland (see Section 3.5.2.1).

3.3.1.1 Death

Deaths related to thyroid cancers (or to other cancers or causes) following the Chernobyl accident are being studied with well-controlled epidemiological designs and dose reconstruction efforts, and possible associations between mortality and radioiodine exposures may become evident once these studies have been completed. Thus far, very few deaths have been attributed to thyroid cancer. Although radiation-related deaths were recorded among emergency response personnel on site during the Chernobyl accident, these deaths were associated with external exposure to gamma radiation from molten fuel areas and not with exposure to radioiodine.

3.3.1.2 Systemic Effects

All of the information on systemic effects of inhaled radioactive iodine in humans relates to endocrine effects from exposures to radioiodine following the BRAVO nuclear bomb test in the Marshall Islands, the Chernobyl accident, and radioiodine releases from the Hanford Nuclear Site. Because oral ingestion of radioiodine is thought to have been the major contributor to exposure, these studies are discussed in detail in Section 3.3.2. No information was located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, body weight, or other systemic effects of inhalation exposure to radioiodine. However, one epidemiological study examined health outcomes of infants of mothers who resided in the Belarus region before or after the Chernobyl accident (Petrova et al. 1997). The health outcomes observed in this study include respiratory, hematological, renal, and dermal effects; however, their association to radioiodine exposure has not been established. This study is discussed in greater detail in the sections of reproductive and developmental effects associated with oral exposures to radioiodine (Sections 3.3.2.5 and 3.3.2.6).

3.3.1.3 Immunological and Lymphoreticular Effects

All of the information on immunological effects of inhaled iodine in humans relates to thyroid gland autoimmunity and exposures to radioiodine following the BRAVO nuclear bomb test in the Marshall

Islands, the Chernobyl accident, and releases of radioiodine from the Hanford Nuclear Site. Because exposures in these incidents are thought to have been largely from oral ingestion of radioiodine, these studies are discussed in detail in Section 3.3.2.

3.3.1.4 Neurological Effects

Although not supported by observations, exposure to radioiodine at sufficient doses to produce hypothyroidism could potentially give rise to neurological manifestations of thyroid gland dysfunction including impairments in neurological development and myopathy (Boyages 2000a, 2000b). Congenital hypothyroidism can be associated with a severe impairment in neurological development of the fetus termed *cretinism*, which usually occurs in areas of endemic iodine deficiency. This condition would be highly unlikely in iodine-induced hypothyroidism secondary to inhalation of iodine.

3.3.1.5 Reproductive Effects

No information was located regarding reproductive effects of inhalation exposure to radioiodine. However, a large-scale retrospective analysis was conducted to evaluate pregnancy health and reproductive outcomes of women who were exposed to radiation resulting from releases from the Chernobyl nuclear power plant, including a major contribution from ^{131}I (Petrova et al. 1997). Although inhalation of radioiodine certainly occurred in this population, internal radiation doses resulting from this incident are thought to have been largely from oral ingestion of radioiodine (IAEA 1991). The study is summarized in greater detail in Section 3.3.2.5, which discusses the reproductive effects of oral exposures to radioiodine.

3.3.1.6 Developmental Effects

No information was located regarding developmental effects associated with inhalation exposure to radioiodine other than those related to the thyroid gland (e.g., Marshall Islands, Section 3.3.2.2). However, one epidemiological study examined health outcomes of infants of mothers who resided in the Belarus region before or after the Chernobyl accident (Petrova et al. 1997). Exposures resulting from this incident are thought to have been largely from oral ingestion of radioiodine (IAEA 1991) and, therefore, a summary of this study can be found in Section 3.3.2.6 on the developmental effects of oral exposures to radioiodine.

3.3.1.7 Cancer

Thyroid cancers have been associated with exposures to radioiodine following the BRAVO nuclear bomb test in the Marshall Islands and the Chernobyl accident. The occurrence of thyroid cancers has also been studied in populations exposed to radioiodine released from nuclear bomb tests at the Nevada Test Site and from operational releases of radioiodine from the Hanford Nuclear Site. Although the inhalation of radioiodine occurred in these incidents, oral ingestion of radioiodine is thought to have been the major contributor to thyroid radiation doses. Summaries of these studies can be found in Section 3.3.2.7 on cancer effects of oral exposures to radioiodine.

3.3.2 Oral Exposure

The section that follows provides background information on the exposure scenarios from the major radioiodine-releasing events for which health effects studies have been reported. The actual study summaries follow. A discussion of the relevant biokinetics of radioiodine is provided in Section 3.5.

Marshall Islands BRAVO Test. Several epidemiologic studies have examined thyroid gland disorders in residents of the Marshall Islands who were exposed to radioactive isotopes of iodine from atmospheric fallout after atmospheric nuclear bomb tests, in particular, the 1954 Castle *BRAVO* test. Residents of islands near and downwind from the test site on Bikini Atoll (e.g., Ailingnae, Rongelap, Utrik) were exposed to both internal radionuclides and external gamma radiation from fallout during the 2 days following the BRAVO test and prior to their evacuation. The estimated cumulative gamma radiation dose on these islands ranged from 69 to 175 rad (0.7–1.75 Gy) or approximately 10–50% of the estimated thyroid dose (Conard 1984). Later studies suggest that external radiation contributed approximately 4–16% of total thyroid dose (Hamilton et al. 1987). Internal exposures to the thyroid, resulting primarily from radioiodines, were much higher. Although inhalation of airborne radioiodine probably occurred during the fallout period immediately after the blast, ingestion of deposited radioiodine on locally prepared foods and drinking water during the subsequent 2 days prior to evacuation is thought to be the major contributor to the internal exposures (Lessard et al. 1985). Nursing infants would also have received internal exposures from ingestion of radioiodine in breast milk. Estimated total absorbed doses to the thyroid gland (external and internal) were 3.3–20 Gy (330–2,000 rad) on Rongelap (highest doses in children), 1.3–4.5 Gy (130–450 rad) on Ailingnae, and 0.3–0.95 Gy (30–95 rad) on Utrik (Conard 1984). Estimates of the internal radiation dose to the thyroid remain uncertain as they were based

primarily on measurements of radioiodine (principally ^{131}I) in a pooled urine sample, collected 16 days after exposure, from a subset of exposed people. Although these measurements allowed back extrapolation of the initial internal ^{131}I exposures, shorter-lived radioiodine species (^{132}I, ^{133}I, ^{135}I) could not be detected in the urine sample. These isotopes are thought to have contributed 2–3 times the thyroid radiation dose of ^{131}I (Conard 1984). It is generally agreed that external radiation exposures resulted nearly entirely from fallout and deposits of radionuclide-containing materials on the skin, rather than from direct photon irradiation from the blast, as the exposed populations were approximately 100–320 miles from the detonation site. In this respect, the Marshall Island exposures are very different from the Hiroshima and Nagasaki exposures, which were the result of an acute (single dose) exposure to mostly gamma radiation (with neutron contribution in Hiroshima). Sixty-six nuclear bomb tests were conducted in the Marshall Islands during the period 1946–1958. Comparisons of contemporary measurements ^{137}Cs in soils in the Marshall Islands with estimates of global fallout in the mid-Pacific region suggest contamination from local fallout occurred over much of the Marshall Islands (i.e., local ^{137}Cs:global ^{137}Cs ratio>1) with particularly high local:global ^{137}Cs ratios (>10) on the islands of Bikini Atoll (test site), Enewatak Atoll (test site), Rongelap Atoll, and Utrik Atoll (Simon and Graham, 1997). The most recent epidemiologic study (Takahashi et al. 1997, 2003) investigated 4,762 inhabitants of the islands who were alive during the weapons testing years.

Chernobyl Accident. In 1986, a chemical explosion and fire at the nuclear power plant in Chernobyl in the Ukraine was caused by improper, unstable operation of the reactor, which allowed an uncontrollable power surge to occur; this resulted in the release of airborne radionuclides to the surrounding regions and contamination of soil and locally grown foods. The external radiation exposures were contributed largely by isotopes of cesium (e.g., ^{137}Cs), which accounted for approximately 90–98% of the external radiation dose accumulated over the subsequent decades of exposure (Mould 2000; UNSCEAR 2000; Vargo 2000). Radioiodine is estimated to have contributed approximately 50% of the internal radiation dose for children born in 1986 in the region and approximately 80% of the total radiation dose received during the first year after the release (Vargo 2000). Estimates of thyroid radiation doses have been derived from external thyroid gland scans that measure radiation (mostly gamma) from radioiodine in the thyroid. These measurements suggest that radioiodine doses to the thyroid gland were highest in small children at the time of the release, and were highest in locations nearest to the nuclear plant where people were not evacuated rapidly. The highest estimated doses were received within 30 km of the Chernobyl plant; median doses ranged from 2.3 Gy (230 rad) at age <1 year to 0.4 Gy (40 rad) in adolescents and adults (UNSCEAR 2000, Annex J, Table 22). Estimated median doses received in populations residing approximately 200 km from the plant (e.g., Mogilev region) were <0.3 Gy (30 rad) for all age groups

(UNSCEAR 2000). Although inhalation of airborne radioiodine is likely to have occurred after the accident, the major contributors to the absorbed thyroid radiation dose are thought to have been from ingestion of milk and leafy vegetables contaminated from atmospheric deposition of radioiodine. Ingestion of human breast milk is also considered to have been a major contributor to doses received by nursing infants. For example, it has been estimated that, in seven Ukraine cities, ingestion of ^{131}I contributed between 87 and 98% of total absorbed radiation dose (IAEA 1991). Endemic goiter in the Belarus population due to iodine deficiency (Gembicki et al. 1997) secondary to differences in the extent of use of stable iodine may have also contributed to the differences in the thyroid doses observed in Belarus compared to similarly contaminated areas of Finland.

Thyroid dose estimates, particularly peak dose rates, are largely based on extrapolations from thyroid gland ^{131}I measurements made within 1 to several weeks after the major release from the Chernobyl plant and ground monitoring of atmospheric deposition of radiocesium. One set of measurements of thyroid gland radioactivity came from postmortem measurements of thyroid glands from 416 people collected over the period from May 3 (8 days after the initial release) to August 4, 1986 in Bratislava (Beno et al. 1991). Back extrapolation of thyroid gland activities and consideration of temporal trends in both the thyroid gland data and atmospheric deposition allowed the estimation of transfer coefficients relating atmospheric deposition of radioiodine (kBq/m^2) and thyroid dose (μSv); the coefficients were 641 $\mu Sv/kBq\text{-}m^2$ in exposed children and 221 $\mu Sv/kBq\text{-}m^2$ in exposed adults (Beno et al. 1992). Based on this approach, and radiocesium measurements made in Belarus, thyroid radiation doses received in Belarus may have ranged from 0.12 to 24 μSv (12–2,400 rem) in children and from 0.04 to 8 μSv (4–800 rem) in adults (Bleuer et al. 1997). In Gomel, where the highest incidence of thyroid cancer in children has been reported, estimated doses were 1.2–12.3 Sv (120–1,230 rem) in children (Drobyshevskaya et al. 1996). Various other approaches have been used to estimate thyroid doses associated with the Chernobyl accident. In Ukraine, most of these rely on exposure estimates based on measured or assumed relationships between radioiodine and ^{137}Cs air levels, and models simulating pathways to humans, including milk ingestion (IIyin et al. 1990; Likhtarev et al. 1995). Estimates of absorbed thyroid doses from ^{131}I based on ^{137}Cs deposition densities in seven Ukraine cities ranged from 80 to 240 cGy (rad) in infants, 64–190 cGy (rad) in children, and 19–57 cGy (rad) in adults (IAEA 1991). Almost all of the internal radiation exposure of the thyroid gland was received in the first 3 months after the accident, during which time, the ^{131}I activity decreased to <0.1% of the initial values. The continued ^{129}I exposure can be considered minimal, although it will persist for several decades for some populations because of environmental contamination and its longer decay half-life.

Nevada Test Site. During the period 1951–1958, 97 atmospheric nuclear bomb tests were conducted at the Nevada Test Site (NTS) in southern Nevada (NCI 1997). These tests were followed by nine surface detonations during the period 1962–1968 and approximately 809 below-ground tests, of which 38 were determined to have resulted in off-site releases of radioactive materials. In response to a mandate from the U.S. Congress, a dose estimation methodology was developed by the National Cancer Institute (NCI 1997), which has enabled estimates of population radiation doses to the thyroid gland of representative persons in each of the approximately 3,100 counties of the United States, from direct and indirect (e.g., ingestion of cow milk) exposures to ^{131}I resulting from the NTS activities, for the purpose of health assessments and epidemiologic investigations (Gilbert et al. 1998). The NCI analysis utilized dose reconstruction methods developed earlier by the off-site Radiation Exposure Review Board Project (ORERP) (Ng et al. 1990). In addition, an epidemiologic study of thyroid disease in a Utah cohort was conducted (Kerber et al. 1993) using dosimetric methods described in Simon et al. (1990). 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 (NCI 1997; NRC 1999). The actual dose received by any individual depended on age of exposure, location, and milk consumption habits. A discussion of the uncertainties and limitations of these population dose estimates for use in epidemiology studies and risk assessment can be found in a review of the NCI (1997) dose estimations conducted by the Institute of Medicine and the National Research Council (NRC 1999).

Hanford Nuclear Site. The Hanford Nuclear Site in southeastern Washington reprocessed uranium to produce plutonium. Radioiodine was released to the atmosphere during the early years of operation of the facility. Approximately 740,000 Ci (27 PBq) of ^{131}I was estimated to have been released to the atmosphere during the period 1944–1957 (CDC 2002). Thyroid radiation doses have been estimated using a dosimetry model developed in the Hanford Environmental Dose Reconstruction Project (Shipler et al. 1996). The estimated mean thyroid radiation dose in a study cohort of 3,191 people who resided near the facility was 174 mGy (±224, standard deviation [SD]) (17.4±22.4 rad), with a range of 0.0029–2,823 mGy (0.00029–282 rad). Mean thyroid doses in females and males were similar; 177 mGy (17.7 rad) and 171 mGy (17.1 rad), respectively. Doses varied geographically, with the highest doses received by people who lived near and downwind from the site.

3.3.2.1 Death

Although radiation-related deaths were recorded among emergency response personnel on site during the Chernobyl accident, these deaths were associated with exposure to gamma radiation from molten fuel areas and not with exposure to radioiodine (see Section 3.2.2 for a more detailed discussion of the exposures from Chernobyl accident). Deaths related to thyroid cancers (or to other cancers or causes) following the accident continue to be studied and possible associations between mortality and radioiodine exposures may eventually become evident. In general, radiation-induced thyroid cancers tend to be papillary carcinomas; these types of tumors tend to be non-fatal (30-year mortality was estimated to be approximately 8% in adults (Mazafaferri and Jhiang 1994). However, papillary carcinomas that occur in young children, the predominant age group for thyroid cancers observed after the Chernobyl accident, are more fatal then when they occur in adults (Harach and Williams 1995).

The LOAEL values in humans for exposures by the oral route are presented in Table 3-1 and plotted in Figure 3-1.

3.3.2.2 Systemic Effects

The major systemic effects of exposures to radioiodine are on the thyroid gland; however, other systemic effects have been observed, including inflammation of the salivary glands (sialadentitis), following relatively high exposures to radioiodine such as those used for ablative treatment of thyroid cancers.

The highest NOAEL values and all reliable LOAEL values in each duration category for systemic (endocrine) effects from exposures by the oral route are presented in Table 3-1 and plotted in Figure 3-1.

Gastrointestinal Effects. The major systemic effects of exposures to radioiodine are on the thyroid gland; however, other systemic effects have been observed, including inflammation of the salivary glands (sialadentitis), following relatively high exposures to radioiodine such as those used for ablative treatment of thyroid cancers.

The highest NOAEL values and all reliable LOAEL values in each duration category for systemic (endocrine) effects from exposures by the oral route are presented in Table 3-1 and plotted in Figure 3-1.

Endocrine Effects.

Effects of Radioiodine on Thyroid Gland Function

Extensive clinical use of radioiodine, principally ^{123}I and ^{131}I, for diagnostic purposes and ^{131}I for treatment of thyrotoxicosis 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 and produces hypothyroidism at absorbed effective doses to the thyroid gland exceeding 2,500 rad (25 Gy). Thyroid gland doses of approximately 10,000-30,000 rad (300 Gy) can completely ablate the thyroid gland (Maxon and Saenger 2000). Cytotoxic doses of ^{131}I are delivered for 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). 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) (Cooper 2000). Current diagnostic uses of radioiodine involve much smaller exposures, typically 0.1–0.4 mCi (4–15 MBq) of ^{123}I or 0.005–0.01 mCi ^{131}I (0.2–0.4 MBq). These exposures correspond to approximate thyroid radiation doses of 1–5 rad (1–5 cGy) and 6–13 rad (6–13 cGy) for ^{123}I and ^{131}I, respectively (McDougall and Cavalieri 2000). However, historically, higher doses have been used for diagnostic procedures (e.g., Dickman et al. 2003; Hall et al. 1996).

Several epidemiological studies have examined the relationship between oral exposure to ^{131}I and thyroid gland nodularity. Thyroid nodules are irregular growths of the thyroid gland tissue that can be benign or cancerous. Nodules can be detected by physical palpation of the gland or by various imaging techniques. Palpation detects only larger (>1 cm) nodules, whereas ultrasound can detect nodules that are not palpable (e.g., 1 cm or less). The complete description of a study by Rallison (1996) and by Kerber et al. (1993) is provided in Section 3.3.2.7, as it primarily relates to thyroid neoplasms. The study reported no difference in prevalence of thyroid nodularity detected by physical examination in a cohort living near the NTS when compared to a nonexposed cohort living remote from the NTS (Rallison 1996). However, when the thyroid radiation dose from ^{131}I was calculated for each subject in each location, there was a correlation between radiation dose and formation of neoplasia of the thyroid, but not to nonneoplastic nodules (Kerber et al. 1993).

The Hall et al. (1996a) study evaluated 1,005 women for thyroid nodularity who had been exposed to diagnostic levels of ^{131}I during the period 1952–1977 and whose diagnosis for thyroid abnormalities were negative. The subjects were evaluated for palpable thyroid nodules during the period 1991–1992. A

comparison group consisted of 248 women who attended a mammography screening clinic with no prior history of exposure to ^{131}I or thyroid disease. The average total administered ^{131}I activity was 0.95 MBq (26 μCi). Absorbed radiation doses to the thyroid gland were estimated based on the administered activity and dosimetry tables from International Commission on Radiological Protection (ICRP 1988). The average dose was 0.54 Gy (54 rad) (10^{th}–90^{th} percentiles, 0.02–1.45 Gy; 2–145 rad). Thyroid nodules were detected in 107 of 1,005 (10.6%) exposed women and 29 of 248 (11.7%) nonexposed women. The relative risk (RR, based on odds ratios [ORs]) for thyroid nodularity for women exposed to ^{131}I was 0.9 (95% CI, 0.6–1.4) and was not statistically significant. A linear quadratic excess relative risk model revealed a statistically significant dose trend for thyroid nodularity (excess RR, 0.9/Gy). Hall et al. (1996a) suggest as an explanation for the lack of a significant RR for thyroid nodularity that the nonexposed control group was self-selected (i.e., the subjects voluntarily sought mammographic screening) and, therefore, may not have been an appropriate control group for comparison to the group of women who received radioiodine.

Clinical cases have been reported in which congenital hypothyroidism occurred after maternal exposures to high doses of ^{131}I during pregnancy for treatment of thyroid gland tumors (Green et al. 1971; Hamill et al. 1961; Jafek et al. 1974; Russell et al. 1957). However, the complex clinical picture and pharmacotherapy of the mothers for their thyroid condition during pregnancy makes direct associations between the radioiodine exposure and the clinical outcomes of the newborns highly uncertain. Exposures in these cases ranged from 11 to 77 mCi (0.4–2.8 GBq). Effects on the fetal and newborn thyroid would be expected if mothers received ablative doses of ^{131}I during pregnancy after approximately 12 weeks of gestation, when the fetal thyroid begins to take up iodide. A study of 73 infants and children born to 70 patients who received ^{131}I for ablative treatment of thyroid cancer 2–10 years (mean, 5.3 years) prior to pregnancy found no thyroid gland disorders (Casara et al. 1993). The maternal ^{131}I exposures ranged from 1.85 to 16.55 GBq (50–450 mCi); the mean exposure was 4.40 GBq (120 mCi). A similar finding was reported in a study of 37 patients (47 infants) who received ^{131}I, 1–60 months prior to conception (mean, 16.5 months); exposures ranged from 1.1 to 13.1 GBq (30–350 mCi), with a mean exposure of 3.67 GBq (100 mCi) (Lin et al. 1998).

Marshall Islands. Shortly after the BRAVO test, residents on three of the Marshall Islands were identified as having been exposed to external gamma radiation during the 2 days prior to their evacuation (Conard 1984): 64 residents of Rongelap (1.90 Gy, 190 rad), 18 residents of Ailingnae (1.10 Gy, 110 rad) and 150 residents of Utrik (0.11 Gy, 11 rad) (see Section 3.3.2 for a more detailed discussion of exposures from the Marshall Islands BRAVO test). Estimated total absorbed doses to the thyroid gland (external

and internal) were 3.3–20 Gy (330–2,000 rad) on Rongelap (highest doses in children), 1.3–4.5 Gy (130–450 rad) on Ailingnae, and 0.3–0.95 Gy (30–95 rad) on Utrik (Conard 1984). As part of a medical evaluation program, these individuals, the so-called BRAVO cohort, were evaluated periodically for health consequences of their exposures. Evidence of acute radiation sickness was prevalent early after exposures, including nausea and vomiting, hematological suppression, and dermal radiation burns. Cases of thyroid gland disorders began to be detected in the exposed population in 1964, 10 years after the exposure, particularly in exposed children; these included cases of apparent growth retardation, myxedema, and thyroid gland neoplasms (Conard et al. 1970). In 1981, when the children from Rongelap island were screened, it was discovered that 83% of the children who were <1 year of age at the time of the BRAVO test were found to have evidence of hypothyroidism (i.e., a serum concentration of TSH >5 mU/L). This group of children had received an estimated thyroid dose exceeding 1,500 rad (15 Gy). Prevalence of hypothyroidism and thyroid radiation dose decreased with exposure age: 25% for ages 2–10 years (800–1,500 rad, 8–15 Gy) and 9% for ages $10 years (335–800 rad, 3.35–8.00 Gy). Prevalences in the exposed groups from Ailignae were 8% for exposure ages >10 years (135–190 rad, 1.35–1.90 Gy) and 1% on Utrik (30–60 rad, 0.3–0.6 Gy). In an unexposed group (Rongelap residents who were not on the island at the time of the BRAVO test), the prevalence was 0.3–0.4% (Conard 1984). At about the same time, in 1964, cases of palpable thyroid gland nodules began to be identified in health screening programs (Conard 1984). The prevalence of thyroid nodularity had an age/dose profile similar to that of thyroid hypofunction (i.e., elevated serum TSH). In 1981, thyroid nodules were found in 77% Rongelap residents exposed before the age of 10 years and in 13% of those exposed after 10 years. Prevalence in the Ailingnae populations was 29% in the population of children exposed before age 10 years and 33% in the population exposed after age 10 years. In the Utrik population, the prevalence of thyroid nodules was 8% in the population of children exposed before age 10 years and 12% in the population exposed after age 10 years. The prevalence of thyroid gland carcinoma, mainly papillary carcinomas, also appeared to be elevated in the exposed Rongelap population (6%) compared to the unexposed group (1%). In 1994, thyroid ultrasound examinations were performed on 117 of the original exposure group, 47 from Rongelap, and 70 for Utrik, and 47 residents of Rongelap who were on Majuro at the time of the BRAVO test, approximately 480 miles south of the test site on Bikini Atoll (Howard et al. 1997). Over the period 1965–1990, the case rate for thyroid nodules was approximately 3–8% per year in the exposed groups and approximately 3 times greater in females than in males. However, the 1994 ultrasound evaluations found relatively high, but not significantly different, prevalences of thyroid nodules in exposed (12–33%) and nonexposed (25%) groups or between males and females (Howard et al. 1997). The differences in the outcomes in 1994 and earlier may reflect the age differences at the time of examination, or possibly that palpation detects only larger (>1 cm) nodules, whereas ultrasound can detect nodules that are not palpable

(e.g., ≤10 mm). Ultrasound is more likely to detect clinically insignificant *nodules* that are actually normal variants of thyroid tissue. Another possible contributor to the differences between outcomes is that earlier studies may have been biased by greater screening/surveillance intensity given to the high-dose groups, whereas the Howard et al. (1997) study was a more systematic comparison across the dose range and used a more objective ultrasound criteria for diagnosing nodularity. Thyroid nodule incidence is highly susceptible to surveillance effects and these studies were not adequately controlled for such effects. A possibly related observation is an apparent high prevalence of iodine deficiency in the Marshall Islands, which may have contributed to a high background prevalence of nodular goiter (Hermus and Huysmans 2000; Takahashi et al. 1999).

A retrospective cohort study reexamined the prevalence of thyroid gland nodularity reported in the 1980s among residents of the Marshall Islands who were potentially exposed to ^{131}I from atmospheric fallout from the BRAVO test in 1954 (Hamilton et al. 1987). This study included residents on islands located 112–589 miles from the test site. The cohort consisted of 7,266 people known to have been residents on the islands (or *in utero*) in 1954 at the time of the BRAVO test. Each subject was examined for palpable thyroid nodules during the period 1983–1985. The examiners were blind to the estimated thyroid radiation dose received by each subject. Radiation doses to the thyroid gland were estimated to have been 21 Gy (2,100 rad) for residents of Rongelap (120 miles from the test site) and 2.80 Gy (280 rad) for residents of Utrik (321 miles). Residents of 12 other islands, who historically were thought not to have received exposures to radioiodine based on location (distance and/or position with respect to prevailing winds), were included in the study. The age-adjusted prevalence of thyroid nodularity was 37% among residents of Rongelap Island and 10.3% for Utrik Island. Prevalence among residents of the other 12 islands ranged from 0.8 to 10.2% and there were no statistically significant differences in prevalence among these 12 less-exposed islands. A prevalence of 2.45% was assumed for nonexposed populations, based on observed prevalence in the two most southern islands (Ebon and Mili), for the purpose of calculating ORs. A logistic regression model yielded a statistically significant effect of sex on OR for thyroid nodularity, with an OR 3.7 times higher in females. The model also yielded a significant trend for decreasing prevalence of thyroid nodularity with both distance and direction from the test site, with prevalence decreasing 3-fold per 100 miles (OR, 0.3 per 100 miles) from the site and 2-fold for every 10 degrees east or west of the site (OR, 0.59 per 10 degrees). The risk estimate for thyroid nodularity among the Marshall Islanders was 1,100 excess cases/Gy/year of exposure per 1 million people (0.0011/person-Gy/year, 0.000011/person-rad/year).

A large-scale screening program for thyroid disease was conducted in the Marshall Islands during the period 1993–1997 (Fujimori et al. 1996; Takahashi et al. 1997, 1999, 2003). Results of screening of 1,322 residents of Ebeye (in the Kwajalein Atoll, approximately 190 miles from Bikini Atoll) are reported in Takahashi et al. (1997). Evaluations included neck palpation, thyroid ultrasound, and fine needle aspiration biopsy if warranted (results on diagnoses relevant to thyroid cancer are discussed in Section 3.3.1.7). The examiners were blind to the estimated thyroid radiation dose received by each subject. Among 815 subjects born before 1954, the date of the BRAVO test, 266 (32.6%) were diagnosed with thyroid nodules, 132 (16.2%) were palpable. The prevalence of thyroid nodules (palpable and detected by ultrasound) was higher in females than males; however, as was observed in the Hamilton et al. (1987) study, the difference was significant only for palpable nodules (palpable: females 17.7%, males 9.3%; total nodules: females 35.9%, males 21.0%). In either case, nodule prevalence was 2–3 times higher among groups born during the bomb testing period (before 1958) than after the testing ended. A logistic regression model applied to the nodule prevalence data revealed significant effects of sex, age, and distance from Bikini Atoll on nodule prevalence (Takahashi et al. 1997). A more recent report on the screening program described the results of thyroid palpation and ultrasound (7,721 subjects), tests of thyroid hormone (1,050 subjects), and iodine status (urinary iodide, 309 subjects) (Takahashi et al. 1999). The study group included 5,263 residents of Majuro (approximately 480 miles from Bikini Atoll), 1,610 residents from Ebeye Island (192 miles), and 348 residents from Mejit (398 miles). Of the 7,221 subjects examined in the study (1993–1997), 4,766 (66%) were of an age to have potential exposures to radioactive fallout from bomb tests. The prevalence of thyroid nodules (palpable and detected by ultrasound) was approximately 3 times higher in females than males; among females, the prevalence was highest (13%, 407 of 3,151) among women born before 1959, the date of the last bomb tests. Thyroid hormone tests (T_4, T_3, and TSH) revealed no evidence of an unusual prevalence of thyroid gland dysfunction. Measurements of urinary iodide levels suggested mild to severe iodine deficiency in the population; approximately 21% of the adult subjects had urinary iodides in the range of 22–45 nmol I/mmol creatinine (25–50 μg I/g creatinine). This corresponds to a urinary excretion rate and iodine intake rate of approximately 40–80 μg I/day (based on an assumed body weight of 60 kg). Thyroid volumes were compared in subjects who had nodules and were iodine deficient with subjects who were iodine sufficient and who did not have nodules. Although there was no apparent indication of excessive prevalence of thyroid enlargement in either the iodine-deficient or -sufficient groups, subjects who had the largest thyroid volumes tended to fall in the deficient-nodular group. Thyroid nodularity occurs in populations that have experienced prolonged iodine deficiency, although it is usually associated with goiter (Hermus and Huysmans 2000). The observation of a high prevalence of iodine deficiency in the Marshall Island population may be an important confounding variable in many of the epidemiology

studies that have attempted to explore relationships between thyroid nodularity and radiation dose in the Marshall Island populations.

Chernobyl Accident. Subsequent to the release of radioactive materials from the Chernobyl power plant in 1986, an increased prevalence of thyroid nodules in children of the Belarus region was reported (Astakhova et al. 1996) (see Section 3.3.2 for a more detailed discussion of exposures from of the Chernobyl accident). An analysis of the results of ultrasound screening of 20,785 people in Belarus conducted during the period 1990–1995 revealed a prevalence of thyroid gland nodules that ranged from 4 to 22 per 1,000. Prevalence was highest (16–22 per 1,000) among residents from districts in which thyroid radiation doses were estimated to have been above 1 Gy (1.3–1.6 Gy, 130–160 rad). Verified diagnoses from patients who were referred for further examination as a result of ultrasound results revealed a prevalence of thyroid cancer of 2.5–6.2 per 1,000, or approximately 13–50% of nodule cases, among cases from districts where thyroid radiation doses were estimated to have been above 1 Gy (1.3–1.6 Gy, 130–160 rad) (see Section 3.3.1.7 for further discussion of thyroid cancer related to the Chernobyl release). Adenoma was diagnosed in 7–12% of thyroid nodule cases, nodular goiter was diagnosed in 5–22% of the thyroid nodule cases, and 7–64% of the nodule cases were diagnosed as benign cysts. In districts in which thyroid doses were estimated to have been <0.1 Gy, benign cysts predominated the diagnoses, with no thyroid cancers; approximately 0–25% were diagnosed as adenomas, 0–8% as nodular goiter, and 75–100% as benign cysts (predominantly cystic-dystropic types of goiter). Dietary iodine status was assessed from measurements of urinary iodine (Astakhova et al. 1996). Urinary iodide levels varied across regions in Belarus. Approximately 30–80% (mean 61%) of children and adolescents had overnight urinary iodine concentrations <100 µg/L, 10–50% (mean 26%) had concentrations <50 µg/L, and 0–25% (mean 9%) had concentrations <20 µg/L. These results suggest a substantial prevalence (on average 26 and 50% in some districts) of dietary iodine intakes below 50–70 µg/day (assuming a daily urine output of 1–1.4 L in children and adolescents). More recent measurements (made in 2000) suggest that dietary iodide deficiency in Belarus appears to have persisted since the Chernobyl accident (Ishigaki et al. 2001). The results of other thyroid screening programs (e.g., the Chernobyl Sasakawa Health and Medical Cooperation Project) also suggest a high prevalence of goiter among people born in Belarus between the years 1976 and 1986, which would be consistent with a high prevalence of iodine deficiency in the population (UNSCEAR 2000). Therefore, iodine deficiency may have contributed to the observed thyroid nodularity and also may be a confounding variable in susceptibility to thyroid cancer (Gembicki et al. 1997; Robbins et al. 2001).

Hanford Nuclear Site. The CDC (2002) has conducted a follow-up prevalence study of thyroid disease in populations that resided near the Hanford Nuclear Site in southeastern Washington during the period 1944–1957 (see Section 3.3.2 for a more detailed discussion of releases from the Hanford Nuclear Site). The study included 3,441 subjects who were born during the period 1940–1946 in counties surrounding the Hanford Nuclear Site. Thyroid disease was assessed from a clinical evaluation of each subject, which included assessments of ultrasound or palpable thyroid nodules, thyroid hormone status, thyroid autoimmunity, and parathyroid hormone status. Historical information on thyroid disease and information on radiation exposures were obtained by interviews and, when possible, review of medical records of participants. Thyroid radiation doses were estimated using a dosimetry model developed in the Hanford Environmental Dose Reconstruction Project. Information on residence history and relevant food consumption patterns (e.g., milk consumption, breast feeding, consumption of locally harvested produce) for each study participant was obtained by interview. The estimated mean thyroid radiation dose, based on 91 participants, was 174 mGy (±224, standard deviation [SD]) (17.4±22.4 rad), and the range was 0.0029–2,823 mGy (0.00029–282 rad). An indication that the statistical power of the study was appreciably limited by the low distribution of thyroid doses is the fact that only 24 (0.8%) of the study population had estimated thyroid doses >1 Gy (100 rad) and only 7 (0.2%) had doses >2 Gy (200 rad). Doses varied geographically, with the highest doses received by people who lived near and downwind from the site. Health outcomes investigated included thyroid carcinoma, thyroid nodules, hypothyroidism, and hyperthyroidism (serum TSH levels), including Graves' disease, thyroid autoimmunity (serum antimicrosomal antibodies and antithyroid peroxidase), goiter, and hyperparathyroidism. Dose-response relationships were assessed using a linear regression model with adjustments for the following confounding and effect modifying variables: sex, age of first exposure, age of evaluation, ethnicity, smoking, and potential exposures from Nevada Test Site releases. Alternatives to the linear model, including linear quadratic and logistic models, were also explored. Incidence of thyroid disease was found to be unrelated to thyroid radioiodine dose for all outcomes evaluated (dose coefficients not significantly different from zero). Estimated dose coefficients, based on the linear model, were: thyroid cancer, 0.002±0.004 per Gy (CI: <-0.001–0.017, p=0.25, 20 cases, 0.6% prevalence); thyroid nodules (of any type), -0.007±0.016 per Gy (CI: <-0.023–0.043, p=0.65, 281 cases, 8.2%); hypothyroidism, -0.006±0.019 per Gy (CI: -0.016–0.047, p=0.61, 267 cases, 7.8%); hyperthyroidism, 0.011±0.015 per Gy (CI: <-0.008–0.052, p=0.22, 161 cases, 4.7%); thyroid autoimmunity, -0.024±0.027 per Gy (CI:<-0.058–0.048, p=0.8, 659 cases, 19.2%); goiter, -0.001±0.008 (95% upper CL: 0.012, p=0.74, 14 cases, 0.4%); hyperparathyroidism, -0.000±0.018 per Gy (95% upper CL: 0.013, p=0.61, 14 cases, 0.4%).

The CDC (2002) study was reviewed by the National Academy of Sciences (NAS 2000), which identified several sources of uncertainty in the study that need to be considered in interpreting the reported results. In particular, reliance on modeling thyroid radiation doses, based on environmental transfer coefficients, rather than direct measurements (which was not possible) may have introduced substantial uncertainty in the risk estimates, that may have been underestimated in the study. In particular, the NAS pointed out that the study utilized a transfer coefficient for radioiodine from cows to cow milk that was approximately twice that estimated from other studies. This could have contributed to an overestimate of thyroid doses in infants and children, and a lower statistical power of the study. Also, the study utilized survey information on the sources and amounts of milk consumed that was collected 40–50 years after the period of interest. Large uncertainties in estimates of these model parameters may have also decreased the statistical power of the study. Loss of power is particularly important in interpreting the generally negative findings of the study.

Effects of Radioiodine on the Parathyroid Gland

Cases of hypo- and hyperparathyroidism are rare outcomes in patients who receive ^{131}I treatments for ablative therapy of thyroid cancer or hyperthyroidism. The parathyroid gland is in close proximity to the thyroid gland. Although in most people, the parathyroid and thyroid glands are separated by more than 1 cm, in approximately 20% of people, the parathyroid gland is located within the thyroid gland capsule (Glazebrook 1987). The latter configuration would result in irradiation of the parathyroid gland with β emission from ^{131}I concentrated in the thyroid gland; β emission from ^{131}I has a tissue penetration distance of approximately 0.5–2 mm (Esselstyn et al. 1982). Cases of parathyroid dysfunction have been reported after exposures to ^{131}I ranging from 4 to 30 mCi (0.15–1.1 GBq) (Better et al. 1969; Burch and Posillico 1983; Eipe et al. 1968; Esselstyn et al. 1982; Fjälling et al. 1983; Freeman et al. 1969; Glazebrook 1987; Jialal et al. 1980; Rosen et al. 1984). A clinical follow-up study evaluated serum calcium status of 125 patients (106 females, 19 males) who received ^{131}I for treatment of hyperthyroidism during the period 1951–1960. The follow-up assessments occurred 16–26 years (mean, 21 years) after exposure to ^{131}I (Fjälling et al. 1983). A group of age- and sex-matched healthy subjects who had no history of irradiation to the head or neck region served as a control group. Exposures to ^{131}I ranged from 75 to 1,400 MBq (2–38 mCi). These corresponded to radiation doses to the parathyroid of 2–5 Gy in subjects whose parathyroid gland was 0.2 cm from the surface of the thyroid gland and 3–7.5 Gy in subjects whose parathyroid gland was at the surface of the thyroid gland. Two patients and two control subjects were found to have hypercalcemia and verified hyperparathyroidism (the exact basis for the verification was not reported). The ^{131}I exposures of the two patients were 140 and 450 MBq (3.8 and 12 mCi), respectively.

Hanford Nuclear Site. Hyperparathyroidism was assessed as part of the CDC (2002) study of health outcomes related to radioiodine releases from the Hanford Nuclear Site (see Section 3.3.2 for a more detailed discussion of releases from the Hanford Nuclear Site). The study included 3,441 subjects who were born during the period 1940–1946 in counties surrounding the site. Parathyroid hormone status was assessed from measurements of serum parathyroid hormone. Historical information on parathyroid disease was obtained by interviews and, when possible, review of medical records of participants. The estimated mean thyroid radiation dose, based on 91 participants, was 174 mGy (±224, standard deviation [SD]) (17.4±22.4 rad), and the range was 0.00029–2,823 mGy (0.002.9–282 rad). Dose-response relationships were assessed using a linear regression model with adjustments for the following confounding and effect modifying variables: sex, age of first exposure, age of evaluation, ethnicity, smoking, and potential exposures from Nevada Test Site releases. Incidence of hyperparathyroidism was found to be unrelated to thyroid radioiodine dose (dose coefficients were not significantly different from zero). Estimated dose coefficients based on the liner model were -0.000±0.018 per Gy (95% upper CL: 0.013, p=0.61) based on 14 cases (0.4% prevalence). Incidence of hyperparathyroidism was found to be unrelated to thyroid radioiodine dose. Uncertainties in the dose estimates for the cases need to be considered in interpreting these results.

Effects of Radioiodine on Testicular Endocrine Function

High exposures to ^{131}I may affect testicular endocrine function. Studies relevant to these end points (Wichers et al. 2000) are described in Section 3.3.2.5 (Reproductive Effects).

3.3.2.3 Immunological and Lymphoreticular Effects

Information on immunological effects of oral exposure to radioiodine in humans relates to thyroid gland autoimmunity. The highest NOAEL values and all reliable LOAEL values in each duration category for immunological and lymphoreticular effects from exposures by the oral route are presented in Table 3-1 and plotted in Figure 3-1.

Cases of autoimmune hyperthyroidism after exposures to ^{131}I for ablative treatment of hyperthyroidism have been reported. In three cases, thyrotoxicosis developed with serum antibodies to TSH receptor 3–6 months after the patients received oral treatments with 40–86 mCi ^{131}I (1.5–3.2 GBq) for reduction of

nontoxic goiter that was compressing the trachea (Huysmans et al. 1997a). Prior to the ^{131}I treatments, the patients were euthyroid and had no detectable TSH antibodies.

Marshall Islands. Large 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 nuclear bombs during the period 1946–1958 (see Section 3.3.1.2, Endocrine, for a more complete description of these studies) (see Section 3.3.2 for a more detailed discussion of exposures from the Marshall Islands BRAVO test). In a thyroid screening program conducted during the period 1993–1997, 7,721 subjects were evaluated for various end points of thyroid size, nodularity, and function (Fujimori et al. 1996, Takahashi et al. 1997, 1999). Antithyroglobulin antibodies in serum were detected in 67 of 2,700 (2.5%) subjects examined (Fujimori et al. 1996). Although this prevalence is unremarkable compared to that found in other populations (10% in healthy adults) (Marcocci and Chiovata 2000; Takahashi et al. 1999), a statistical comparison with an appropriate referent population was not conducted. Furthermore, no attempt was made in this study to assess the relationship between antibody levels and radioiodine exposure.

Chernobyl Accident. A study that compared thyroid cancers in Belarus and Ukraine diagnosed after the Chernobyl releases with those diagnosed in Italy and France during the same time period found that the Belarus-Ukraine cases had a higher incidence of thyroid autoimmunity (i.e., elevated antithyroid peroxidase and thyroglobulin antibodies) than the Italy-France cases (Pacini et al. 1997) (see Section 3.3.2 for a more detailed discussion of exposures from of the Chernobyl accident). It is unclear to what extent the autoimmunity may be related to the exposures to radioiodine. Serum antithyroglobulin antibody titres were measured in 53 children ages 7–14 years (in 1993–1994) who received 0.4–3.2 Gy (40–320 rad) as a result of the Chernobyl release (Chernyshov et al. 1998). Antibody titres were detected in 80.6% of exposed children compared to 16.7% of a reference group that had no estimated exposure to ^{131}I, and there was a significant positive correlation between antibody titre and estimated thyroid ^{131}I dose. These results suggest a possible contribution of thyroid radioiodine exposure to thyroid autoimmunity. Other screening programs conducted in Belarus have not found relationships between thyroid autoimmunity and radiation exposure, as assessed by ^{137}Cs soil levels or body ^{137}Cs levels (UNSCEAR 2000). One of the largest programs, the Chernobyl Sasakawa Health and Medical cooperation project (1991–1996), conducted thyroid examinations, including serum antithyroperoxidase and antithyroglobulin measurements, on approximately 160,000 children who were <10 years old at the time of the accident. No association between body or soil ^{137}Cs activity and thyroid antibody levels was observed in an analysis of this screening program (UNSCEAR 2000, Annex J).

Hanford Nuclear Site. Thyroid autoimmunity was assessed as part of the CDC (2002) study of health outcomes related to radioiodine releases from the Hanford Nuclear Site (see Section 3.3.2 for a more detailed discussion of releases from the Hanford Nuclear Site). The study included 3,441 subjects who were born during the period 1940–1946 in counties surrounding the site. Thyroid autoimmunity was assessed from measurements of serum antimicrosomal antibody and antithyroid peroxidase. Historical information on thyroid disease, including autoimmunity and related disorders (e.g., Graves' disease), was obtained by interviews and, when possible, review of medical records of participants. The estimated mean thyroid radiation dose in a population of 3,191 people who resided near the facility was 174 mGy (±224, standard deviation [SD]) (17.4±22.4 rad), and the range was 0.0029–2,823 mGy (0.00029–282 rad). Dose-response relationships were assessed using a linear regression model with adjustments for the following confounding and effect modifying variables: sex, age of first exposure, age of evaluation, ethnicity, smoking, and potential exposures from Nevada Test Site releases. Incidence of thyroid autoimmunity was found to be unrelated to thyroid radioiodine dose (dose coefficients were not significantly difference from zero). Estimated dose coefficients, based on the linear model, were -0.024±0.027 per Gy (CI: <-0.058–0.048, p=0.8) based on 659 cases (19.2% prevalence). Alternatives to the linear model including linear quadratic and logistic models were also explored.

Uncertainties in the dose estimation methodology used in this study have been discussed in NAS (2000). Major sources of uncertainty derived from the reliance on modeling thyroid radiation doses, based on environmental transfer coefficients, rather than direct measurements. In particular, the NAS pointed out that the study utilized a transfer coefficient for radioiodine from cows to cow milk that was approximately twice that estimated from other studies. This could have contributed to an overestimate of thyroid doses in infants and children, and a lower statistical power of the study. Also, the study utilized survey information on the sources and amounts of milk consumed that was collected 40–50 years after the period of interest. Large uncertainties in estimates of these model parameters may have also decreased the statistical power of the study. Loss of power is particularly important in interpreting the generally negative findings of the study.

3.3.2.4 Neurological Effects

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. An example is a case of severe hypothyroidism with

neurological sequellae that developed at age 8 months in an infant whose mother received 99 mCi (3.7 GBq) of ^{131}I during her 6th week of pregnancy (Goh 1981).

3.3.2.5 Reproductive Effects

A clinical study of the outcomes of 70 pregnancies in patients who received ^{131}I for ablative treatment of thyroid cancer 2–10 years (mean, 5.3 years) prior to pregnancy revealed only two spontaneous abortions (Casara et al. 1993). The maternal ^{131}I exposures ranged from 1.85 to 16.55 GBq (50–450 mCi); the mean exposure was 4.40 GBq (120 mCi). Maternal gonadal radiation doses ranged from 11 to 20 cGy (11–20 rad). In a similar study, 37 patients received ^{131}I prior to conception (mean, 16.5 months prior to conception; range 1–60 months); at exposures ranging from 1.1 to 13.1 GBq (30–350 mCi) with a mean exposure of 3.67 GBq (100 mCi) (Lin et al. 1998); of 58 pregnancies reported, there were 8 spontaneous abortions and 2 threatened abortions. In a retrospective review of pregnancy outcomes of 154 women who received ablative ^{131}I therapy for thyroid cancer, two cases of infertility occurred in 35 patients who attempted to conceive (Smith et al. 1994). The ^{131}I exposure range was 77–250 mCi (2.8–9.2 GBq) with a mean exposure of 148 mCi (5.5 GBq). The above studies did not have control comparison groups.

The ATSDR (2000a) conducted a retrospective analysis of pregnancy outcomes (pre-term birth rates, fetal death) and infant deaths among residents who lived near the Hanford Nuclear Site (see Section 3.3.2 for a more detailed discussion of releases from the Hanford Nuclear Site). The study reviewed records of outcomes of 72,154 births, 1,957 infant deaths, and 1,045 fetal deaths that occurred in Washington counties dear the Hanford Nuclear Site during the period 1940–1952. Subjects were assigned to one of four exposure categories based on the subject's address (zip code) at the time of the subject birth or infant death, and estimated ^{131}I exposures in 1945 in those areas were obtained from the Hanford Environmental Dose Reconstruction (HEDR) project (CDC 2002). The exposure categories were: *low*, #50th percentile of the 1945 HEDR estimate for the entire study area; *medium low*, >50th percentile and <75th percentile; *medium high*, ≥75th percentile and # 90th percentile; and *high*, >90th percentile (radioiodine doses associated with these percentiles are not reported in CDC 2002). Associations between ^{131}I exposure and outcomes were evaluated in a multivariate logistic regression model. Co-variates that were explored included sex of infant, age of mother, race of mother, occupation of father, and history of previous pregnancies, stillbirths, or infant mortality. Models were evaluated for outcomes recorded for 1945, the year in which exposures were estimated to be the highest, and also for the period May 1, 1945–April 30, 1946, which could have included exposures to the highest levels during early pregnancy. The adjusted odds ratios (low-exposure as the reference) for infant death for the high-exposure category were 1.1

(95% CI, 0.7–1.8) for the year 1945 and 1.3 (CI, 0.8–2.1) for the 1945–1946 period. The adjusted ORs for fetal death for the high-exposure category were 0.6 (CI, 0.2–1.6) for the year 1945 and 0.7 (CI, 0.3–1.7) for the 1945–1946 period. These results suggest that neither infant nor fetal death were significantly associated with estimated ^{131}I exposures. The adjusted odds ratios for preterm birth for the high-exposure category were 1.6 (CI, 1.0–2.6) for the year 1945 and 1.9 (CI, 1.2–3.0) for the 1945–1946 period, suggesting a possible association between preterm birth and ^{131}I exposures.

An assessment of uncertainties in the CDC (2002) study is provided in NAS (2000). Major sources of uncertainty derived from the reliance on modeling thyroid radiation doses, based on environmental transfer coefficients, rather than direct measurements, use of a relatively high value for the transfer coefficient for radioiodine from cows to cow milk, and reliance on survey information on the sources and amounts of milk consumed that was collected 40–50 years after the period of interest. Large uncertainties in estimates of these model parameters may have decreased the statistical power of the study. Loss of power is particularly important in interpreting the negative findings of the study.

A retrospective analysis was conducted to evaluate pregnancy health and reproductive outcomes of women who were exposed to radiation resulting from releases from the Chernobyl nuclear power plant, including a major contribution from ^{131}I (Petrova et al. 1997) (see Section 3.3.2 for a more detailed discussion of exposures from the Chernobyl accident). Interpretation of the results of this study, in terms of the contribution of radioiodine to the outcomes, is highly uncertain, as other factors could have affected the outcomes, including exposure to other forms of radiation, nutrition, or other chemical exposures. Nevertheless, because it is one of the only large-scale epidemiological studies that has focused on reproductive and developmental outcomes, and because of the substantial contribution that radioiodine made to radiation exposures after the Chernobyl releases, a brief description of the study is presented here. In the retrospective analysis, clinical records on 755,297 pregnancies that occurred in Belarus during the period 1982–1990 were evaluated. Approximately half of the women resided in Gomel and Mogilev, two districts that were relatively heavily contaminated with radioiodine and other radionuclides, and approximately half of the women lived in two relatively lightly contaminated areas, Brest and Vitebsk. Three categories of outcomes were evaluated: pregnancy outcome, including stillbirths, low birth weight, and neonatal or postneonatal mortality; maternal morbidity; and infant health, including intrauterine hypoxia, perinatal infection, respiratory disorders, and congenital anomalies. Annual incidence of maternal anemia, renal insufficiency (elevated serum BUN and creatinine), and toxemia appeared to increase more sharply in the heavily contaminated districts after 1986, the year of the Chernobyl releases (a statistical analysis of trend was not reported). Incidence of congenital

abnormalities and neonatal respiratory disorders also appeared to increase more sharply in the heavily contaminated districts after 1986 (no statistical analysis of trend was reported). Fetal death rates appeared to increase or not decline in contaminated districts to the same extent as in less contaminated districts.

A cohort study was conducted as part of this retrospective analysis (Petrova et al. 1997). Health records on 757 infants and their mothers who resided in radiation-contaminated or relatively uncontaminated areas of Belarus were analyzed. The prevalence of maternal toxemia was 4–5 times greater among women who resided in contaminated areas (25–30%) compared to women from the control areas. The prevalence of atopic dermatitis in infants who resided in contaminated areas was approximately 2 times higher (approximately 40%) compared to infants from control areas. The prevalence of anemia (low blood hemoglobin levels) was 6–7 times higher in infants from contaminated areas (18–20%). The contribution of radioiodine to the observed outcomes is highly uncertain as other factors could have affected the outcomes, including exposure to other forms of radiation, nutrition, or other chemical exposures.

Clinical cases of impaired testicular function have been reported following oral exposures to ^{131}I for ablative treatment of thyroid cancer (Ahmed and Shalet 1985; Handelsman and Turtle 1983; Pacini et al. 1994). Effects observed included low sperm counts, azospermia (absence of spermatozoa), and elevated serum concentrations of follicle stimulating hormone (FSH), which persisted for more than 2 years of follow-up. Exposures to radioiodine ranged from 50 to 540 mCi (1.8–20 GBq). A study of 103 patients who received ^{131}I treatments for thyroid cancer found low sperm counts and elevated serum FSH concentrations in some patients when examined 10–243 months after treatment (mean, 94 months) (Pacini et al. 1994). Exposures to radioiodine ranged from 30 to 1,335 mCi (1.1–49.4 GBq) with a mean exposure of 167 mCi (6.2 GBq).

Wichers et al. (2000) examined testicular endocrine function in 25 patients before and after they received ^{131}I for ablative treatment of thyroid carcinoma. The mean cumulative exposure was 9.8"0.89 GBq (260 mCi). Serum concentrations of follicle stimulating hormone (FSH), luteinising hormone (LH), inhibin B, and testosterone were significantly different from pre-exposure levels. Increases in FSH (300%) and LH (100%), and decrease in inhibin B concentrations (88%) showed similar temporal patterns, with peak responses 3–6 months after exposure and a return to pre-exposure levels within 18 months following exposure. Peak levels of FSH (21 UU/L) exceeded the upper limit of the normal range (1.8–9.2 IU/L) and the lowest post-exposure levels of inhibin B (22 pg/mL) were below the lower limit of the normal range (75-350 pg/mL). Serum concentrations of LH remained within the normal

range (1.6–9.2 IU/L). Serum concentrations of testosterone were significantly higher (50%) than pre-exposure levels 12 and 18 months after exposure; however, concentrations remained within the normal range (10.4–34.7 nmol/L). These results suggest that exposures to high levels of ^{131}I may affect testicular endocrine function. A major limitation of this study is the lack of observations in a set of controls who underwent thyroidectomy but who were not exposed to ^{131}I.

The highest NOAEL values and all reliable LOAEL values in each duration category for reproductive effects from exposures by the oral route are presented in Table 3-2 and plotted in Figure 3-2.

3.3.2.6 Developmental Effects

A clinical study of the outcomes of 70 pregnancies in patients who received ^{131}I for ablative treatment of thyroid cancer 2–10 years (mean, 5.3 years) prior to pregnancy revealed only two spontaneous abortions (Casara et al. 1993). Of 73 infants born to the patients, one was diagnosed with tetrology of Fallot's (pulmonic stenosis, atrial septal defect, and right ventricular hypertrophy) and the two other infants had low birth weights with subsequent normal growth rates. The maternal ^{131}I exposures ranged from 1.85 to 16.55 GBq (50–450 mCi); the mean exposure was 4.40 GBq (120 mCi). Maternal gonadal radiation doses ranged from 11 to 20 cGy (11–20 rad). A similar study was reported of 37 patients who received ^{131}I 1–60 months prior to conception (mean, 16.5 months); exposures ranged from 1.1 to 13.1 GBq (30–350 mCi) with a mean exposure to 3.67 GBq (100 mCi) (Lin et al. 1998); of 58 pregnancies reported, there were 8 spontaneous abortions and 2 threatened abortions. Birth weights of newborns of women who received ^{131}I were not different from newborns of maternal age-matched controls who did not receive ^{131}I and who were not thyroid cancer patients. A retrospective review of pregnancy outcomes of women who received ablative ^{131}I therapy for thyroid cancer found 3 spontaneous abortions and 4 premature deliveries out of 67 pregnancies in 32 patients (Smith et al. 1994). Two infants were born within 1 year of the maternal ^{131}I therapy and both died of congenital abnormalities; severe hypoparathyroidism and hypothyroidism in one case, and Down's syndrome and cardiac anomalies in the second case. The ^{131}I exposure range was 77–250 mCi (2.8–9.2 GBq) with a mean exposure of 148 mCi (5.5 GBq). Goh (1981) reported a case of cretinism that developed at age 8 months in an infant whose mother received 99 mCi (3.7 GBq) of ^{131}I during her 6th week of pregnancy.

ATSDR (2000b) conducted a retrospective analysis of pregnancy outcomes (pre-term birth rates, fetal death) and infant deaths among residents who lived near the Hanford Nuclear Site (see discussion of Reproductive Effects of Radioactive Iodine for a more detailed description of this study and Section 3.3.2

Table 3-2 Levels of Significant Exposure to Iodine - Radiation Toxicity - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL			Reference Chemical Form
					Less Serious (rad)		Serious (rad)	
	ACUTE EXPOSURE							
	Systemic							
1	Human		Endocr			145	(thyroid gland nodularity)	Astakhova et al. 1996 131 I
2	Human		Endocr			325	(thyroid gland nodularity)	Conard 1984 131 I
3	Human		Endocr			2000	(thyroid gland nodularity)	Hamilton et al. 1987 131 I
4	Human		Endocr			180	(thyroid gland nodularity)	Pacini et al. 1997 131 I
	Cancer							
5	Human					30	(thyroid cancer)	Astakhova et al. 1998 131 I
6	Human					30	(thyroid cancer)	Drobyshevskaya et al. 1996 131 I
7	Human	(F)				5	(kidney and liver cancer)	Holm et al. 1991 131 I

Table 3-2 Levels of Significant Exposure to Iodine - Radiation Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL				Reference Chemical Form
					Less Serious (rad)		Serious (rad)		
8	Human	(F)					6000	(thyroid cancer)	Ron et al. 1998 131 I
9	Human						20	(thyroid cancer)	Tronko et al. 1996 131 I
	CHRONIC EXPOSURE								
	Systemic								
10	Human	(F)	Endocr	17					CDC 2002 131 I
	Cancer								
11	Human	(F)					9	(thyroid neoplasm)	Gilbert et al. 1998 131 I
12	Human	(F)					325	(thyroid neoplasm)	Kerber et al. 1993 131 I
13	Human	(F)					25	(thyroid neoplasm)	Rallison 1996 131 I

a the number corresponds to entries in Figure 3-2.

Endocr = endocrine; (f) = feed; LOAEL = lowest-observed-adverse-effect level

Figure 3-2. Levels of Significant Exposure to Iodine - Radiation Toxicity - Oral

Acute (≤14 days)

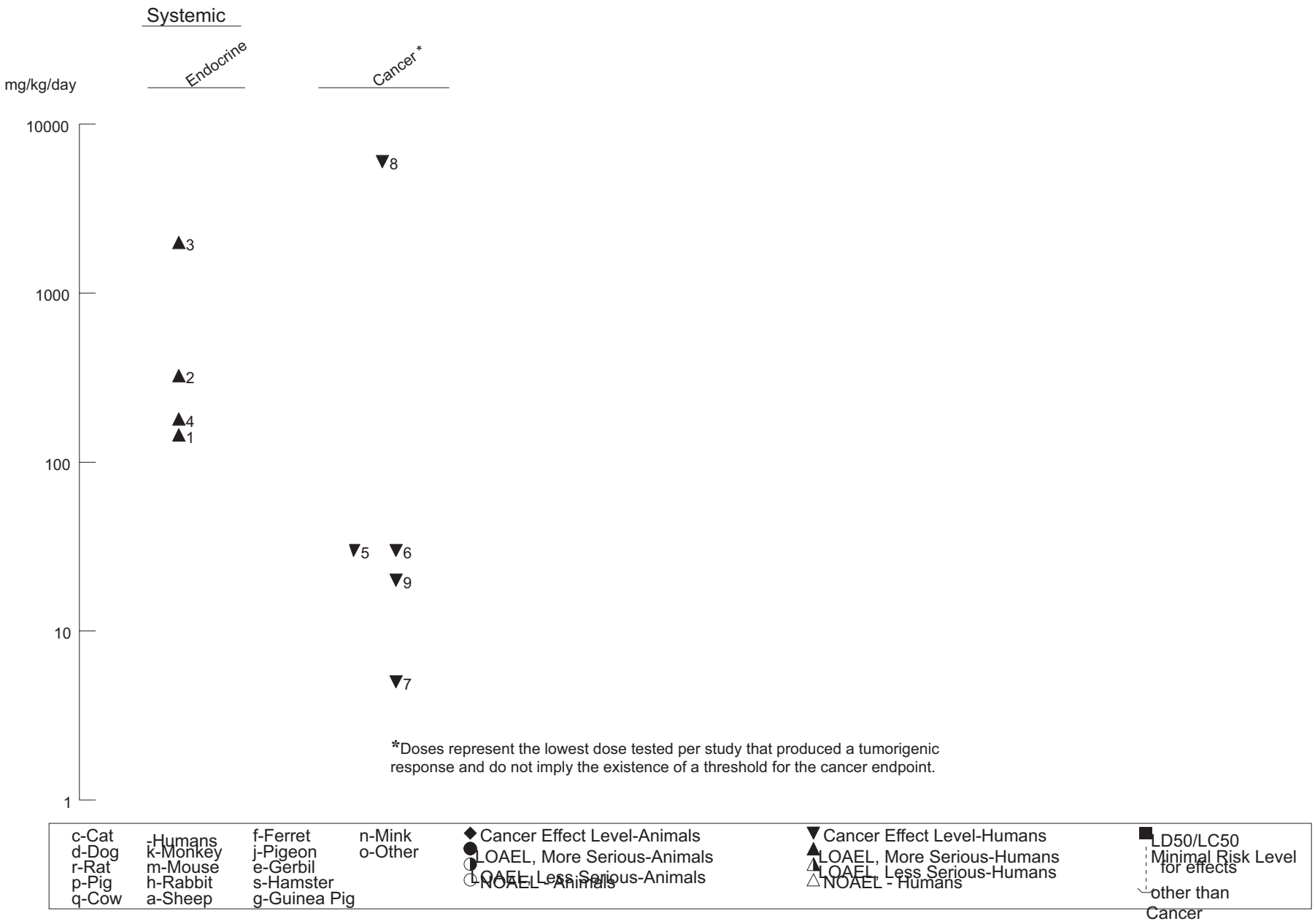
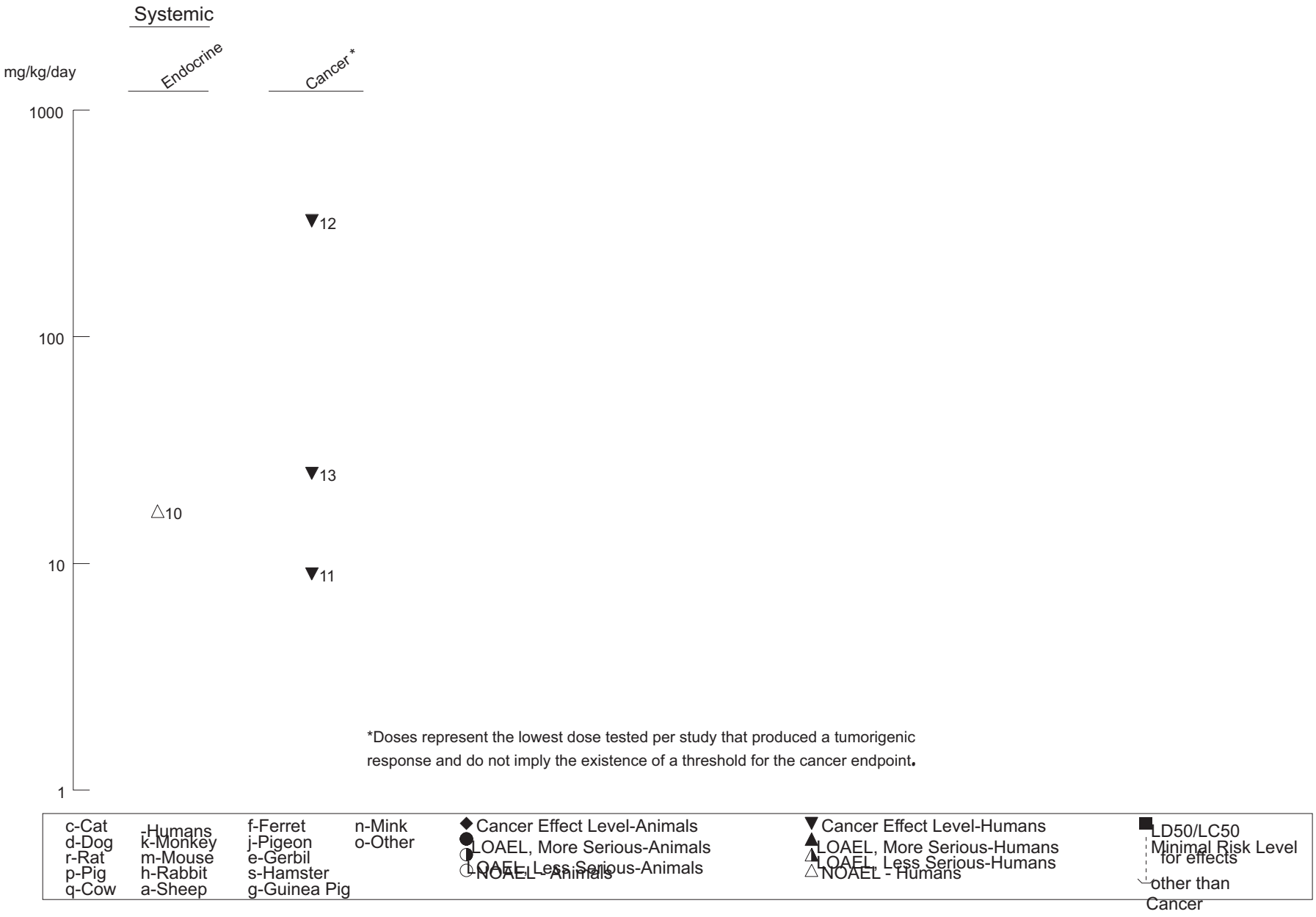


Figure 3-2. Levels of Significant Exposure to Iodine - Radiation Toxicity - Oral (*Continued*)

Chronic (≥365 days)



for a more detailed discussion of releases from the Hanford Nuclear Site). The study reviewed records of outcomes of 72,154 births, 1,957 infant deaths, and 1,045 fetal deaths that occurred in Washington counties dear the Hanford Nuclear Site during the period 1940–1952. Subjects were assigned to one of four exposure categories (low, medium low, medium high, high) based on the subject's address (zip code) at the time of the subject birth or infant death, and estimated ^{131}I exposures in 1945 in those areas were obtained from the Hanford Environmental Dose Reconstruction (HEDR) project (CDC 2002). Associations between ^{131}I exposure and outcomes were evaluated in a multivariate logistic regression model. Models were evaluated for outcomes recorded for 1945, the year in which exposures were estimated to be the highest, and also for the period May 1, 1945–April 30, 1946, which could have included exposures to the highest levels during early pregnancy. The adjusted odds ratios (low-exposure as the reference) for infant death for the high-exposure category were 1.1 (95% CI, 0.7–1.8) for the year 1945 and 1.3 (CI: 0.8–2.1) for the 1945–1946 period. The adjusted odds ratios for fetal death for the high-exposure category were 0.6 (CI: 0.2–1.6) for the year 1945 and 0.7 (CI: 0.3–1.7) for the 1945–1946 period. These results suggest that neither infant nor fetal death were significantly associated with estimated ^{131}I exposures. The adjusted odds ratios for preterm birth for the high-exposure category were 1.6 (1.0–2.6) for the year 1945 and 1.9 (1.2–3.0) for the 1945–1946 period, suggesting a possible association between preterm birth and ^{131}I exposures.

One epidemiological study has examined health outcomes of infants of mothers who resided in the Belarus region before or after the Chernobyl accident (Petrova et al. 1997) (see Section 3.3.2 for a more detailed discussion of exposures from of the Chernobyl accident). Interpretation of the results of this study, in terms of the contribution of radioiodine to the outcomes, is highly uncertain, as other factors could have affected the outcomes, including exposure to other forms of radiation, nutrition, or other chemical exposures. Nevertheless, because it is the only epidemiological study that has focused on reproductive and developmental outcomes, and because of the substantial contribution that radioiodine made to radiation exposures after the Chernobyl releases, a brief description of the study is presented here. As part of a retrospective cohort study, health records were analyzed on 757 infants and their mothers who resided in heavily radiation-contaminated areas of Belarus resulting from radionuclide releases from the Chernobyl nuclear power plant or relatively uncontaminated areas (Petrova et al. 1997). Prevalence of atopic dermatitis in infants who resided in contaminated areas was approximately 2 times higher (approximately 40%) compared to infants from control areas. The prevalence of anemia (low blood hemoglobin levels) was 6–7 times higher in infants from contaminated areas (18–20%). Interpretation of the results of this study, in terms of the contribution of radioiodine, to the outcomes, is

highly uncertain, as other factors could have affected the outcomes, including exposure to other forms of radiation, nutrition, or other chemical exposures.

The highest NOAEL values and all reliable LOAEL values in each duration category for developmental effects from exposures by the oral route are presented in Table 3-2 and plotted in Figure 3-2.

3.3.2.7 Cancer

Cancer effect levels (CELs) for iodine exposures by the oral route are presented in Table 3-2 and plotted in Figure 3-2.

The thyroid gland receives the highest radiation dose of any organ or tissue following an internal exposure to radioiodine (see Section 3.5, Toxicokinetics) and, therefore, cancer of the thyroid gland is the major health concern associated with radioiodine exposures. Children, in particular, are highly vulnerable to radioiodine toxicity. Cancer morbidity and mortality among populations that received exposures to radioiodine have been examined in several large-scale 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 (Table 3-3): (1) exposure to high doses (10–20 mCi, 370–740 MBq; >10,000 rad, >100 Gy) achieved when ^{131}I is administered to treat hyperthyroidism (even higher doses are used to treat thyroid cancer); (2) exposures to moderately high 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 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 high doses from exposures to releases from nuclear power plant accidents (Chernobyl, 10–500 rad, cGy); and (5) low to high environmental exposures from operational releases from nuclear fuel processing plants (Hanford Nuclear Site, 0.0001–284 rad, cGy). As a point of reference, the dose-response relationship for thyroid cancer and external radiation appears to extend down to thyroid doses of 0.1 Gy (10 rad) and predicts an excess relative risk (ERR) of 7/Gy for ages <15 years at exposure (Ron et al. 1995). Studies of thyroid cancers and external radiation exposure have found a strong dependence of thyroid cancer risk on age at exposure. Risk is substantially greater

Table 3-3. Estimated Thyroid Radiation Doses in Populations Studied for Radioiodine-related Cancers[a]

Type of exposure	Estimated thyroid radiation dose (cGy)[a]	Reference[b]
Radioiodine therapy for hyperthyroidism	>5,000[c]	Holm et al. 1991; Ron et al. 1998
Clinical diagnosis of thyroid gland disorders	80–130[c]	Hall et al. 1996b
Marshall Islands BRAVO test	280–2,100[c]	Hamilton et al. 1987; Lessard et al. 1985
Chernobyl power plant accident	<1–200[d]	Astrakova et al. 1998
Nevada Test Site nuclear bomb tests	1–30[c]	Gilbert et al. 1998; Kerber et al. 1993; Rallison 1996
Hanford Nuclear Site releases	17±22 (0.003–282)[d]	CDC 2002

[a]1 cGy=1 rad
[b]See text for additional references
[c]Cohort means
[d]arithmetic mean ± SD (range)

for radiation doses received prior to age 15 years when compared to risks for doses received at older ages, and this increased risk persists, possibly for the lifetime (Ron et al. 1995). 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. The relatively high and acutely cytotoxic radiation doses to the thyroid gland that are achieved in the treatment of thyroid gland disorders, and outcomes on the thyroid, are not relevant for predicting outcomes from the much lower environmental exposures that occur in most U.S. populations; for example, exposures received as a result of nuclear bomb testing (Nevada Test Site) or operational releases from nuclear plants (Hanford Nuclear Site). This is in part because cell killing effects decrease the number of viable cells that might otherwise be transformed by radiation-associated mutagenesis. Uncertainties in estimating thyroid doses are also greater in persons who have thyroid abnormalities because of the nonuniform distribution of radioiodine in the thyroid gland (NCRP 1985). Nevertheless, high-dose studies are summarized because they provide useful information about the magnitude of radioiodine exposures that would present an elevated risk for thyroid and extrathyroidal cancers. Although not specified in most of these studies, it is likely that radioiodine was administered as a single dose by the oral route as either potassium or sodium iodide, as these are the common clinical practices. However, it is also possible, but highly unlikely, that some patients received the radioiodine by injection. Since absorption of an oral dose of iodide is nearly complete, this is unlikely to be a significant issue in interpreting the outcomes of the studies, except in considering the radiation dose to the gastrointestinal tract.

Breast cancer is also a concern with exposures to high levels of radioiodine after ablative therapy for hyperthyroidism because breast expresses NIS and can transport and accumulate iodide (see Sections 3.5.4.2 and 3.6.1, Distribution). However, the epidemiological literature to date has not implicated such exposures as a significant risk factor for breast cancer (Goldman et al. 1988; Green et al. 1995).

Therapeutic Doses of Radioiodine

Several studies have explored possible associations between radioiodine therapy for thyroid disease and cancer incidence or mortality. The Ron et al. (1998) study specifically assessed cancer outcomes in patients who received only ^{131}I, and distinguished these patients from those who received other types of treatments alone, or in combination with ^{131}I. This is an important design feature, as the study showed that other forms of treatment appear to be risk factors for cancer mortality. The Ron et al. (1998) study used a retrospective cohort design to examine cancer mortality in 35,593 patients (79% females; mean age, 46 years, 3% younger than 20 years) treated for hyperthyroidism (91% Graves' disease, 8% toxic

nodular goiter) in 25 U.S. hospitals and 1 British hospital (Ron et al. 1998). The mean total activity administered was 10.4 mCi (385 MBq; 5th–95th percentile, 3–27 mCi, 111–999 MBq). The mean total administered activity was 10.0 mCi (370 MBq) for treatment of Graves' disease and 17.0 mCi (629 MBq) for toxic nodular goiter. Cancers that occurred between the first visit of the patient to the clinic during the enrollment period (1946–1964) until either the death of the patient or the end of the calendar year 1990 were considered in the analysis. Estimates of expected numbers of cancer deaths were based on U.S. national mortality rates for the period 1958–1985. Patients were stratified into various categories of treatment, distinguishing those who received ^{131}I as the only form of treatment from those who received antithyroid drugs or surgical treatments, alone or in combination with ^{131}I. SMRs (observed/expected deaths) were calculated for various treatments (^{131}I, surgery, antithyroid drugs, or combinations). This design allowed an assessment of the effects of possible associations between ^{131}I exposure and cancer outcomes, independent of the potential effect of other treatments. The study identified 2,960 cancer deaths, 29 of which were classified as thyroid cancers. Among patients who received ^{131}I as treatment alone (only ^{131}I), SMRs were significantly elevated only for thyroid cancer (4.91; 95% CI, 2.45–8.79), but not for other cancers, or all cancers. Among all patients treated with ^{131}I, alone or in combination with other treatments (any ^{131}I), SMRs were also significantly elevated for thyroid cancer (3.94, 252–5.86), only. When stratified by latency (1–4 years, 5–9 years, 10 years or longer), in the latter group (any ^{131}I), SMRs for thyroid cancer were highest 1–4 years after treatment (12.32, 6.38–21.61), but remained significantly elevated in the 10 years or longer group (2.78, 1.38-4.97). Radiation doses to specific organs were estimated for each patient based on the administered activity and dosimetry tables developed by the ICRP (1988). The estimated thyroid dose was 50–70 Gy (5,000–7,000 rad). When stratified by administered ^{131}I activity (as a surrogate for thyroid dose), the SMRs for thyroid cancer in this group (any ^{131}I) increased with increasing exposure, suggesting a possible dose effect on thyroid cancer mortality. The highest SMRs occurred in the group that received 15 mCi or more (7.05, 3.05–13.95), and in the group treated for toxic nodular goiter (18.88, 7.58–38.98), who would have received higher exposures and doses than Graves' disease patients (2.84, 1.62–4.61). SMRs for cancers in other tissues were also significantly elevated in the any ^{131}I group; colorectal cancer, 1–4 years after treatment (1.42, 1.04–1.90); lung cancer 1–4 years (1.49, 1.01–2.12) and 5-9 years (1.41, 1.02–1.89) after treatment; and for non-chronic lymphatic leukemia, 5–9 years after treatment (2.10, 1.14–3.52). However, interpretation of these findings, in terms of the potential contribution of ^{131}I to cancer mortality, is complicated by the finding of elevated SMRs in extra-thyroidal tissues in the groups that received treatments other than ^{131}I, including bucal cavity, lung, breast, and brain. The results of this study indicate that high exposures to ^{131}I for treatment of hyperthyroidism did not increase overall cancer mortality; however, it did appear to increase mortality for thyroid cancer. Interpretation of the effect on thyroid cancer mortality is

complicated by the potential impact of thyroid cancers that may have existed in these patients, undiagnosed, prior to the treatment. The observation that much of the apparent excess risk for thyroid cancer deaths occurred during the first 1–4 years after ^{131}I treatment, suggests a remarkably short latency for radiation-induced cancer mortality, or possibly other factors contributed to the outcome. Other uncertainties in this study include the use of exposure levels (mCi) as a surrogate for absorbed radiation dose to the thyroid. The relationship between administered activity and thyroid dose in hyperthyroid patients can be complicated by disease-related variation in thyroid gland size and iodide transport activity. Also, administered activity can co-vary with the severity of the initial hyperthyroidism; patients who received the highest activities tend to have the most severe disease, and disease severity could vary, independently with cancer mortality.

A retrospective cohort study conducted in Sweden examined cancer incidence among 10,552 patients (85% females; age 13–74 years) who received ^{131}I therapy for treatment of Graves' disease (51%) or toxic nodular goiter (42%) (Holm et al. 1991). The mean total activity administered was 506 MBq (13.7 mCi); however, this varied with the objectives of the therapy; 360 MBq (9.7 mCi) for treatment of Graves' disease and 700 MBq (18.9 mCi) for toxic nodular goiter. The distribution of the administered activity in the study population was as follows: 30% <220 MBq (5.9 mCi), mean, 150 MBq (4.1 mCi); 38% 221–480 MBq (6–13 mCi), mean 315 MBq (8.5 mCi); and 32% >480 MBq (13 mCi), mean 1,063 MBq (28.7 mCi). Cancers that occurred from 1 year after treatment (on or after 1958) until either the death of the patient or the end of the calendar year 1985 were considered in the analysis. Expected numbers of cancers were estimated from data from the Swedish Cancer Register for the period 1958–1985. Standard incidence ratios (SIR, observed/expected cancers) were significantly elevated for cancers of the lung (1.32, 95% CI, 1.07–1.59) and kidney (1.39, 95% CI, 1.07–1.76). Among toxic nodular goiter patients, who received, on average, twice the dose as Graves' disease patients, the SIR was also significantly elevated for liver cancer (2.14, 1.20–3.52). Among 10-year survivors, significantly elevated SIRs included stomach (1.33, 1.01–1.71), kidney (1.51, 1.06–2.08), and brain (1.63, 1.10–2.32). Doses to specific organs were estimated for each patient based on the administered activity and dosimetry tables developed by the ICRP (1988). Estimated average radiation doses to these tissues were: thyroid gland, >10,000 cGy (>10,000 rad); stomach, 25 cGy (25 rad); lung, 7 cGy (7 rad); kidney, 5 cGy (5 rad); liver, 5 cGy (5 rad); and brain (not reported). There were no significant dose trends. Notably, SIRs for thyroid cancer were not significantly elevated (SIR 1.29, 0.76–2.03). Some of the patients in this study received treatments other than ^{131}I for thyroid disorders, including antithyroid drugs (14%), surgery (3%), and/or thyroid hormone supplements (2%). Cancer mortality was examined in the same cohort (Hall et al. 1992a). Standard mortality ratios (SMRs) were calculated based on data from the Swedish Cause-of-

Death Registry. SMRs were significantly elevated for all cancers (1.14, 1.04–1.24), digestive tract cancers (1.28, 1.16–1.45), and respiratory tract cancers (1.31, 1.01–1.66) among patients who had greater than a 10-year follow up from the date of their exposure to ^{131}I, and for thyroid gland cancer during the first year (11.45, 2.8–33.72). There were no significant dose trends, although the SMR for thyroid gland cancer was approximately 4 times higher in patents who received >480 MBq (13 mCi) than in patients who received <221 MBq (6 mCi). The results of this study suggest that exposure to high levels of ^{131}I for treatment of hyperthyroidism increases cancer risk; however, several uncertainties complicate the interpretation of results, in terms of the contribution of ^{131}I to the elevated cancer risk. These include the lack of a dose trend for increased cancer incidence or mortality, and the potential contribution of treatments, other than ^{131}I to cancer incidence and mortality, which were not quantified in this study. Surgical treatment and antithyroid drug therapy appear to be cancer risk factors in hyperthyroid patients (Ron et al. 1998).

A retrospective study examined cancer morbidity and mortality in 7,417 patients (83% females; mean age, 57 years ± 13, SD) treated for hyperthyroidism in the West Midlands region of the United Kingdom during the period 1950–1991(Franklyn et al. 1999). The mean total activity administered was 308 MBq (8.3 mCi); 49% received <220 MBq (<6 mCi) and 17% received >481 MBq (>13 mCi). The follow-up period ranged from 1 year (74%) to $20 years (18%). Estimates of expected numbers of cancer deaths in England and Wales were based on International Agency for Research on Cancer (IARC) and World Health Organization (WHO) data. The SIR for all cancer types was 0.83 (95% CI, 0.77–0.90). The SIR for thyroid cancer was 3.25 (1.69–6.25) and for cancer of the small bowel, 4.81 (2.16–10.72). SIRs for all other cancers were <1. Similarly, SMRs were 0.90 (0.82–0.98) for all cancer types, 2.78 (1.16–6.67) for thyroid cancer, and 7.03 (3.16–15.66) for cancer of the small bowel. Significant positive trends for increasing incidence with increasing cumulative radiation exposure were observed for bladder cancer and uterine cancer, although SIRs and SMRs for these cancers were not significantly greater than 1. The results of this study, consistent with those of the Hall et al. (1992a) and Ron et al. (1998), suggest that exposure to high levels of ^{131}I for treatment of hyperthyroidism increases the risk of cancer mortality; however, similar to the Hall et al. (1992a) study, the potential contribution of treatments other than ^{131}I (e.g., surgical treatment and antithyroid drug therapy, Ron et al. 1998), to cancer incidence and mortality, were not quantified in this study. Surgical treatment and antithyroid drug therapy appear to be cancer risk factors in hyperthyroid patients (Ron et al. 1998). Other potential uncertainties in interpreting the Franklyn et al. (1999) study include: (1) thyroid radiation doses were not reported; thus, it is difficult to compare the doses received to subjects in this studies with those in the Ron et al. (1998), Holm et al. (1991), and Hall et al. (1992a) studies; (2) the Franklyn et al. (1999) study did not stratify the subjects by

radiation exposure or dose, which may have varied depending on the nature of the original diagnosis of hyperthyroidism; and (3) the size of the cohort in the Franklyn et al. (1999) study was smaller than the other three studies (7,417 compared to 35,593 in Ron et al. 1998 study, and 10,552 in Holm et al. 1991 study).

A follow-up cohort study was conducted of cancer morbidity and mortality among 1,762 women who received ablative ^{131}I therapy for hyperthyroidism during the period 1946–1964 (Goldman et al. 1988). The follow-up period was 17 years. SMRs and SIRs were estimated based on age-, date-, sex-, and race-specific mortality incidence and mortality of the United States or Massachusetts population. The cohort was stratified into treatment categories that included only ^{131}I or ^{131}I in addition to other therapies for hyperthyroidism. SIRs in the ^{131}I-only group were not significantly elevated for any cancer type or group. SMRs in the ^{131}I-only group were significantly elevated for cancers of all causes (SMR, 1.2, 1.1–1.4, 95% CI, 10 cases). There were no significant radiation dose trends. Exposures ranged from 0.1 to >10 mCi (4–370 MBq). Although, like the Ron et al. (1998) study, cancer mortality risk was evaluated in patients who received only ^{131}I as treatment, the much smaller size of the Goldman et al. (1988) study makes it difficult to interpret comparisons of results to those from the Ron et al. (1998) study. Like the Ron et al. (1998) study, Goldman et al (1988) found elevated cancer mortality in patients who received treatments other than ^{131}I.

A follow-up study was conducted of cancer morbidity among 1,771 patients (21% males) who received ablative ^{131}I therapy for treatment of thyroid cancer during the period 1950–1990 (de Vathaire et al. 1997). The follow-up period was 10 years. Excess relative risk (ERR) was modeled using linear models (a quadratic model was also explored), taking into account sex, age at time of treatment, and cumulative activity of ^{131}I administered as variables. The mean administered activity of ^{131}I was 7.2 GBq (range, 3.8–57.6; 195 mCi, range, 103–156 mCi) which corresponded to a mean radiation dose to bone marrow of 0.34 Sv (range, 0.13–2.8; 34 rem, range, 13–280 rem). Using the cancer outcomes of patients who received 1–0.19 GBq of ^{131}I as the reference group, ERRs for colorectal cancer increased with increasing administered activity. In the patient group that received >3.7–7.5 GBq (>100–203 mCi) the ERR was 4.0 (90% CI, 1.3–12.2) and in the group that received >7.5 GBq>(203 mCi), the ERR was 4.9 (1.2–18.5). While this is a relatively small study, it supports an outcome of the much larger Ron et al. (1998) study in which SMRs for colorectal cancer were elevated among patients who received lower administered activities of ^{131}I for treatment of hyperthyroidism (mean 10.4 mCi, 385 MBq).

Diagnostic Doses of Radioiodine

A retrospective cohort study examined thyroid cancer incidence among 34,104 patients (80% females, 1–75 years of age) in Sweden who received ^{131}I for diagnosis of thyroid disorders during the period 1950–1969. The follow-up period was from 1958 to 1990 (Hall et al. 1996b). A total of 2,408 patients (7%) were exposed before 20 years of age and 316 patients were exposed before 10 years of age (1%). The diagnostic test was for a suspected thyroid tumor in 10,785 (32%) patients and for hypothyroidism, hyperthyroidism, or other reasons in 23,319 (68%) patients. The follow-up period ranged from 5 to 39 years after exposure (thyroid cancers detected within 5 years of the diagnostic test were excluded on the basis that they may have been related to cancer present at the time of the diagnostic test). The mean total activity administered was 2.4 MBq (65 μCi) for patients suspected of having a thyroid gland tumor and 1.6 MBq (43 μCi) for other patients. Radiation doses to the thyroid gland were estimated for each patient based on the administered activity and dosimetry tables developed by the ICRP (1988). The mean absorbed dose was 1.3 Gy (130 rad) for suspected thyroid tumor patients and 0.8 Gy (80 rad) for other patients. SIRs were calculated based on sex-, age-, and date-adjusted cancer incidence rates based on the Swedish Cancer Registry. Sixty-seven thyroid tumors were identified during the period of the study, of which 42 (63%) were in patients who received ^{131}I for diagnosis of a suspected thyroid gland tumor. SIRs were significantly elevated only in the latter group (2.86, 95% CI, 2.06–3.86), but not in patients tested for other suspected thyroid disorders. There were no significant dose trends for thyroid cancer in either group, and the presence of cancer may have predated the exposures to ^{131}I. A subsequent follow-up of this same cohort was conducted, which extended the follow-up period an additional 8 years from that reported in Hall et al. (1996b) and included thyroid cancers diagnosed as early as 2 years after diagnostic administration of ^{131}I, making the follow-up period 2-47 years (Dickman et al. 2003). Patients (1,767) who received diagnostic X-rays to the neck, prior to receiving ^{131}I, were also included in the study to explore the effects of external radiation on thyroid cancer incidence. Among patients who did not receive X-rays to the neck and who were not referred for diagnostic ^{131}I for suspicion of a possible thyroid tumor, the SIR for thyroid cancer was 0.91 (95% CI, 0.64–1.26). The estimated dose to the thyroid in this group was 0.94 Gy (94 rad). However, among patients who did receive X-rays prior to ^{131}I, the SIR was 9.8 (6.3–14.6). The results support the previous findings in this cohort (Hall et al. 1996b) that radiation doses to the thyroid resulting from diagnostic administration of ^{131}I are not associated with excess risk of thyroid cancer. The study also identifies X-ray exposures as an important variable that, if not controlled for, could confound studies of cancer outcomes in patients exposed to ^{131}I.

The incidence of cancer in extrathyroidal organs was examined in this same cohort (Holm et al. 1989). At that time, the cohort consisted of 35,074 patients, 31% of whom received ^{131}I for diagnosis of a suspected

thyroid gland tumor, 42% for suspected hyperthyroidism, 16% for suspected hypothyroidism, and 8% for other reasons (the basis for the diagnostic procedure could not be determined for 3% of the patients). The mean total activity administered was 52 μCi (range 1–960 μCi) (1.9 MBq, 0.04–36 MBq). The mean total administered activity was 71 μCi (2.6 MBq) for patients suspected of having a thyroid tumor, 48 μCi (1.8 MBq) for diagnostic tests for hyperthyroidism, and 40 μCi (1.5 MBq) for other diagnostic purposes. SIRs were significantly elevated for cancers of the endocrine organs other than thyroid gland (1.93, 1.62–2.29), lymphomas (1.24, 1.03–1.48), and leukemias (1.34, 1.11–1.60). The SIR for nervous system cancers was 1.19 (1.00–1.41). The SIR for thyroid cancer was significantly elevated only in the 5–9-year period of follow-up. There were no significant dose trends. In this study, unlike the Hall et al. (1996b) study, SIRs were calculated for all patients, regardless of the intended purpose of the diagnostic test, including patients who were administered ^{131}I for the diagnosis of suspected thyroid tumors.

A smaller retrospective cohort study compared thyroid cancer incidence among 789 patients (74% females) in Germany who received ^{131}I for diagnosis of thyroid disorders before the age of 18 years with 1,118 patients who received a diagnostic procedure on the thyroid that did not involve radioiodine (68% females) (Hahn et al. 2001). Diagnostic procedures occurred between 1958 and 1978 in the treatment group, and between 1959 and 1978 in the control group. The diagnosis made at the initial referral in the treatment groups was nodular goiter in 385 (49%) in patients, *no evidence of thyroid disease* in 199 (25%) patients, and hypothyroidism, hyperthyroidism, or other reasons in 205 (26%) patients. In the control group, the diagnoses included 600 (54%) cases of goiter, 327 (29%) of *no evidence of thyroid disease,* and 131 (12%) hypothyroidism, hyperthyroidism, or other reasons. Patients who had a history of external radiotherapy of the head or neck regions or thyroid cancer were excluded from the study. The follow-up period (1989–1997) ranged from 13 to 33 years in the treatment group and 9–33 years in the control group. The median total ^{131}I activity administered in the treatment groups was 0.9 MBq (24 μCi). Radiation doses to the thyroid gland were estimated for each patient based on the administered activity and dosimetry tables developed by the ICRP (1988). The mean absorbed dose was 1.0 Gy (100 rad); however, this varied with age of diagnosis; the range was 0.6–1.2 Gy (60–120 rad). SIRs were calculated based on sex-, age-, and date-adjusted cancer incidence rates based on the German Democratic Republic cancer registry for the period 1980–1989. Three cases of thyroid cancer were identified in the treatment group during the study period and two cases in the control group. SIRs were 5.3 (95% CI, 0.5–15.1) in the treatment group and 5.3 (1.1–15.3) in the control group. The relative risk (treatment compared to control) was 0.9 (0.1–5.1). Risk of thyroid cancer was not significantly associated with exposure to diagnostic levels of ^{131}I. A complication in the interpretation of these findings is that the response rate was very low: 3 cases in 1,058 patients, 0.28%; 2 in 795 in the treatment group.

A prospective study examined thyroid outcomes of children and adolescents (<20 years old) who received diagnostic doses of ^{131}I during the period 1946–1967 (Hamilton et al. 1987). Study groups consisted of 3,503 subjects who received diagnostic ^{131}I, 2,495 control subjects who did not receive ^{131}I and who were matched with the exposed subjects by sex-, age-, and diagnostic-test date, and a group of 1,070 siblings of the control group. The follow-up period was from entry into the study until 1986. Participants were surveyed with a questionnaire to identify those who had thyroid or neck surgery during the study period, and pathology reports and specimens were retrieved and reviewed by a panel of pathologists; neoplasms were classified and the results were compared with hospital pathology reports. The dose to the thyroid gland was estimated for each exposed subject based on the reported activity administered, percent thyroid uptake, and thyroid weight estimated from published thyroid growth tables. The median total absorbed dose was 20–40 rad (0.2–0.4 Gy) (95th percentile, 200–330 rads 2–3 Gy). The survey response rate was 63%. A total of 34 surgeries were reported, of which 19 were on subjects who did not have any thyroid disorder diagnosed at the time of entry into the study; 16 of these subjects had confirmed thyroid tumors; 10 benign, 8 of which occurred in the exposed group, and 6 malignant tumors, 5 of which occurred in the exposed group. Although these results are suggestive of a possible effect of ^{131}I exposure on thyroid tumor incidence, the differences between the exposed and control groups were not statistically significant. Shore (1992) reviewed the results of the Hamilton et al. (1987) study and calculated a relative risk for thyroid cancer of 2.9 (90% CI, 0.6–15) based on the internal comparison of the exposed and unexposed groups in the Hamilton et al. (1987) study. Based on the Surveillance, Epidemiology and End Results (SEER) cancer data for 1973–1981 (U.S. DHHS 1985), 3.7 thyroid cancers would have been expected in the Hamilton et al. (1987) study, compared to the 4 observed during the period of 5 or more years after the diagnostic test (one of the cancers reported in the Hamilton et al. (1987) study occurred with a latency of 2 years), which, according to Shore (1992), indicates an SIR of 1.1 (95% CI, 0.3–2.6).

Marshall Islands Nuclear Bomb Test BRAVO. Several epidemiological studies have examined thyroid gland disorders in residents of the Marshall Islands who were exposed to radioiodine from atmospheric fallout resulting from nuclear bomb tests (including the so-called BRAVO test; see Section 3.3.2 for a more detailed discussion of exposures from the Marshall Islands BRAVO test). A more complete discussion of these studies is presented in Section 3.3.1.2 (Endocrine), as the studies provide dose-response information on thyroid disorders other than cancer. However, cancer outcomes have been examined in what has become known as the BRAVO cohort, as well as in larger samples of the Marshall Island population. Almost all that is known about radioiodine doses to the thyroid from the BRAVO test exposures derive from a few urinary measurements collected 15 days after the exposures. These have

been estimated to have been (external and internal): 3.3–20 Gy (330–2,000 rad) on Rongelap (highest doses in children), 1.3–4.5 Gy (130–450 rad) on Ailingnae, and 0.3–0.95 Gy (30–95 rad) on Utrik (Conard 1984). The BRAVO test was not the only potential source of radioiodine exposure in the Marshall Island population, as numerous bomb tests were conducted in the Marshall Islands during the period 1946–1958.

The strengths of the Marshall Island studies include the relatively high range of thyroid radiation doses and the multiple thyroid screenings, which included, in the more recent studies, relatively objective assessments of nodularity by ultrasound. Limitations of the studies include: (1) large dose uncertainties in terms of total thyroid dose; (2) further dose uncertainties in terms of the fraction of the dose that was from ^{131}I rather than from short-lived isotopes of iodine and gamma radiation; (3) no attempt to estimate individual thyroid doses; (4) inequities between the exposed and unexposed populations in the intensity of thyroid screening; (5) the relatively small number of exposed subjects in the BRAVO cohort; (6) the potential confounding effects of prophylactic iodide administration and thyroid surgery in highly exposed subjects; and (7) thyroid radiation dose estimates not available for larger scale studies of populations in the Marshall Islands.

Evidence for a higher prevalence of thyroid cancer among the original 250 people known to have been heavily exposed as a result of the BRAVO incident has not been established; however, this may reflect the small size of the cohort (see section 3.3.2 for a more detailed discussion of exposures from the Marshall Islands BRAVO test). In 1982, a review of the diagnoses for thyroid nodules detected in 250 exposed and 1,303 nonexposed Marshallanese revealed 9 definitive carcinomas (3.6%) and 7 adenomas (2.8%) in the exposed group, and 6 carcinomas (0.5%) and 14 adenomas (1%) in the nonexposed comparison group (Conard 1984). Subsequent reviews of the thyroid pathology more or less agree with the conclusions of Conard (1984), although differences in the composition of comparison group have contributed to slightly different estimates of prevalence in the nonexposed population. For example, Howard et al. (1997) reported four cancers (1.8%) and one adenoma (0.4%) in a nonexposed comparison group. Takahashi et al. (1997) reviewed diagnoses of 22 cases of thyroid nodularity discovered in 1993 in an ultrasound screening program that evaluated 1,275 Marshall Island residents (mainly from Ebeye). The prevalence of thyroid cancer among patients referred for surgery-based thyroid gland ultrasound assessments suggested an overall prevalence of thyroid cancer of approximately 1.2% (15/1,275) in the population evaluated, or a 12% prevalence (15/123) of thyroid cancer among those who had palpable nodules. A follow-up to this study included the results of thyroid disease screening of 3,709 Marshall Island residents who were born before the BRAVO test and who lived anywhere in the

Marshall Islands during the period of bomb testing. The study group included an estimated 60% of the still-living population who resided in the Marshall Islands during this period. Combining findings from the previous study (Takahashi et al. 1997) and the follow-up, a total of 57 thyroid cancers were identified (1.5%), of which 92% were diagnosed as papillary cancers. Several factors confound attempts to associate thyroid cancers in the Marshall Islands population with radioiodine exposures, including lack of definitive dosimetry, outside of the small BRAVO cohort. Changes occurred in diagnostic techniques used to detect thyroid nodules, which would direct further diagnostic attention; in particular, the use of ultrasound for detecting small thyroid nodules began only in 1994. More recent studies have also suggested a relatively high prevalence of iodine deficiency in the Marshall Islands, which may have affected background thyroid cancer prevalence (Takahashi et al. 1999).

Nevada Test Site Nuclear Bomb Tests. During the period 1951–1958, 119 atmospheric nuclear bomb tests were conducted at the Nevada Test Site (NTS) in southern Nevada (NCI 1997). These tests were followed by 9 surface detonations during the period 1962–1968 and approximately 809 below-ground tests, of which 38 were determined to have resulted in off-site releases of radioactive materials. A dose estimation methodology was developed by the National Cancer Institute (NCI 1997), which has enabled estimation of population radiation doses to the thyroid gland from direct and indirect (e.g., *in utero*, ingestion of cow milk) exposures to ^{131}I resulting from the NTS activities for the purpose of health assessments and epidemiologic investigations (Gilbert et al. 1998; Kerber et al. 1993). A discussion of the uncertainties and limitations of these population dose estimates for use in epidemiology studies and risk assessment can be found in a review of the NCI (1997) dose estimations conducted by the Institute of Medicine and the National Research Council (NRC 1999).

The strengths of the NTS studies described above include the attempt to develop a systematic sampling frame, the careful, multiple thyroid screenings (two or more times), the relatively high follow-up rate, and the extensive attempt to characterize individual ^{131}I doses. Limitations of the studies include: (1) the substantial dose uncertainties, since no thyroid exposure measurements were available and individual milk and vegetable consumption was recalled more than 30 years after the fact; (2) the food-consumption and behavioral questionnaire was conducted after subjects knew their thyroid outcomes; (3) the modest sample size and, therefore, small number of thyroid neoplasms found, which limited the statistical power and precision; (4) the relatively low dose range, which also limited the statistical power and precision; (5) the restriction of the thyroid examinations to palpation (no ultrasound); and (6) the fact that the thyroid examinations were only partially blinded (i.e., examiners often knew the subject's geographic region).

A cohort study examined thyroid nodularity and performed diagnostic follow up in 2,678 adolescents (age 11–18 years) who resided in Utah or Nevada near the NTS during the early 1950s and in a comparison population of 2,132 adolescents who lived in Arizona. Examinations were conducted during the period 1965–1970 (Rallison et al. 1974). In a follow-up study conducted in 1985–1987, 1,962 of the original Utah-Nevada group and 1,160 from the Arizona group were reexamined (Rallison et al. 1990). Radioiodine doses were estimated for each Utah-Nevada subject based on histories of residence, local milk and leafy vegetable consumption, records of transport and deposition of radionuclides at their town and/or county of residence, and age-specific transfer factors relating iodine ingestion with iodine uptake in the thyroid gland (Kerber et al. 1993; Simon et al. 1990). Mean thyroid dose estimates were 150 mGy (15 rad) (maximum 4.6 Gy, 460 rad) in the Utah group, 50 mGy (5 rad) (maximum 0.84 Gy, 84 rad) in the Nevada group, and 13 mGy (1.3 rad) (maximum 0.45 Gy, 45 rad) in the Arizona group (the group names refer to cohort designations used in the study, which were based on the place of residence during the potential exposure period, and not necessarily where the entire radiation dose for each individual was received). In the 1965–1968 examinations, 76 of 4,819 people examined had palpable thyroid gland nodules, 22 of which were subsequently diagnosed as adenomas (20) or carcinomas (2). The prevalence of nodules was higher in the Utah-Nevada group (19.7/1,000) than in the Arizona group (10.8/1,000). Fifteen of the 22 neoplasms were found in the Utah-Nevada group (5.6/1,000) and 7 in the Arizona group (3.3/1,000) (Rallison et al. 1974). In 1985–1987, 125 new cases of thyroid nodularity were identified, 65 of which were diagnosed as neoplasms and 5 of the latter were carcinomas. Five carcinomas were reported in the group during the interval between the two examinations. Combining the results of the first and second evaluations, including the five carcinomas observed during the interval (a total of 12 carcinomas), resulted in similar prevalences in the two groups for nodules (Utah-Nevada 48.6/1,000, Arizona 36.6/1,000). Prevalence of neoplasms was not disparate: Utah-Nevada, 2.8/1,000 and Arizona, 4.8/1,000 (Rallison et al. 1990). Thyroid nodules were detected in 56 of 2,473 subjects; 38 of these lesions were diagnosed as nonneoplastic (28 were colloid adenomas, the other 10 were miscellaneous nonneoplastic lesions), 11 were benign adenomas (of these, 8 were follicular adenomas and there was one each of papillary, fetal, and Hurthle cell adenomas), and 8 were papillary carcinomas (Rallison 1996). Stratifying the outcomes by estimated thyroid radiation dose revealed a significant dose trend for neoplasms, but not for all nodules or for carcinomas alone. The group that received a dose exceeding 0.25 Gy (25 rad) had a thyroid neoplasm prevalence of 21–24/1,000, whereas groups that received <0.25 Gy had a prevalence of 4–5/1,000. The excess relative risk estimates per Gy were: neoplasms, 7.0 (lower 95% confidence limit [CL], 0.74, p=0.019); nodules, 1.2 (95% CL<0, p=0.16); and carcinomas, 7.9 (95% CL<0, p=0.096) (Kerber et al. 1993).

In a large scale ecological study, mortality and incidence of thyroid cancer in 3,053 U.S. counties were compared to estimated exposures to ^{131}I from releases from the NTS (Gilbert et al. 1998). Thyroid cancer mortality data were obtained from the National Center for Health Statistics for 1957–1994 and thyroid cancer incidence data from SEER for the period 1973–1994. County-specific or state-specific cumulative radiation doses were reconstructed based on NCI (1997) and were as follows (cGy, where 1 cGy = 1 rad): *in utero*, 4.3 cGy; 0–<1 year, 12.6 cGy; 1–4 years, 10.0 cGy; 5–9 years, 6.7 cGy; 10–14 years, 4.4 cGy; 15–19 years, 3.1 cGy; $20 years, 1.1 cGy. During the study period, there were 12,657 cases of thyroid cancer and 4,602 thyroid cancer deaths. Age-, calendar-, sex-, and count-specific mortality and incidence rates in the United States were analyzed in relation to ^{131}I dose estimates, taking into consideration geographic location, age at exposure, and birth cohort. There were no significant dose-related trends (linear excess relative risk model) in either thyroid cancer mortality or incidence when all exposure age groups were composited or when exposure age groups 1–5 years or 1–15 years were considered separately. However, when the exposure age group <1 year was analyzed, a dose trend was weakly suggested by highly positive excess relative risks (ERR) for thyroid cancer deaths when doses were county-specific (ERR 10.6 per Gy, 95% CI, -1.1–29, p=0.085) or state-specific (16.6 per Gy, -0.2–43, p=0.054), and for thyroid cancer incidence when doses were county-specific (2.4 per Gy, -0.5–5.6). These outcomes were strongly influenced by two deaths and nine cases of thyroid cancer that occurred in individuals who received estimated cumulative doses exceeding 9 cGy (9 rad) before they were 12 months of age.

Chernobyl Nuclear Power Plant Accident. Clinical records and cancer registries from the Republics of Belarus and Ukraine show an increase in the incidence of thyroid cancer in children and adolescents, which became apparent approximately 4 years after the release of radioactive materials from the Chernobyl nuclear power plant in April 1986, but which has not been increasing in recent years, especially among those exposed at older ages (Cherstvoy et al. 1996; Drobyshevskaya et al. 1996; Prisyazhuik et al. 1991; Tronko et al. 1996) (see Section 3.3.2 for a more detailed discussion of exposures from the Chernobyl accident). Belarus recorded an annual incidence of 0.09 cases per 100,000 in 1986 among children between the ages of 4 and 17 years and 2.46 per 100,000 in 1991, with the highest incidence in the Gomel oblast; from 0.24 cases per 100,000 in 1986 to 12.5 per 100,000 in 1991 (Drobyshevskaya et al. 1996). In the Ukraine, annual incidence of thyroid cancer in children and adolescents (under 15 years of age) increased from approximately 0.05 per 100,000 prior to 1986 to 0.43 per 100,000 in 1992 (Tronko et al. 1996). In 1994, the incidence (per 100,000) was highest in regions nearest to Chernobyl: Chernihiv, 3.8; Zhytomyr, 1.6; and Kiev, 1 (Tronko et al. 1996). Jacob et al

(1998) estimated excess absolute risk of thyroid cancers in Belarus and Northern Ukraine for the period 1991–1995 using the cancer incidence in southern Ukraine as the control. The relationship between thyroid cancer risk and the estimated radiation dose to the thyroid was linear, with a slope of 2.3 (95% CI 1.4–3.8) per 10,000 person-year Gy. Although the available data strongly show that radiation exposure from the accident has led to the excess risk of thyroid cancer, especially in persons exposed as children, there is also much uncertainty in the radiation dose estimates. The observed trends for increased prevalence of thyroid cancer, as well as the magnitude of the thyroid cancer risk associated with radioiodine are highly uncertain because of factors that complicate the epidemiological picture, including the contribution external exposure, the effect of the intensive screening for thyroid cancer that followed the accident (Astakhova et al. 1998) on the baseline incidence of thyroid cancer, and the potential effects of iodine deficiency and endemic goiter in the population (Gembicki et al. 1997; Robbins et al. 2001).

The relationship between childhood thyroid cancer and radiation exposure was examined in a case-control study of children from Belarus (Astakhova et al. 1998). Cases included all children under age 15 years at the time of the accident who had confirmed pathology diagnoses of thyroid cancer during the period 1987–1992 and who could participate in the study (107 of 131 applicable cases in Minsk State Medical Institute records). Cases were matched with two control groups; one control group (Type 1) was randomly selected from an area of Belarus thought to have relatively low or no exposures from the Chernobyl accident (Brest, Grodno, and Vitebsk oblasts in north and west Belarus) but was otherwise matched with cases for age, sex, and urban/rural residence. A second control group (Type 2) was drawn from each Belarus district, including the more heavily exposed oblasts near Chernobyl (Minsk, Mogilev, and Gomel), in numbers proportional to the population census and was matched to cases by pathway to diagnosis, in addition to age, sex, and urban/rural residence. The objective of matching the pathway to diagnosis was to control for screening intensity as a possible contributor to an increased incidence. Diagnosis pathways were classified into three elements: (1) systematic endocrine screening; (2) incidental finding during physical examination not necessarily related to the Chernobyl releases; or (3) examination prompted by referral because of a swelling of the neck or other symptoms of possible thyroid enlargement or nodularity.

Average thyroid radiation doses were reconstructed based on thyroid gland ^{131}I measurements made on 200,000 residents of Belarus, after the Chernobyl release, and estimates of cow milk contamination and consumption for the area of residence of each case or control (vegetable and goat milk consumption was not included in the exposure estimates). If no cow milk consumption was thought to have occurred, exposure was assumed to have occurred principally from inhalation. Age-group thyroid doses were

constructed for each area of residence included in the study. Mean (standard deviation) of thyroid doses in the case group and controls were as follows: cases, 535 mGy (848) mGy; Type I controls, 188 mGy (386); and Type II controls, 207 mGy (286). For the purpose of estimating odds ratios (ORs), cases and controls were stratified into three thyroid dose categories. The resulting estimated dose distributions among thyroid cancer cases were 64/107 (59.8%) in the <0.3 Gy dose category, 26/107 (24.3%) in the 0.3–0.99 Gy dose category, and 17/107 (15.9%) in the $1 Gy dose category. The corresponding distributions in Type 1 controls were 88/107 (82.2%) for <0.3 Gy, 15/107 (14.0%) for 0.3–0.99 Gy, and 4/107 (3.7%) $1 Gy. The corresponding OR for the $0.3 Gy category compared to <0.3 Gy was 3.11 (95% CI, 1.67–5.81) and for the $1 Gy category compared to <0.3 Gy was 5.84 (1.96–17.3). ORs were significant when Type 2 controls were the comparison group (controls for pathway to diagnosis). For routine endocrine screening, ORs were 2.08 (1.0–4.3) for comparison of the dose categories $0.3 Gy and <0.3 Gy, and 5.04 (1.5–16.7) when the dose category $1 Gy was compared to <0.3 Gy. The OR for incidental findings was significant, 8.31 (1.1–58) when the dose category $0.3 Gy was compared to <0.3 Gy. These results suggest that, after controlling for the effects of intensive screening for thyroid cancer that occurred after the accident, radiation dose to the thyroid gland was a significant contributor to thyroid cancers diagnosed in children who lived in Belarus during and after the Chernobyl releases and that this contribution is evident at doses exceeding 0.3 Gy. The OR estimates, however, are highly uncertain because of the relatively large uncertainties in the dose estimates.

An analysis of 251 thyroid cancer cases in children (14 years or younger) from Belarus who were diagnosed during the period 1986–1993 revealed a dose trend in incidence when the cases were organized by districts that reflected their respective mean thyroid doses (Drobyshevskaya et al. 1996). Incidence ranged from 81 to 201 per 100,000 where estimated average thyroid doses were above 1 Gy (1.2–1.6 Gy, 120–160 rad), and 14–55 per 100,000 where doses were between 0.1 and 0.5 Gy (10–50 rad). The highest incidence occurred in Bragin where individual thyroid doses were estimated to have ranged from 0.8 to 20 Gy (560, 80–2,000 rad) (mean, 5.6 Gy, 560 rad). Incidence was 9 per 100,000 in Braslav where the lowest measurable thyroid doses were reported (mean, 0.005 Gy, 0.5 rad). Children who were under 3 years old or *in utero* at the time of exposure accounted for 53% of thyroid cancer cases. This age-group was estimated to have received a thyroid radiation dose that was approximately 2–3 times that for older children (approximately 1.4 Gy average dose). However, 52% of the cancers were diagnosed in children who received an estimated thyroid dose of <0.3 Gy and 84% in children who received doses <1 Gy. Children under 3 years old accounted for 38% of the cancer cases among children exposed to <0.3 Gy. These results suggest that young children were particularly susceptible to lower radiation doses.

An analysis of 531 thyroid cancer cases in children and adolescents (under 18 years of age) from Ukraine who were diagnosed during the period 1986–1994 revealed that 55% of the cases were under age 6 years on the date of the Chernobyl release (Tronko et al. 1996). The annual incidence of thyroid cancer in children and adolescents (under 19 years of age) increased from approximately 0.05 per 100,000 prior to 1986 to 0.43 per 100,000 in 1992. In 1994, the incidence (per 100,000) was highest in regions nearest to Chernobyl: Chernihiv, 3.8; Zhytomyr, 1.6; and Kiev, 1 (Tronko et al. 1996). Thyroid radiation doses were estimated to have ranged from 0.01 to >1.5 Gy in the case group analyzed. Approximately 20% of the cases were estimated to have been exposed to 0.01–0.05 Gy (1–5 rad) and 80% to 0.1–0.3 Gy or less (10–30 rad).

A comparison of the demographics and pathology of thyroid cancers in Belarus and Ukraine, following the Chernobyl accident, with those diagnosed in Italy and France during the same time period also is suggestive of unique causes for the thyroid cancers in Belarus and Ukraine (Pacini et al. 1997). Thyroid cancers cases in 472 children and adolescents <21 years of age diagnosed in Belarus and Ukraine during the period 1986–1995 were evaluated. These included approximately 98% of all childhood cases reported during that period. The comparison group consisted of 369 cases of the same age groups consecutively diagnosed at two clinics in Italy (n=219) and France (n=150). The study revealed several differences in the Belarus-Ukraine cases when compared with the Italy-France cases. Most of the Belarus-Ukraine cases were 5 years of age or less, whereas most of the Italy-France cases occurred after age 14 years. The female:male ratio of the Italy-France cases was significantly higher (2.5) than the ratio in the Belarus-Ukraine cases (1.6). Most (94%) of the Belarus-Ukraine cases were papillary carcinomas with follicular carcinomas accounting for only 5% of cases, whereas 82% of the Italy-France cases were papillary and 15% were follicular carcinomas. Cancers diagnosed in the Belarus-Ukraine group, typical of thyroid cancer in early childhood, tended to be more invasive with extrathyroidal involvement more frequently than in the Italy-France cases. The Belarus-Ukraine cases also had a higher incidence of thyroid autoimmunity (i.e., elevated antithyroid peroxidase and thyroglobulin antibodies) than the Italy-France cases. These results suggest different factors contributed to the Belarus-Ukraine and Italy-France cases, radiation dose possibly being at least one factor.

In both Belarus and the Ukraine, the highest rates of childhood thyroid cancer have occurred in areas where exposure to other industrial contaminants are 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 (Nikiforov and Fagin 1998).

The strengths of the Chernobyl thyroid studies described above include: (1) the large number of children who received substantial thyroid doses; (2) the studies included thyroid exposure measurements on more than 100,000 children; (3) the generally high level of thyroid surveillance in the population after the accident; and (4) that many children were screened with ultrasound, which provides relatively objective evidence of thyroid nodularity; one study (Astakhova et al. 1996) attempted to control for the intensity of thyroid surveillance. Limitations of these studies include: (1) substantial dose uncertainties and use of average doses in many of the studies rather than estimates of individual doses; (2) no thyroid dose estimates for many of the thyroid cancer cases; (3) the presence of iodine deficiency in the study populations may have affected both the thyroid radiation dose received from ^{131}I as well as the likelihood of a thyroid neoplasm; (4) greater intensity of thyroid screening and surveillance in the areas of highest exposure than in areas of lower exposure; and (5) lack of rigorous epidemiologic study designs in many of the studies (i.e., no systematic sampling design, no blinding of examiners with respect to likely thyroid dose, and irregular variations in thyroid screening). Several international efforts are underway to address these issues and to provide better information on health risk associated with the exposures that occurred following the Chernobyl accident (UNSEAR 2000).

Hanford Nuclear Site Releases. The CDC (2002) has conducted a follow-up prevalence study of thyroid cancer in populations that resided near the Hanford Nuclear Site in southeastern Washington during the period 1944–1957. The study included 3,441 subjects who were born during the period 1940–1946 in counties surrounding the Hanford Nuclear Site. Thyroid disease was assessed from a clinical evaluation of each subject, which included assessments of ultrasound or palpable thyroid nodules. Historical information on thyroid disease and information on radiation exposures were obtained by interviews and, when possible, review of medical records of participants, including pathology slides to confirm cancer diagnosis. Thyroid radiation doses were estimated using a dosimetry model developed in the Hanford Environmental Dose Reconstruction Project. Information on residence history and relevant food consumption patterns (e.g., milk consumption, breast feeding, consumption of locally harvested produce) for each study participant was obtained by interview. The estimated mean thyroid radiation dose, based on 91 participants, was 174 mGy (±224, standard deviation [SD]) (17.4±22.4 rad), and the range was 0.0029–2,823 mGy (0.00029–282 rad). Doses varied geographically, with the highest doses received by people who lived near and downwind from the site. Dose-response relationships were assessed using a linear regression model with adjustments for the following confounding and effect modifying variables:

sex, age of first exposure, age of evaluation, ethnicity, smoking, and potential exposures from Nevada Test Site releases. Alternatives to the linear model were also explored including linear quadratic and logistic models. Incidences of thyroid carcinoma or nodules were found to be unrelated to thyroid radioiodine dose. As noted above, a final report of conclusions has not been published and the study is currently under review by the National Research Council. Strengths of the Hanford study include: (1) the extremely careful study design and methods; (2) the systematic sampling and high rates of subject location and participation; (3) blinded thyroid assessments by multiple examiners, along with ultrasound, which is a more objective assessment of thyroid nodularity; and (4) extensive attempts to model thyroid radiation doses in various locales, combined with self-reported or parent-reported estimates of milk and vegetable consumption to estimate individual thyroid doses. Limitations of the Hanford study include substantial individual dose uncertainties, since no thyroid exposure measurements were available and individual milk and vegetable consumption estimates were recalled 30–40 years after the exposure period studied; and statistical power and precision were limited by the model's sample size and relatively low dose range (0.8% of the study population had estimated thyroid doses >1 Gy [100 rad] and 0.2% had doses >2 Gy [200 rad]).

3.3.3 External Exposure

No studies were located on the toxicity of external exposures to radioiodine. The four radioactive isotopes of iodine that are of particular interest with respect to human exposures (^{123}I, ^{125}I, ^{129}I, and ^{131}I) emit, primarily, beta radiation, which would not be expected to produce adverse effects from external exposures, other than possibly to the upper layers of the skin.

3.4 GENOTOXICITY

Potassium iodide, I_2, and povidone iodine (0.1–10 mg/mL) did not show mutagenic effects in L5178Y mouse lymphoma cells or in transforming activity in Balb/c 3T3 cells grown in culture (Kessler et al. 1980; Merkle and Zeller 1979). Potassium iodide and I_2 did not produce lethal mutations in *Drosophila melanogaster* when eggs were incubated in 0.38 mg/mL I_2 or 0.75 mg/mL potassium iodide (Law 1938). I_2 did not show mutagenic activity in His+ revertant assay in *Saccharomyces cerevisiae* (Mehta and von Borstel 1982a) Iodide is a free-radical scavenger and has been shown to decrease hydrogen peroxide-induced reversion in strain TA104 of *Salmonella typhimurium* (Han 1992).

Sodium iodate ($NaIO_3$) was not mutagenic when tested in the bacterial Ames assay, mouse bone marrow micronucleus test, or recessive lethal test in *D. melanogaster* (Eckhardt et al. 1982). Sodium iodate has radiosensitizing activity and has been shown to increase the number of gamma radiation-induced single-strand DNA breaks in bacteria (Myers and Chetty 1973). Iodate is a more active radiosensitizing agent than is iodide (Kada 1970; Kada et al. 1970; Noguti et al. 1971)

Chromosome aberrations (breakages, dicentrics, micronuclei) have been found in peripheral blood cells of patients who received ^{131}I ablative therapy for hyperthyroidism, in infants born to mothers who received such therapy during pregnancy, and in children exposed to radioiodine released from the Chernobyl nuclear power plant (Ardito et al. 1987; Ballardin et al. 2002; Baugnet-Mähieu et al. 1994; Boyd et al. 1974; Catena et al. 1994; Goh 1981; Gutierrez et al. 1999a; Lehmann et al. 1996; Monteiro et al. 2000; Ramírez et al. 1997, 2000) (see Section 3.3.2 for a more detailed discussion of exposures from the Chernobyl accident). The range of ^{131}I exposures in these cases was 15–200 mCi (0.6–7.4 GBq).

A significantly higher frequency of chromosome translocations (number of translocations per cell) was observed in blood lymphocytes from nine patients who received ^{131}I for ablative treatment of multinodular or autonomous goiter (0.55–0.85 GBq, 15–23 mCi) compared to lymphocytes obtained from six healthy adults (Lambert et al. 2001). A study of 21 patients who received various exposures to ^{131}I for ablative treatment of thyroid carcinoma found a significantly higher frequency of micronuclei in peripheral blood cells of patients compared to a group of 93 healthy controls (Catena et al. 1994). A significant exposure response relationship was observed at exposures that ranged from 35 to 202 mCi (1.3–7.5 GBq). A study of 10 patients who received ^{131}I for ablative treatment of thyroid carcinoma compared the outcomes of cytogenetic assessment of peripheral blood lymphocytes before or 1 and 10 days after their ^{131}I exposures (Baugnet-Mahieu et al. 1994). The patients received two oral doses of 840 MBq (13.7 mCi) given on 2 consecutive days. A small but statistically significant increase in "abnormal cells" (2.69%) and dicentrics (1.91%) occurred after exposure to ^{131}I. The presence of micronuclei and binucleated lymphocytes with micronuclei (BNMN) in blood lymphocytes was assessed in six patients, before and after they received who received ^{131}I (2.96–5.50 GBq, 80–149 mCi) for treatment of thyroid carcinoma (Ballardin et al. 2002). The estimated radiation dose to bone marrow was 25.5–52.5 cGy (25.5–52.5 rad). BNMN frequency increased after exposure to ^{131}I, reaching a peak response (3.6-fold increase above pre-exposure values) 7 days after exposure. Cytogenetic assessments of peripheral blood lymphocytes of five patients who received 15–40 mCi (0.6–1.5 GBq) for treatment of hyperthyroidism and four control subjects revealed dicentrics and rings in the treated patients, but no such abnormalities in the control subjects (Boyd et al. 1974). An increase in the frequency of micronuclei in

peripheral blood lymphocytes was observed of 12 adult women 1 week after they received 100–150 mCi ^{131}I (3.7–5.6 GBq) for treatment of thyroid cancer (Ramírez et al. 1997). The frequency of chromosome translocations in thyroid tumor tissue was compared among groups of patients who had tumors but no radiation history (n=24), patients who received ^{131}I or external radiation therapy (n=7), and children (n=40) who were residents of the Gomel, Brest, or Minsk regions of Belarus at the time of the Chernobyl accident (Lehmann et al. 1996). The frequency of translocations was highest in the patients who received radiation therapy and lowest in the patients that had no history of exposure to radiation. Translocation frequencies among Belarussian children were lower than in the radiation therapy patients and higher than in the patients who had no radiation history. The highest translocation frequencies among Belarussian children were observed in children from the Gomel region where ^{131}I exposures and thyroid radiation doses are considered to have been the highest of the three regions studied.

Goh (1981) reported a case of cretinism that developed at age 8 months in an infant whose mother received 99 mCi (3.7 GBq) of ^{131}I during her 6th week of pregnancy. The infant was hypothyroid and had no detectable thyroid gland function. Cytogenetic studies conducted on peripheral blood lymphocytes revealed chromosomal breakages in both the infant and mother.

3.5 TOXICOKINETICS

3.5.1 Absorption

3.5.1.1 Inhalation Exposure

Molecular iodine (I_2) is absorbed when humans are exposed to I_2 vapor. In volunteers who inhaled radioiodine I_2 vapor, essentially all of the inhaled vapor was retained and cleared from the respiratory tract with a half-time of approximately 10 minutes (Black and Hounam 1968; Morgan et al. 1968). Much of the clearance of the iodine from the respiratory tract was transferred to the gastrointestinal tract, suggesting that the initial deposition was primarily in the conducting airways and subject to mucocilliary clearance mechanisms. Observations in humans of relatively rapid absorption of inhaled I_2 are supported by studies in mice, rats, dogs, and sheep (Bair et al. 1963; Willard and Bair 1961).

Methyl iodide is also inhaled when humans are exposed to methyl iodide vapor. In volunteers who inhaled tracer concentrations of [^{132}I]methyl iodide, approximately 70% of the inhaled iodine was retained with a half-time in the respiratory tract of approximately 5 seconds, suggesting extremely rapid absorption at the alveolar-blood interface (Morgan and Morgan 1967; Morgan et al. 1967a, 1967b).

Studies of the absorption of inhaled inorganic iodide in humans are not available. However, in monkeys that inhaled particulate aerosols of radioiodine as sodium iodide (mass median diameter, 2.32 μm±1.15 SD), inhaled iodide was retained in the respiratory tract with a half-time of approximately 10 minutes (Perrault et al. 1967; Thieblemont et al. 1965). In dogs and rats that were exposed to cesium chloride aerosols containing ^{131}I (mass median aerodynamic diameter, 1.4 μm±1.7 SD), iodine was retained and rapidly cleared from the respiratory tract (McClellan and Rupprecht 1968; Thomas et al. 1970). Retention and relatively rapid absorption of iodine has also been observed in mice and sheep that inhaled radioiodine as either sodium iodide or silver iodide particulate aerosols (mean count diameter, 0.25 μm) (Bair et al. 1963; Willard and Bair 1961).

3.5.1.2 Oral Exposure

Gastrointestinal absorption of iodine is generally considered to be approximately 100% after an ingested dose of water soluble iodide salts, such as potassium or sodium iodide. This conclusion is based on several types of observations made in human subjects who received oral doses of radioiodine compounds (the reader should note that where the chemical form of the radioiodine compound was not reported, which is the case for most of the radioiodine tracer studies described here, it is likely that it was sodium iodide, as this is a common form supplied commercially for pharmaceutical use). Fecal excretion of ^{131}I was <1% of the dose in seven euthyroid adult subjects who ingested a single tracer dose of ^{131}I, suggesting near complete absorption of the ingested radioiodine (Fisher et al. 1965). In the same study, 20 euthyroid adults received daily oral doses of potassium iodide for 13 weeks (0.25 or 1.0 mg I/day). Daily urinary iodine excretion was approximately 80–90% of the estimated daily intake, also suggesting near complete absorption. Similarly, in an acute ingestion study of nine healthy subjects, urinary and thyroid radioiodine accounted for 97% (±5, SD) of a single ingested tracer dose of radioiodine (^{131}I or ^{132}I), suggesting near complete absorption of the tracer dose (Ramsden et al. 1967). In this same study, two subjects ingested the tracer dose together with a dose of 5 or 15 mg stable iodide (the chemical form of the stable iodide was not specified, but presumably, it was either potassium or sodium iodide) and the recoveries of radioiodine in thyroid and urine were 96 and 98%, respectively. In one subject who ingested the tracer dose either after a fast (duration not specified) or with a “full stomach”, the recoveries of radioiodine in thyroid and urine were 97 and 98%, respectively (Ramsden et al. 1967).

Measurement of radioiodine uptake in the thyroid gland is also an indicator of absorption, although such measurements alone do not allow an accurate quantitative estimate of absorption without other

assumptions about the pharmacokinetics of iodine. Studies of iodine kinetics in subjects who received intravenous injections of tracer doses of radioiodine have shown that the fraction of an injected dose that accumulates in the thyroid is affected by many variables; however, it does not vary greatly among individuals who have the same iodine intake and whose thyroid glands are "normal" (see Section 3.5.2.2). This fraction has been shown to be similar (20–35%) when radioiodine (^{123}I, ^{125}I, or ^{131}I) is administered to adults by the intravenous or oral routes, suggesting extensive, if not complete, absorption of ingested radioiodine (Bernard et al. 1970; Gaffney et al. 1962; Ghahremani et al. 1971; Oddie and Fisher 1967; Pittman et al. 1969; Robertson et al. 1975; Sternthal et al. 1980; Van Dilla and Fulwyler 1963). Although the fraction of the oral dose of radioiodine taken up by the thyroid 1–2 days after an oral dose may be slightly higher in females than males, there is no evidence that this difference results from differences in absorption (Ghahremani et al. 1971; Quimby et al. 1950; Robertson et al. 1975).

Gastrointestinal absorption of iodine appears to be similar in children, adolescents, and adults, as assessed from measurements of 24-hour thyroid uptakes of radioiodine administered orally (Cuddihy 1966; Oliner et al. 1957; Van Dilla and Fulwyler 1963). Absorption in infants, however, may be lower than in children and adults. Evidence for this comes from studies in which thyroid uptake of radioiodine was measured in newborns who received tracer doses of radioiodine orally or by injection. In general, injection of the radioiodine intramuscularly or intravenously resulted in higher thyroid uptakes than when the radioiodine was administered by gastric tube, suggesting incomplete absorption of the oral dose. For example, in 8 healthy newborn infants (<36 hours postnatal) who each received a tracer dose of ^{131}I by gastric tube, the average peak thyroid uptake (30 hours after the dose) was approximately 50% of the dose compared to an average of 70% (25 hours after the dose) in 17 infants who received the tracer dose as an intramuscular injection (Morrison et al. 1963). The ratio of the thyroid uptakes after the oral and injected iodine doses suggests a fractional oral absorption of approximately 70%. In a study involving slightly older newborns (72–96 hours old), 15 newborns each received a tracer dose of ^{131}I by gastric tube and the average 24-hour uptake of radioiodine in the thyroid was 20% (range, 6–35%) (Ogborn et al. 1960). By contrast, in a study of seven healthy infants (<3 days old), the mean thyroid uptake 24 hours after an intramuscular tracer dose of ^{131}I was 70% (range, 46–97) (van Middlesworth 1954). In a study of 26 healthy newborns (<48 hours old) who each received an intravenous tracer dose of ^{131}I, the mean 24-hour thyroid uptake was 62% (range, 35–88) (Fisher et al. 1962). The rapid changes in iodine status and biokinetics in the early weeks of postnatal life make interpretations of comparisons between injection data for a few groups of infants with ingestion data for other groups highly uncertainty. Most or all of the differences in the thyroid uptakes observed in the above three studies may reflect differences in age and iodine status

Iodide incorporated into food appears to be nearly completely absorbed. In a dietary balance study in which dietary iodide intakes (170–180 µg/day) and excretion were measured in 12 healthy adult women over two 7-day periods, urinary iodide excretion was 96–98% of the daily intake (Jahreis et al. 2001). Iodine incorporated into bovine milk appears to be nearly completely absorbed when ingested. Cuddihy (1966) measured thyroid uptakes of radioiodine in euthyroid subjects who ingested radioiodine-contaminated cow milk for 14 days. The milk was collected from a cow that was fed ^{131}I in feed (endogenously incorporated). Thyroid uptake 24 hours after the last milk dose was approximately 23% of the dose. Since this value is within the range of 20–35% observed when a tracer dose of ^{131}I was administered orally or intravenously, it suggests that iodine that is endogenously incorporated into cow milk is extensively, if not completely, absorbed. A slightly different observation leads to a similar conclusion. Comar et al. (1963) compared radioiodine uptakes in each of 11 healthy adults who ingested ^{131}I in a capsule (containing an aqueous solution of radioiodine) or ^{131}I endogenously incorporated into cow milk. The 24-hour thyroid uptakes were nearly identical under each dosing condition (means, 19 and 20% of the dose) suggesting a similar absorbed fraction of the dose. Pendleton et al. (1963) measured ^{131}I in dairy cow milk from farms near the NTS, and in the thyroids or total bodies of families who lived on these farms (measured from external thyroid or total body counting). The average uptake of ^{131}I in 24 individuals was 17% (range, 5–47%) which is similar to that observed after ingestion or injection of radioiodine. Assessments of gastrointestinal absorption of iodine in other foods are not available, although Wayne et al. (1964) reported that radioiodine incorporated into watercress was completely absorbed when ingested by an adult (no details provided).

Little information is available on the gastrointestinal absorption of forms of iodine other than iodide. Iodine compounds, such as I_2 and iodates (e.g., $NaIO_3$), may undergo reduction to iodide before being absorbed in the small intestine, and absorption may not be complete (Cohn 1932). Iodine from the sodium salt of the thyroid hormone thyroxine (T_4) is absorbed when T_4 is ingested. In two adults who each received a single oral dose of 80 µg [^{131}I]-T_4, the rate of fecal excretion of radioiodine was similar to that observed in three subjects who received the same dose intravenously (10–15% of the dose), suggesting substantial absorption from the gastrointestinal tract (Myant and Pochin 1950). In this same study, the sum of urinary excretion of radioiodine and thyroid uptake of radioiodine, 24 hours after the oral dose of [^{131}I]-T_4, was approximately 25% of the dose, compared to an average of 33% (±7) in six subjects who received the [^{131}I]-T_4 dose intravenously. This observation is also consistent with substantial, if not complete, absorption of T_4 from the gastrointestinal tract (at least 75% of the dose).

Observations in humans that indicate extensive absorption of ingested inorganic iodine are supported by experiments in animals. Iodine is extensively absorbed in rats when it is ingested as either I_2 or NaI. When fasted rats were administered oral gavage tracer doses of ^{131}I as either I_2 or NaI, 8–9% of the dose was excreted in feces in 72 hours and 34–35% of the dose was excreted in the urine (Thrall and Bull 1990). In the same study, similar results were obtained in rats that were allowed free access to food before the oral radioiodine dose; 6–7% of the dose was excreted in feces in 78 hours and 22–29% was excreted in urine (22% of the I_2 dose and 29% of the NaI dose). These results suggest that tracer doses of ingested iodine from NaI and I_2 are both nearly completely absorbed from the gastrointestinal tract in rats. In cows, tracer doses of ^{131}I ingested in the diet is nearly completely absorbed (Vandecasteele et al. 2000). When tracer levels of radioiodine (^{131}I) were administered orally, intravenously, or subcutaneously to four sheep, the peak thyroid uptake of radioiodine was similar, 17–19% of the dose (these values are not corrected for radioactive decay of the ^{131}I), suggesting extensive absorption from the oral route (Wood et al. 1963).

Povidone-iodine is a complex of I_2 and polyvinyl pyrrolidone that is widely used as topical antiseptic. Povidone-iodine preparations contain approximately 9–12% iodine, of which only a small fraction is free in solution (Lawrence 1998; Rodeheaver et al. 1982). Absorption of iodine ingested as povidone-iodine has been studied in rats. Rats that received single gavage doses of ^{125}[I]I-povidone (dose not specified) absorbed approximately 3% of the dose, as assessed by measurements of the radioiodine that was retained in the gastrointestinal tract 24 hours after the dose (Abdullah and Said 1981). In the same study, absorption was approximately 10 or 5% when the povidone-iodine was administered in 10% ethanol solution and 5% when administered as a 0.2% solution of benzalkonium chloride.

3.5.1.3 Dermal Exposure

Systemic iodine toxicity has occurred following dermal exposures to iodine compounds, suggesting that these compounds of iodine are absorbed across the skin of humans (see Section 3.2.3). Harrison (1963) attempted to estimate absorption rates for solutions of potassium iodide or iodine (I_2), and gaseous I_2 in humans. Subjects received topical applications of ^{131}I as potassium iodide or iodine (I_2) and absorption was estimated from measurements of the cumulative urinary excretion of radioactivity and the 24-hour activity in the thyroid. Three subjects received a topical application of tracer concentrations of [^{131}I]KI on a 12.5 cm^2 area of the forearm. The site was left uncovered and after 2 hours, all of the applied radioactivity could be detected on the skin and approximately 90% of the radioactivity could be recovered from the skin by washing with soap and water. Absorption was estimated to be approximately 0.1% of

the applied dose (range, 0.09–0.13) based on 3-day cumulative urine radioactivity. Thyroid radioactivity 24 hours after the topical dose was below the limits of detection. If it was assumed that the 24-hour thyroid uptake was 30% of the absorbed dose and that the all of the absorbed activity that was not recovered in urine was in the thyroid, absorption was approximately 0.16% in the three subjects (range, 0.13–0.19). In two subjects in this same study who received a similar topical application of aqueous tracer $[^{131}I]I_2$ along with 0.1 mg of $[^{127}I]I_2$ carrier, the absorption was estimated to be 0.06–0.09% of the applied dose, with the higher estimate assuming thyroid uptake of 30% of the absorbed dose. This study also estimated iodine absorption after dermal exposure to $[^{131}I]I_2$ vapor. When a 12.5 cm^2 area of skin was isolated and placed in contact with I_2 vapor for 30 minutes or 2 hours, approximately 90% of the total iodine content of the vapor was deposited on the skin. Approximately 50% of the deposited dose could be washed off with soap and water. Absorption varied depending on the amount of $[^{127}I]I_2$ carrier in the vapor (the concentration was not reported). At the lowest carrier amount (approximately 0.8 mg applied to the skin), absorption of ^{131}I was 1.2% of the activity that was on the skin at the end of the 2-hour exposure. With exposure to 3–5 mg carrier, which produced visible irritation of the skin (reddening or blistering), absorption was 27–78%. These observations suggest that exposure to I_2 vapors can result in deposition of iodine onto the skin and that dermal irritation produced by I_2, and possibly other irritants, may substantially increase the absorption of iodine after dermal exposure to I_2. Dermal absorption of I_2 vapor was indicated in an experimental study in which ^{131}I was detected in the thyroid glands of seven male adult volunteers who were exposed, whole body and without respiratory intake, to $^{131}I_2$ vapor (the exposure appears to have been to tracer levels) for up to 4 hours (Gorodinskiy et al. 1979).

Povidone-iodine, a complex with iodine and polyvinyl-pyrrolidone, and alcohol tinctures of iodine are widely used as a topical antiseptic. Iodine is absorbed to some extent when such preparations are applied to the skin, although quantitative estimates of the amount absorbed are not available for humans. Urinary iodine excretion has been shown to increase following the topical application of povidone-iodine to the hands and arms as part of a surgical scrub routine, indicating systemic absorption (Connolly and Shepard 1972). Increases in iodine concentration in maternal urine and umbilical cord blood have been observed in pregnant women who received dermal or vaginal applications of povidone-iodine prior to delivery for disinfection of the skin and fetal scalp electrodes, suggesting that absorption of iodine occurs with these uses of povidone-iodine as well (l'Allemand et al. 1983; Bachrach et al. 1984). Thyroid enlargement, hypothyroidism, and elevated urinary iodine excretion also have been observed in hospitalized infants who received frequent topical antiseptic scrubs with iodine-alcohol preparations as part of preparations for various clinical procedures (Brown et al. 1997; Chabrolle and Rossier 1978a, 1978b).

Some quantitative information is also available on dermal absorption of iodine in animals. When tracer levels of radioiodine (^{131}I) were applied to the shaved skin (50–100 cm^2) of four sheep, the peak thyroid uptake of radioiodine was 2–6% of the applied dose compared to 17–19% when the dose was given orally, subcutaneously, or intravenously (these values are not corrected for radioactive decay of the ^{131}I) (Wood et al. 1963). In a second study, two sheep received a tracer dose of radioiodine as either an oral dose or a topical dose; the peak thyroid uptake was 9–14% of the dose at 48–96 hours after the topical dose, compared to 30% at 48 hours after the oral dose (both values corrected for radioactive decay). The report of these studies does not specify whether the topical applications were occluded or whether the animals were restrained in any way from ingesting the topically applied radioiodine (e.g., licking the site of application). If ingestion of the radioiodine did not occur, then these studies suggest substantial absorption of topically applied iodine since, during the first 1–4 days after topical dosing, thyroid radioiodine uptake was approximately 30–50% of that observed after oral dosing, and thyroid uptakes after oral and parenteral dosing were similar.

Additional evidence for dermal absorption of iodine comes from a study of pigs. A solution (solvent not specified) containing a mixture of 85% [^{131}I]I_2 and 15% [^{131}I]NaI was applied to a 150 cm^2 area of abdominal skin on each of four immature pigs and allowed to dry on the skin; the site of application was not covered and it is not clear if the site was accessible to licking and ingestion of the applied radioiodine (Murray 1969). Approximately 95% of the applied dose was removed from the skin by washing the site of application 2 hours after the dosing. Peak thyroid uptake of radioiodine was approximately 0.2% of the dose, 1–2 days after dosing (the report does not indicate whether the radioiodine measurements were corrected for radioactive decay). In the same study, a 150 cm^2 area of clipped flank skin on each of four immature pigs was exposed for 25 minutes to a vapor of ^{131}I containing 85% gaseous ^{131}I, presumably [^{131}I]I_2. The exposed areas were not covered or washed subsequent to exposure. Peak thyroid uptake of radioiodine was approximately 0.3% of the applied dose 5–7 days after dosing. The lower amount of absorption of radioiodine in the pigs compared to the results obtained in sheep (Wood et al. 1963) cannot be interpreted with the available information. It may reflect species differences in skin permeability to iodine, differences in the chemical form iodine applied to the skin (I_2 or I^-), or differences in the amounts of topically applied radioiodine that were ingested from licking the site of application.

Povidone-iodine, an ingredient of some iodine-based topical disinfectants, is absorbed across the skin of dogs. Topical application of povidone-iodine in dogs resulted in elevated serum iodide concentrations within 2 hours after application; the amount of iodine absorbed was not determined in this study (Moody et al. 1988). Evidence for absorption of iodine from topically applied povidone-iodine is also provided by

experiments with rats and mice. Topical application of povidone-iodine to 15–20 mm^2 of the shaved skin of either rats or mice 2 hours prior to an injection of radioiodine decreased radioiodine uptake in the thyroid by 90%, suggesting competition between the absorbed topically applied iodine and the injected radioiodine for thyroid uptake (Furudate et al. 1997).

3.5.1.4 Other Routes of Exposure

Iodine is absorbed systemically after intravaginal applications of povidone-iodine. Increases in iodine concentration in maternal urine, umbilical cord blood, and breast milk, and in infant urine have been observed following vaginal applications of povidone-iodine to pregnant women prior to delivery for disinfection of fetal scalp electrodes (l'Allemand et al. 1983). Increases in serum iodine concentrations have also been observed following irrigation of the lower colon and rectum with povidone-iodine during surgical procedures, suggesting absorption from the lower bowel (Tsunoda et al. 2000).

3.5.2 Distribution

3.5.2.1 Inhalation Exposure

The distribution of absorbed iodine is expected to be similar regardless of the route of exposure to inorganic iodine. This is supported by studies in which humans were exposed to tracer levels of $[^{132}I]CH_3I$ and approximately 20–30% of the iodine retained in the respiratory tract was distributed to the thyroid gland and 30–60% was excreted in urine in approximately 10 hours; essentially identical results were obtained when a tracer dose of ^{132}[I]NaI was ingested (Morgan et al. 1967a, 1967b). Similar results were obtained when volunteers inhaled tracer levels of radioiodine as I_2 (Black and Hounam 1968; Morgan et al. 1968). The distribution of inhaled particulate aerosols of sodium iodide in monkeys also appears to be similar to ingested iodide (Perrault et al. 1967; Thieblemont et al. 1965). A complete discussion of the distribution of iodine after oral exposures to inorganic iodine is presented in Section 3.5.2.2, and is applicable to inhalation exposures.

3.5.2.2 Oral Exposure

The human body contains approximately 10–15 mg of iodine, of which approximately 70–90% is in the thyroid gland, which accumulates iodine in producing thyroid hormones for export to the blood and other tissues (Cavalieri 1997; Hays 2001; Stather and Greenhalgh 1983). The concentration of iodine in serum

is approximately 50–100 µg/L under normal circumstances (Fisher et al. 1965). Approximately 5% in serum is in the inorganic form as iodide; the remaining 95% consists of various organic forms of iodine, principally protein complexes of the thyroid hormones T_4 and T_3 (Fisher et al. 1965; Nagataki et al. 1967; Sternthal et al. 1980; Wagner et al. 1961).

The tissue distribution of iodide and organic iodine are very different and are interrelated by metabolic pathways that lead to the iodination and deiodination of proteins and thyroid hormones in the body (see Section 3.5.3.2). Iodide is largely confined to the extracellular fluid compartment, with the exception of tissues that possess specialized transport mechanisms for accumulating iodide; these include the thyroid, salivary glands, gastric mucosa, choroid plexus, mammary glands, placenta, and sweat glands (Brown-Grant 1961) (see Section 3.5.1). Serum concentrations of iodide, indicative of extracellular fluid concentrations, normally range from 5 to 15 µg/L; this would suggest a total extracellular iodide content of the human body of approximately 85–170 µg, assuming an extracellular fluid volume of approximately 17 L (Cavalieri 1997; Saller et al. 1998).

Iodide concentrations in the thyroid are usually 20–50 times that of serum (0.2–0.4 mg/dL, 15–30 nM); however, concentrations in excess of 100 times that of blood occur when the gland is stimulated by thyrotrophin (a TSH) and concentrations in excess of 400 times blood have been observed (Wolff 1964). Other tissues that can accumulate iodide to a concentration greater than that of blood or serum include the salivary glands, gastric mucosa, choroid plexus, mammary glands, placenta, and sweat glands (Brown-Grant 1961). Iodide taken up by the thyroid gland is utilized in the production of thyroid hormones, which are stored in the gland (see Section 3.5.3.2). This organic fraction of the thyroid iodine content accounts for approximately 90% of the iodine in the thyroid gland and includes iodinated tyrosine and tyrosine residues that comprise the thyroid hormones, T_4 and T_3, and their various synthesis intermediates and degradation products.

The thyroid hormones, T_4 and T_3, account for approximately 90–95 and 5% of the organic iodine in plasma, respectively (Fisher et al. 1965; Sternthal et al. 1980). Nearly all (>99%) of the T_4 and T_3 in plasma is bound to protein. The major binding protein for T_4 and T_3 is thyroxine-binding globulin (TBG), which has a high affinity for both hormones (Table 3-4) (Larsen et al. 1998; Robbins 1996). Other proteins that bind thyroid hormones, with lower affinity, include transthyretin (thyroxine-binding prealbumin), albumin, and various apoproteins of the high density lipoproteins HDL_2 and HDL_3 (3–6% of plasma hormones). The distribution of protein-bound thyroid hormones is largely confined to the plasma space, whereas the free hormones distribute to the intracellular space of a wide variety of tissues where

Table 3-4. Binding Characteristics of Major Human Thyroid Hormone-Binding Proteins

Parameter	Thyroxine-binding globulin	Transthyretin	Albumin
Molecular weight of complex (D)	54,000	54,000 (subunit)[a]	66,000
Plasma concentration (µmol/L)	0.27	4.6	640
T_4 binding capacity (µg T_4/dL)	21	350	50,000
Association constants (M^{-1})			
T_4	$1x10^{10}$	$7x10^7$	$7x10^5$
T_3	$5x10^8$	$1.4x10^7$	$1x10^5$
Fraction of sites occupied by T_4[b]	0.31	0.02	<0.001
Distribution volume (L)	7	5.7	7.8
Turnover rate (percent/day)	13	59	5
Distribution of thyronines (percent/protein)			
T_4	68	11	20
T_3	80	9	11

[a]Transthyretin consists of four subunits (54 kD) complexed with retinol binding protein
[b]In euthyroid state

T_3 = 3,5,3ℕ-triiodo-L-thyronine; T_4 = 3,5,3ℕ,5ℕ-tetraiodo-L-thyronine (thyroxine)

Source: Larsen et al. 1998

they exert the metabolic effects attributed to thyroid hormones. TBG and other binding proteins serve as reservoirs for circulating thyroid hormones and contribute to the maintenance of relatively constant free hormone concentrations in plasma.

Uptake of T_4 and T_3 into liver, skeletal muscle, and other tissues occurs by a saturable, energy-dependent carrier transport system (see Section 3.6.1). Lipoprotein transport mechanisms may also play a role in the uptake of thyroid hormones into certain tissues (Robbins 1996). Intracellular T_4 and T_3 exist as free hormone and are bound to a variety of intracellular proteins.

Maternal exposure to iodine results in exposure to the fetus (ICRP 2002). Radioiodine accumulation in the fetal thyroid commences in humans at approximately 70–80 days of gestation, and precedes the development of thyroid follicles and follicle colloid, which are generally detectable at approximately 100–120 days of gestation (Book and Goldman 1975; Evans et al. 1967). Fetal iodide uptake activity increases with the development of the fetal thyroid and reaches its peak at approximately 6 months of gestation, at which point, the highest concentrations in thyroid are achieved, approximately 5% of the maternal dose/g fetal thyroid (approximately 1% of the maternal dose) (Aboul-Khair et al. 1966; Evans et al. 1967). Fetal radioiodine concentrations 1–2 days following a single maternal dose of radioiodine generally exceed the concurrent maternal thyroid concentration by a factor of 2–8 with the highest fetal/maternal ratios occurring at approximately 6 months of gestation (Book and Goldman 1975; Millard et al. 2001). Following long-term exposure, either from ingestion of administered radioiodine or from exposure to radioactive fallout, the fetal/maternal ratio for thyroid radioiodine concentration has been estimated to be approximately 2–3 (Beierwaltes et al. 1963; Book and Goldman 1975; Eisenbud et al. 1963).

Iodine uptake into the thyroid gland is highly sensitive to the iodide intake. At very low intakes, representing iodine deficiency (e.g., 20 μg/day), uptake of iodide into the thyroid gland is increased (Delange and Ermans 1996). This response is mediated by TSH, which stimulates iodide transport and iodothyronine production in the thyroid gland (see Section 3.6.1). At very high intakes of iodine, representing an intake excess (e.g., >1 mg/day), iodine uptake into the thyroid gland decreases, primarily as a result of decreased iodothyronine synthesis (Wolff-Chaikoff effect) and iodide transport into the gland (Nagataki and Yokoyama 1996; Saller et al. 1998). The fraction of an ingested (or injected) tracer dose of radioiodide that is present in the thyroid gland 24 hours after the dose has been measured in thousands of patients who received radioiodine for treatment of various thyroid disorders or for the assessment of thyroid function; these provide a comparative index of effects of various factors on the

distribution of absorbed iodide to the thyroid gland. A single oral dose of 30 mg iodide (as sodium iodide) decreases the 24-hour thyroid uptake of radioiodine by approximately 90% in healthy adults (Ramsden et al. 1967; Sternthal et al. 1980). The inhibition of uptake was sustained with repeated oral doses of sodium iodide for 12 days, with complete recovery to control (presodium iodide) uptake levels within 6 weeks after the last sodium iodide dose (Sternthal et al. 1980) or within 8 days after a single dose (Ramsden et al. 1967). Repeated oral doses of 1.5–2.0 mg iodide/m^2 of surface area produced an 80% decrease in thyroid uptake in children (Saxena et al. 1962).

The National Cancer Institute (NCI 1997) has analyzed data on 24-hour thyroid uptakes of radioiodine reported over the period from 1950 to 1980 and concluded that thyroid uptakes in adults have decreased in the United States over time from approximately 20–40% of the dose in the 1950–1960 period to approximately 15–20% currently (Cuddihy 1966; Dunning and Schwartz 1981; Kearns and Phillipsborn 1962; Kereiakes et al. 1972; Oddie and Fisher 1967; Oliner et al. 1957; Pittman et al. 1969; Van Dilla and Fulwyler 1963). This decrease appears to be related to a concurrent increase in the average dietary intake of iodide in the population from approximately 200 μg/day to approximately 800 μg/day (NCI 1997).

Twenty-four-hour radioiodine uptakes into the thyroid gland in males and females who experience similar iodide intakes are similar, although uptakes in females, as a percentage of the dose, appear to be 10–30% higher than in males (Ghahremani et al. 1971; Oddie et al. 1968a, 1970; Quimby et al. 1950; Robertson et al. 1975). Thyroid uptakes in newborns are 3–4 times greater during the first 10 days of postnatal life than in adults, and decline to adult levels after approximately age 10–14 days (Fisher et al. 1962; Kearns and Phillipsborn 1962; Morrison et al. 1963; Ogborn et al. 1960; Van Middlesworth 1954).

3.5.2.3 Dermal Exposure

The distribution of absorbed iodine is expected to be similar regardless of the route of exposure to inorganic iodine. A complete discussion of the distribution of iodine after oral exposures to inorganic iodine is presented in Section 3.5.2.2, and is applicable to inhalation exposures.

3.5.2.4 Other Routes of Exposure

The distribution of absorbed iodine is expected to be similar regardless of the route of exposure to inorganic iodine. A complete discussion of the distribution of iodine after oral exposures to inorganic iodine is presented in Section 3.5.2.2, and is applicable to inhalation exposures.

3.5.3 Metabolism

3.5.3.1 Inhalation Exposure

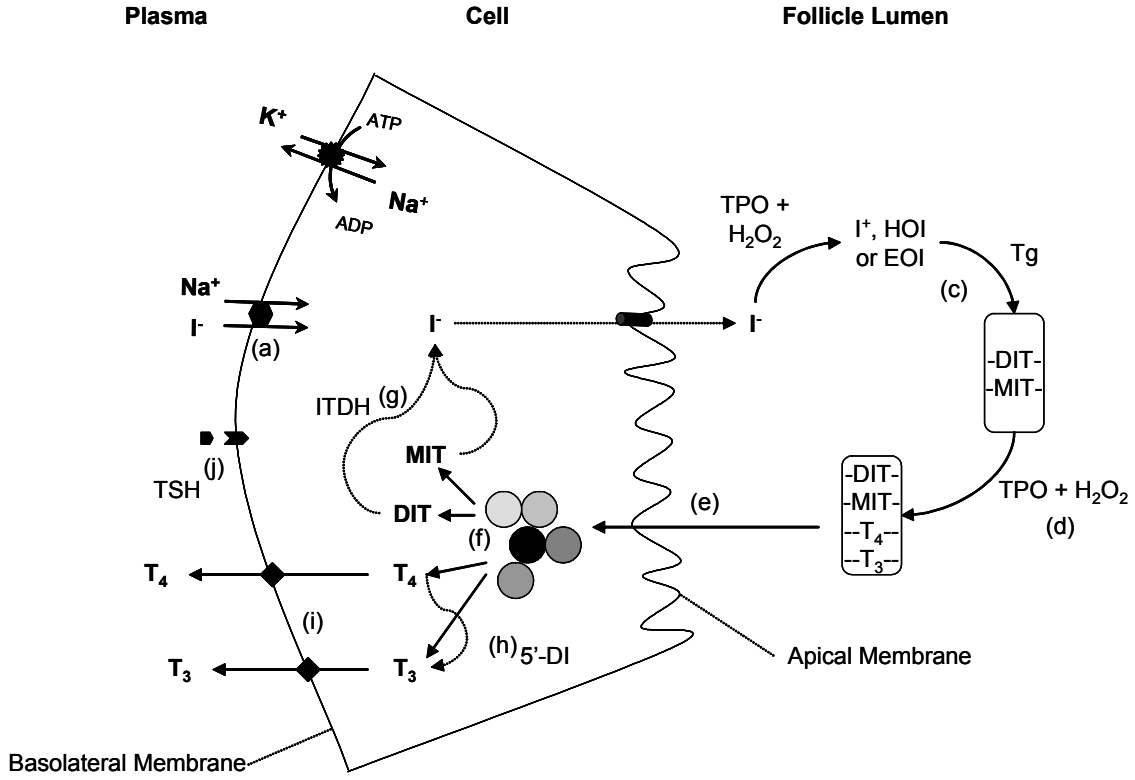
The metabolism of absorbed iodine is expected to be similar regardless of the route of exposure to inorganic iodine. Inhaled methyl iodide and I_2 appear to undergo rapid conversion to iodide based on nearly identical distribution and excretion kinetics of radioiodine when it is inhaled as either methyl iodide or I_2, or ingested as sodium iodide (Black and Hounam 1968; Morgan and Morgan 1967; Morgan et al. 1967a, 1967b, 1968). A complete discussion of the metabolism of iodine after oral exposures to inorganic iodine is presented in Section 3.5.3.2, and is applicable to inhalation exposures.

3.5.3.2 Oral Exposure

Iodide in the thyroid gland is incorporated into a protein, thyroglobulin, as covalent complexes with tyrosine residues (Figure 3-3). The iodination of thyroglobulin is catalyzed by the enzyme thyroid peroxidase, which resides predominantly in the apical membrane of thyroid follicle cells, with the active sites of the enzyme facing the follicular lumen (see Section 3.5.1). The iodination reactions occur at the follicular cell-lumen interface and consist of the oxidation of iodide to form a reactive intermediate, the formation of monoiodotyrosine and diiodotyrosine residues in thyroglobulin, and the coupling of the iodinated tyrosine residues to form T_4 (coupling of two diiodotyrosine residues) or T_3 (coupling of a monoiodotyrosine and diiodotyrosine residue) in thyroglobulin (Figure 3-4). The T_4/T_3 ratio in the thyroid is approximately 15:1; however, the relative amounts of T_4 and T_3 produced depend, in part, on the availability of iodide. Low levels of iodide result in a lower T_4/T_3 synthesis ratio (Taurog 1996).

Thyroglobulin is stored in the follicular lumen. When the thyroid gland is stimulated to produce and release thyroid hormones, thyroglobulin is transported into the follicular cells (Taurog 1996). Uptake of thyroglobulin occurs by endocytosis at the apical membrane, which is followed by fusion of endocytotic vesicles with lysosomes. Proteolytic enzymes in the lysosomes break down the thyroglobulin into

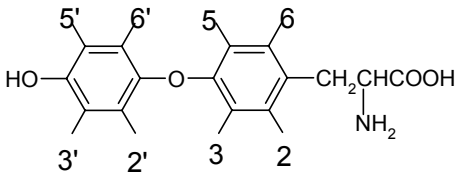
Figure 3-3. Pathways Uptake and Metabolism of Iodide in the Thyroid Gland



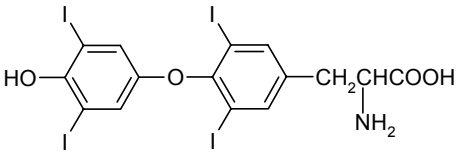
METABOLIC STEP	INHIBITOR
a. Iodine uptake	ClO_4^-, SCN^-, I^-
b. Iodine efflux	
c. Iodination	PTU, MMI
d. Coupling	PTU, MMI
e. Colloid resorption	Colchicine, Li^{2+} I^-, Cytoclasin B
f. Proteolysis	I^-
g. Deiodination of DIT and MIT	Dinitrotyrosine
h. Deiodination of T_4	PTU
i. Secretion of T_3 and T_4	
j. TSH receptor binding	

Figure 3-4. Thyroid Hormones and Metabolic Precursors

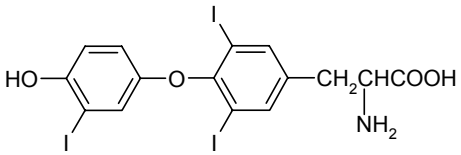
Thyronine



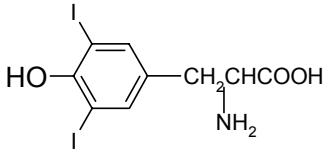
3,5,3',5'-Tetraiodothyonine (thyroxine, T_4)



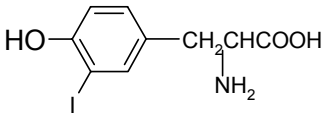
3,5,3'-Triiodothyonine (T_3)



Diiodotyrosine



Iodotyrosine

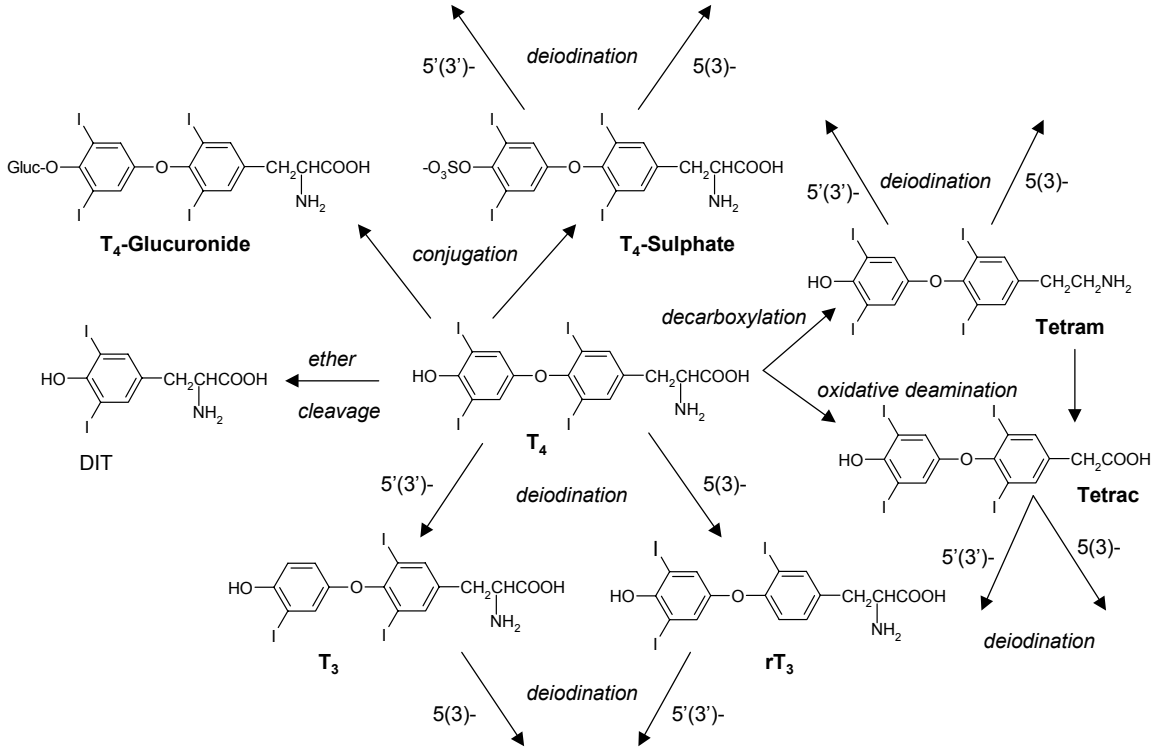


constituent amino acid residues, including T_4, T_3, monoiodotyrosine, and diiodotyrosine. T_4 and T_3 are exported to the blood, while monoiodotyrosine and diiodotyrosine residues are retained in the cell and deiodinated, and the iodide is recycled into the follicular lumen where it is reincorporated into thyroglobulin. Under circumstances of extreme stimulation of the thyroid gland, monoiodotyrosine, diiodotyrosine, and iodide can be released into the blood from the gland along with T_4 and T_3. Although the T_4/T_3 ratio in thyroglobulin is approximately 15:1 in the iodide replete state, the hormone secretion ratio is lower, approximately 10:1; thus, some T_4 appears to undergo monodeiodination to T_3 in the thyroid gland.

All of the major steps of thyroid hormone synthesis and release are stimulated by the pituitary hormone, TSH, including uptake of iodine by the thyroid gland, iodination of thyroglobulin, endocytosis of thyroglobulin from the follicle lumen, and proteolysis of thyroglobulin to release thyroid hormone for export to blood (see Section 3.5.1). Hormone synthesis is also responsive to serum iodide concentration. An acute exposure to high oral doses of iodide (e.g., >1 mg) inhibits the production of iodothyronine in the thyroid gland; this effect is not dependent on changes in circulating TSH levels, and is referred to as the Wolff-Chaikoff effect (Wolff and Chaikoff 1948). The effect is temporary, and with repeated exposure to high doses of iodide, the thyroid gland escapes from the Wolff-Chaikoff effect and hormone synthesis resumes to normal levels (Wolff et al. 1949). The mechanism for the Wolff-Chaikoff effect appears to involve inhibition of both iodide transport and iodination reactions, possibly through an inhibition of the expression of NIS and thyroid peroxidase that is mediated by iodide or an iodinated metabolic intermediate (Eng et al. 1999; Spitzweg et al. 1999; Uyttersprot et al. 1997). Escape occurs when transport of iodide into the thyroid gland and the thyroid iodide concentration are sufficiently depressed to release the gland from inhibition of thyroid peroxidase, or other steps in the production of iodothyronines (Saller et al. 1998). A variety of chemical inhibitors of iodine thyroid metabolism have been described (Figure 3-3, see Section 3.10).

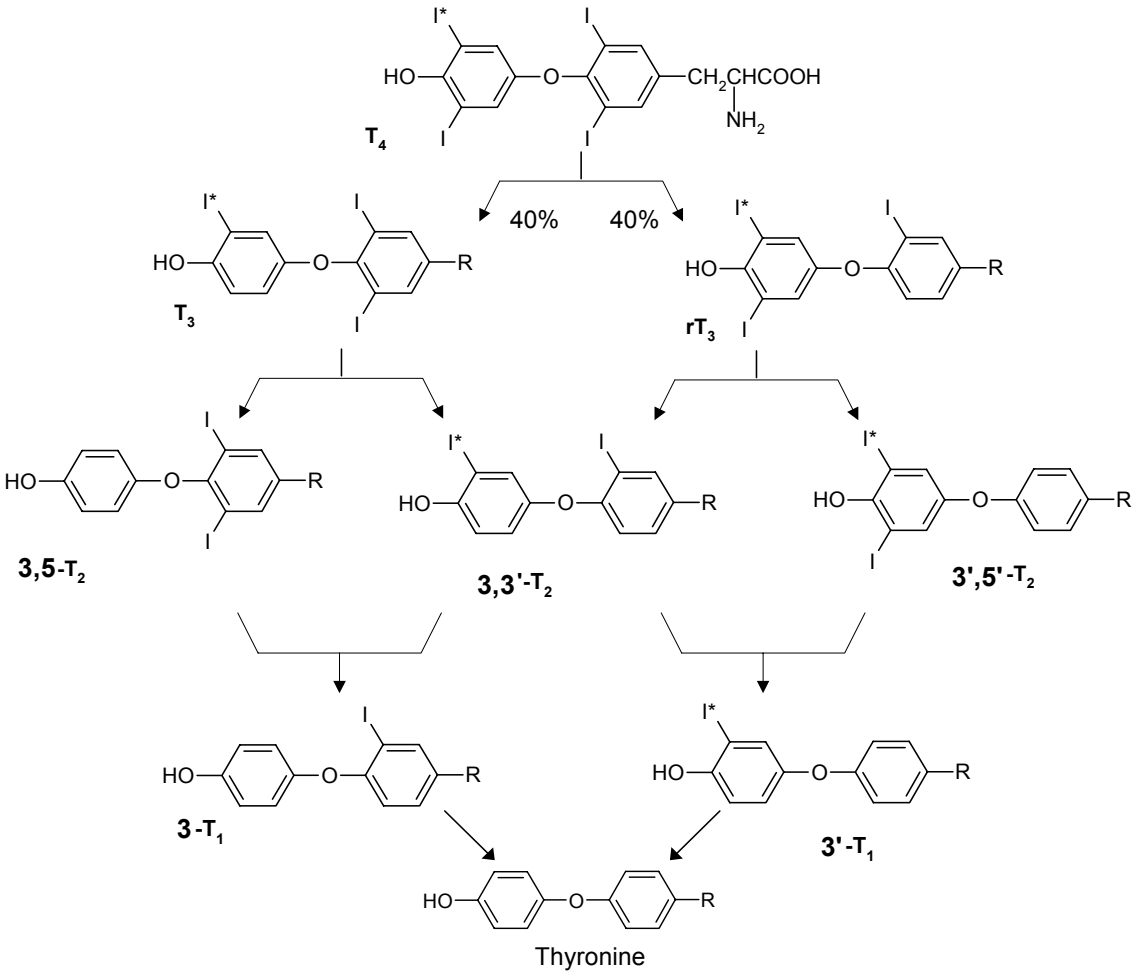
The major pathways of metabolism of iodine that occur outside of the thyroid gland involve the catabolism of T_4 and T_3, and include deiodination reactions, ether bond cleavage of thyronine, oxidative deamination and decarboxylation of the side chain of thyronine, and conjugation of the phenolic hydroxyl group on thyronine with glucuronic acid and sulfate (Figure 3-5). Deiodination products formed in peripheral tissues are depicted in Figure 3-6. The monodeiodination of T_4 to T_3 is the major source of production of peripheral T_3, which has a greater hormonal potency than T_4, and together with the production of 3,3',5-triiodo-L-thyronine (reverse T_3, rT_3), account for approximately 80% of total T_4 turnover in humans (Engler and Burger 1984; Visser 1990). The liver and kidney are thought to be major

Figure 3-5. Pathways of Metabolism of Iodothyronines



Source: Köhrle et al. 1987

Figure 3-6. Major Deiodination Pathways of Thyroid Hormones in Peripheral Tissues



Source: Engler and Burger 1984

sites of production of T_3 in the circulation; however, local tissue production of T_3 from T_4 is thought to be the predominant source of T_3 in the brain and pituitary. Iodothyronine deiodinases also catalyze the inactivation of T_4 and T_3. The activities of deiodinases are under feedback control, mediated by T_3, T_4, and reverseT_3 (rT_3), an inactive deiodination product of T_4 (Darras et al. 1999; Peeters et al. 2001). Deiodination of T_4 and T_3 also functions to deactivate the thyroid hormones. Iodide released from the deiodination reactions is either taken up by the thyroid gland or excreted in urine (see Section 3.5.4.2). Deiodination is catalyzed by selenium-dependent deiodinase enzymes (selenodiodinases) (see Section 3.6.1).

Oxidative deamination and decarboxylation of the alanine side chain of the iodothyronines represents approximately 2 and 14% of total of T_4 and T_3 turnover, respectively (Braverman et al. 1970; Gavin et al. 1980; Pittman et al. 1980; Visser 1990). Enzymes that catalyze these reactions have not been well characterized. Activity has been demonstrated in homogenates of rat kidney and brain, and the metabolites have been detected in a variety of tissues, including kidney, liver, and skeletal muscle (Engler and Burger 1984). The products of side chain deamination and decarboxylation, the acetic acid analogues of the iodothyronines, undergo deiodination and conjugation with glucuronic acid and sulfate (Engler and Burger 1984; Green and Ingbar 1961; Pittman et al. 1972).

Sulfate conjugation of the phenolic group of iodothyronines occurs in the liver and probably in other tissues. In humans, the reaction in liver is catalyzed by phenolic arylsulfotransferase (Young 1990). Iodothyronines having one iodine moiety on the phenolic ring are preferentially sulfated (Sekura et al. 1981; Visser 1994). The sulfated products undergo deiodination. Although a minor metabolite of the thyroid hormones under normal conditions, the sulfation pathway becomes more important when Type I deiodinase is inhibited; for example, by treatment with propylthiourea (Visser 1994).

Glucuronide conjugation of the phenolic hydroxyl group of the iodothyronines occurs in the liver and probably other tissues. The identity of the glucuronytransferase enzymes that participate in the conjugation of iodothyronines has not been determined in humans; however, in rats, the activity has been shown to occur for the microsomal bilirubin, *p*-nitrophenol, and androsterone uridine diphosphate (UDP)-glucuronyltransferases (Visser et al. 1993). The activity of the pathway is increased by a variety of chemicals that induce microsomal enzymes, including benzopyrene, phenobarbital, 3-methylcholanthrene, polychlorinated biphenyls (PCBs), and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Visser 1990).

Ether bond cleavage is a minor pathway of metabolism of iodotyrosines under normal conditions; however, it explains the observation of diiodotyrosine in serum of some patients who received high dosages of T_4 or who had severe bacterial infections (Meinhold et al. 1981, 1987, 1991). The reaction has been observed in phagocytosing leukocytes, which would be abundant during bacterial infections (Klebanoff and Green 1973).

3.5.3.3 Dermal Exposure

The metabolism of absorbed iodine is expected to be similar regardless of the route of exposure to inorganic iodine. A complete discussion of the metabolism of iodine after oral exposures to inorganic iodine is presented in Section 3.5.3.2, and is applicable to inhalation or dermal exposures.

3.5.4 Elimination and Excretion

3.5.4.1 Inhalation Exposure

The excretion of absorbed iodine is expected to be similar regardless of the route of exposure to inorganic iodine. This is supported by studies in which humans were exposed to tracer levels of radioiodine as either I_2 or methyl iodide, and in studies in which monkeys inhaled particulate aerosols of sodium iodide (Black and Hounam 1968; Morgan et al. 1967a, 1967b, 1968; Perrault et al. 1967; Thieblemont et al. 1965). A complete discussion of the metabolism of iodine after oral exposures to inorganic iodine is presented in Section 3.5.3.2, and is applicable to dermal exposures.

3.5.4.2 Oral Exposure

Absorbed iodine is excreted primarily in the urine and feces, but is also excreted in breast milk, exhaled air, sweat, and tears (Cavalieri 1997). Urinary excretion normally accounts for >97% of the elimination of absorbed iodine, while fecal excretion accounts for approximately 1–2% (Hays 2001; Larsen et al. 1998). The whole-body elimination half-time of absorbed iodine has been estimated to be approximately 31 days in healthy adult males (Hays 2001); however, there appears to be considerable inter-individual variability in the half-time (Van Dilla and Fulwyler 1963).

The glucuronide and sulfate conjugates of T_4, T_3, and metabolites are secreted into bile. Estimates of the magnitude of the biliary pathway have been obtained from analyses of bile samples collected from

patients who underwent surgical cholecystectomy; the total secretion of T_4 and metabolites was approximately 10–15% of the daily metabolic clearance of T_4 (Langer et al. 1988; Myant 1956). More extensive quantitative information is available on the biliary secretion of iodothyronines conjugates in experimental animals, although these models may not represent the patterns or amounts of biliary secretion that occurs in humans. In rats, approximately 30% of T_4 clearance is accounted for by the biliary secretion of the glucuronide conjugate and 5% as the sulfate conjugate; once secreted, the conjugates undergo extensive hydrolysis with reabsorption of the iodothyronine in the small intestine (Visser 1990).

Iodide is excreted in human breast milk (Dydek and Blue 1988; Hedrick et al. 1986; Lawes 1992; Morita et al. 1998; Robinson et al. 1994; Rubow et al. 1994; Spencer et al. 1986). Simon et al. (2002) estimated a transfer coefficient for ^{131}I from intake to breast milk (ratio of steady-state ^{131}I concentration in breast milk to ^{131}I intake rate) to be approximately 0.12 day/L milk (" 1.5 SD). The fraction of the absorbed iodide dose excreted in breast milk varies with functional status of the thyroid gland and with iodine intake. A larger fraction of the absorbed dose is excreted in breast milk in the hypothyroid state compared to the hyperthyroid state. In the hypothyroid state, uptake of absorbed iodide into the thyroid and incorporation into iodothyronines is depressed, resulting in greater availability of the absorbed iodide for distribution to the mammary gland and breast milk. Several examples of this have been reported in the clinical case literature. A woman who was hyperthyroid and received an oral tracer dose of radioiodine as [^{123}I]NaI during lactation excreted approximately 2.5% of the dose in breast milk collected over a 5.5-day period (Morita et al. 1998). The peak excretion (48.5% of the dose) occurred in the first postdosing collection of breast milk, which occurred 7 hours after the dose. A similar result, approximately 2.6% of the oral dose excreted in breast milk, was reported by Hedrick et al. (1986) for a hyperthyroid patient. By contrast, a hypothyroid patient excreted 25% of an oral dose of radioiodine (as [^{123}I]NaI) in breast milk in 41 hours (Robinson et al. 1994). The fractional transfer of absorbed iodine to breast milk in goats and cows decreases with increasing intake rates (Crout et al. 2000; Vandecasteel et al. 2000).

Iodide is excreted in human tears. In an adult patient (hypothyroid with thyroid hormone supplementation) who received an oral tracer dose of ^{123}I radioiodine, approximately 0.01% of the dose was recovered in tears collected over a 4-hour period. The peak activity in tears was observed 1 hour after the dose and activity was present in tears 24 hours after the dose (Bakheet et al. 1998).

Iodide is secreted in saliva in humans (Brown-Grant 1961; Mandel and Mandel 2003; Wolff 1983). Salivary secretion of iodide may be an important pathway for recycling of iodine (Mandel and Mandel 2003). The quantitative contribution of the saliva pathway to excretion of iodine has not been reported, and is probably minimal, given the relatively small rate of production of saliva under normal circumstances, most of which is ingested (Brown-Grant 1961; Wolff 1983).

Appreciable amounts of iodide can be excreted in sweat, under conditions of strenuous physical activity (Mao et al. 2001).

Iodide appears to be excreted into the intestine by a mechanism other than biliary secretion of iodothyronine (and metabolic conjugates). Evidence in support of this comes from observations of radioactivity in the colon of patients who have no functioning iodothyronine production and who received doses of radioiodine. Kinetic analyses of the fecal excretion of radioiodine in euthyroid subjects also supports a direct blood-to-intestine excretion route for iodide (Hays 1993). Further support for a possible colonic excretory pathway in humans comes from experimental studies in cats and rats (Hays et al. 1992; Pastan 1957).

3.5.4.3 Dermal Exposure

The excretion of absorbed iodine is expected to be similar regardless of the route of exposure to inorganic iodine. A complete discussion of the metabolism of iodine after oral exposures to inorganic iodine is presented in Section 3.5.3.2, and is applicable to dermal exposures.

3.5.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

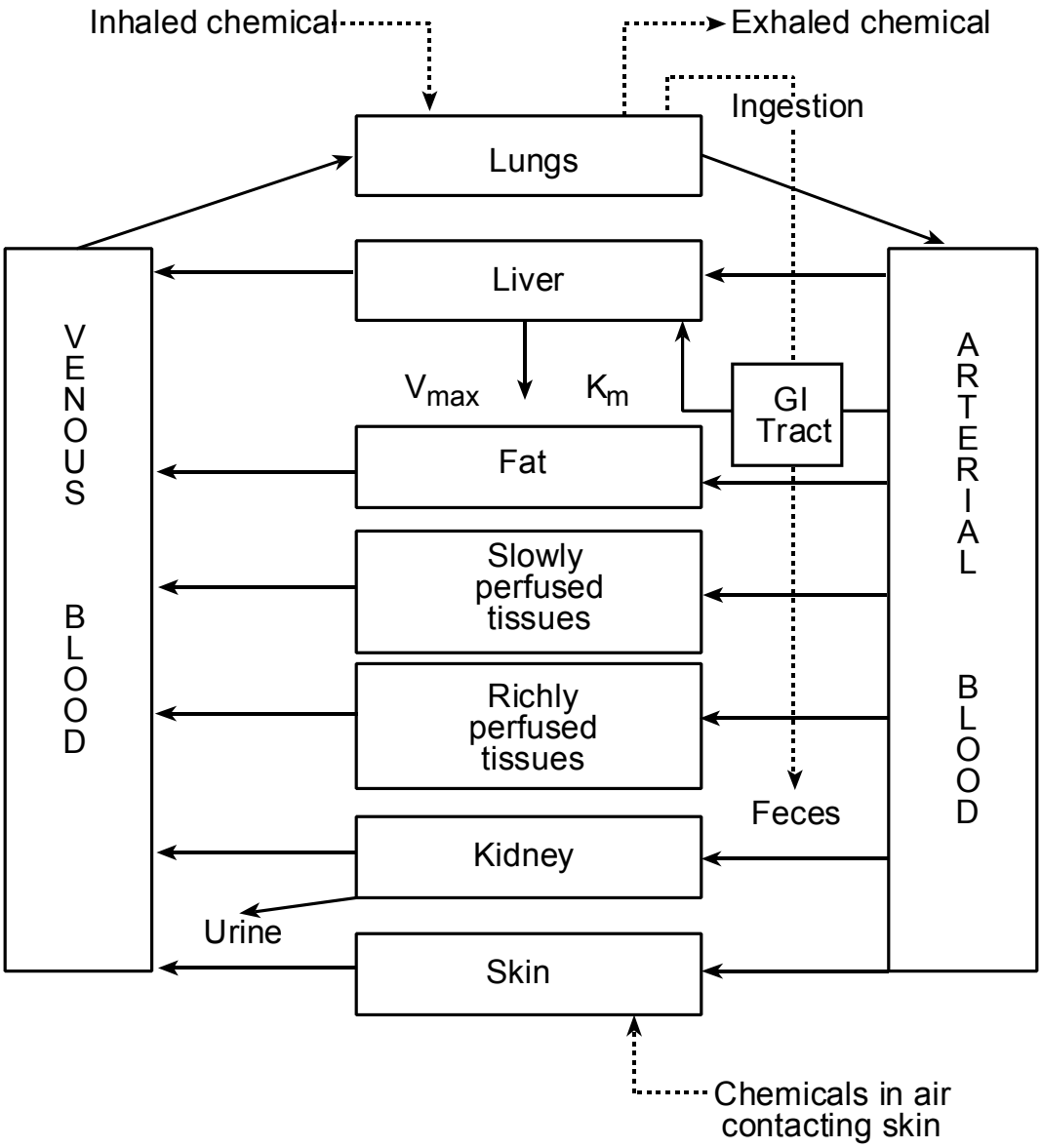
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). Similar models have been developed for radionuclides. These models provide a scientifically sound means to predict the target tissue dose of chemicals and radiation in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-7 shows a conceptualized representation of a PBPK model. Figures 3-8 through 3-15 show models for radionuclides

Figure 3-7. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan et al. 1994

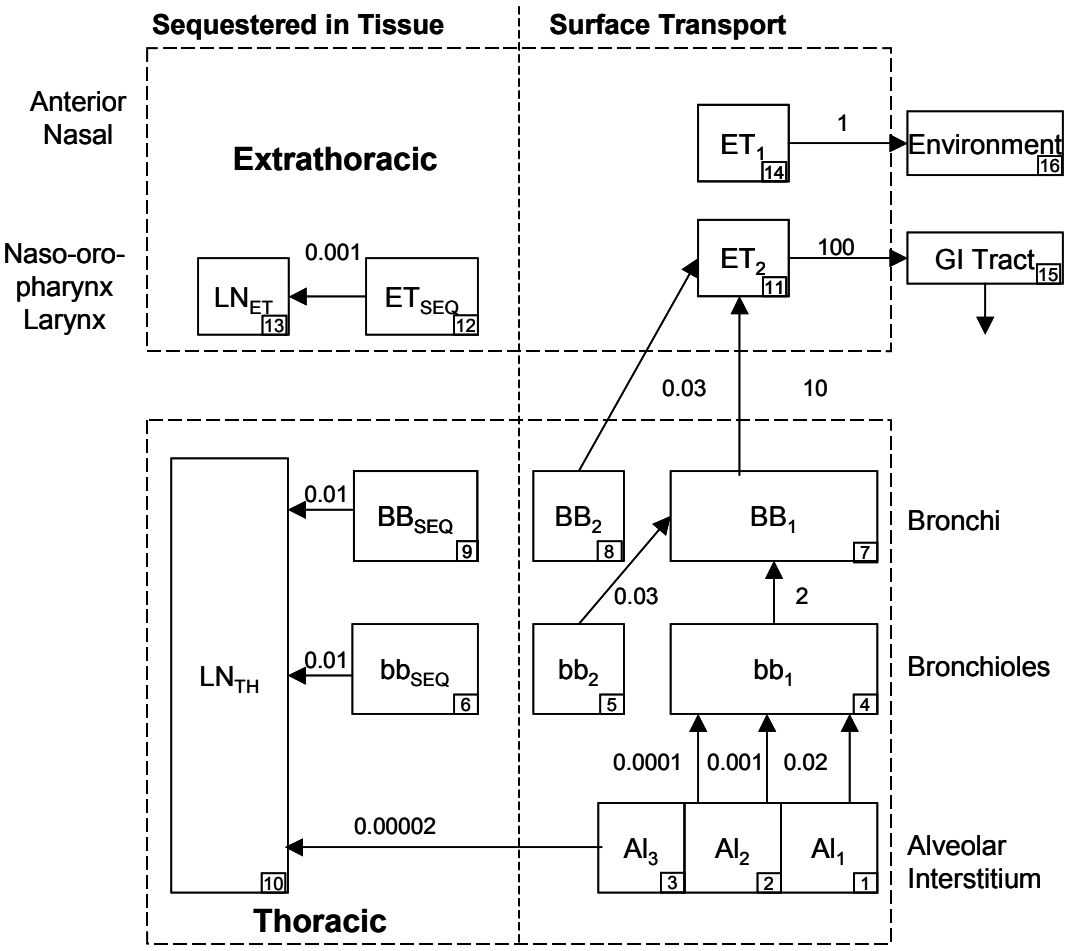
in general or specifically for iodine. The ICRP (1994b, 1996) developed a Human Respiratory Tract Model for Radiological Protection, which contains respiratory tract deposition and clearance compartmental models for inhalation exposure that may be applied to gases and vapors of iodine compounds and particulate aerosols of iodine. The ICRP (1979, 1989) also developed a biokinetic model for human oral exposure that applies to iodine. Several other multicompartmental models of iodine pharmacokinetics have been described, two of which are also described below because of either their extensive history of use in clinical applications of radioiodine (Oddie et al. 1955) or their potential value in environmental risk assessment (Stather and Greenhalgh 1983). The EPA (1998) has adopted the ICRP (1989, 1994a, 1995) models for assessment of radiologic risks from iodine exposures. The National Council on Radiation Protection and Measurements (NCRP) has also developed a respiratory tract model for inhaled radionuclides (NCRP 1997). At this time, the NCRP recommends the use of the ICRP model for calculating exposures for radiation workers and the general public. Readers interested in this topic are referred to NCRP Report No. 125; Deposition, Retention and Dosimetry of Inhaled Radioactive Substances (NCRP 1997). In the appendix to the report, NCRP provides the animal testing clearance data and equations fitting the data that supported the development of the human model.

Human Respiratory Tract Model for Radiological Protection (ICRP 1994)

Deposition. The ICRP (1994b) has developed a deposition model for behavior of aerosols and vapors in the respiratory tract. It was developed to estimate the fractions of radioactivity in breathing air that are deposited in each anatomical region of the respiratory tract. ICRP (1994b) provides inhalation dose coefficients that can be used to estimate the committed equivalent and effective doses to organs and tissues throughout the body based on a unit intake of radioactive material. The model applies to three levels of particle solubility, and a wide range of particle sizes (approximately 0.0005–100 μm in diameter) and parameter values, and can be adjusted for various segments of the population (e.g., sex, age, level of physical exertion). This model also allows the evaluation of the bounds of uncertainty in deposition estimates. Uncertainties arise from natural biological variability among individuals and the need to interpret some experimental evidence that remains inconclusive. It is applicable to gases and vapors of volatile iodine compounds (e.g., I_2 and methyl iodide) and particulate aerosols containing iodine, but was developed for a wide variety of radionuclides and their chemical forms.

The ICRP deposition model estimates the amount of inhaled material that initially enters each compartment (see Figure 3-8). The model was developed with 5 compartments: (1) the anterior nasal passages (ET1); (2) all other extrathoracic airways (ET2) (posterior nasal passages, the naso- and oropharynx, and the larynx); (3) the bronchi (BB); (4) the bronchioles (bb); and (5) the alveolar

Figure 3-8. Compartment Model to Represent Particle Deposition and Time-Dependent Particle Transport in the Respiratory Tract*



*Compartment numbers shown in lower right corners are used to define clearance pathways. The clearance rates, half-lives, and fractions by compartment, as well as the compartment abbreviations are presented in Table 3-6.

Source: ICRP 1994b

interstitium (AI). Particles deposited in each of the regions may be removed from each region and redistributed either upward into the respiratory tree or to the lymphatic system and blood by different particle removal mechanisms.

For extrathoracic deposition of particles, the model uses experimental data (where deposition is related to particle size and airflow parameters) and scales deposition for women and children from adult male data. Similar to the extrathoracic region, experimental data served as the basis for lung (bronchi, bronchioles, and alveoli) aerosol transport and deposition. A theoretical model of gas transport and particle deposition was used to interpret data and to predict deposition for compartments and subpopulations other than adult males. Table 3-5 provides reference respiratory values for the general Caucasian population under several levels of activity.

Deposition of inhaled gases and vapors is modeled as a partitioning process that depends on the physiological parameters noted above as well as the solubility and reactivity of compound in the respiratory tract (Figure 3-9). The ICRP (1994b) model defines three categories of solubility and reactivity: SR-0, SR-1, and SR-2:

- Type SR-0 compounds include insoluble and nonreactive gases (e.g., inert gases such as H_2, He). These compounds do not significantly interact with the respiratory tract tissues and essentially all compound inhaled is exhaled. Radiation doses from inhalation of SR-0 compounds are assumed to result from the irradiation of the respiratory tract from the air spaces.

- Type SR-1 compounds include soluble or reactive gases and vapors that are expected to be taken up by the respiratory tract tissues and may deposit in any or all of the regions of the respiratory tract, depending on the dynamics of the airways and properties of the surface mucous and airway tissues, as well as the solubility and reactivity of the compound. Molecular iodine (I_2) and methyl iodide are classified as SR-1 compounds (ICRP 1995). Deposition of molecular iodine vapor is assumed to occur in ET1 (10%), ET2 (40%), and BB (50%) regions of the respiratory tract, whereas 70% of inhaled methyl iodide is assumed to deposit uniformly in ET2 and deeper regions of the respiratory tract (ICRP 1995).

- Type SR-2 compounds include soluble and reactive gases and vapors that are completely retained in the extrathoracic regions of the respiratory tract. SR-2 compounds include sulfur dioxide (SO_2) and hydrogen fluoride (HF).

Mechanical Clearance from the Respiratory. This portion of the model identifies the principal clearance pathways within the respiratory tract. The model was developed to predict the retention of various radioactive materials. The compartmental model is linked to the deposition model (see Figure 3-8) and to reference values presented in Table 3-6. Table 3-6 provides clearance rates and deposition fractions for each compartment for insoluble particles. The table provides rates of insoluble particle transport for each

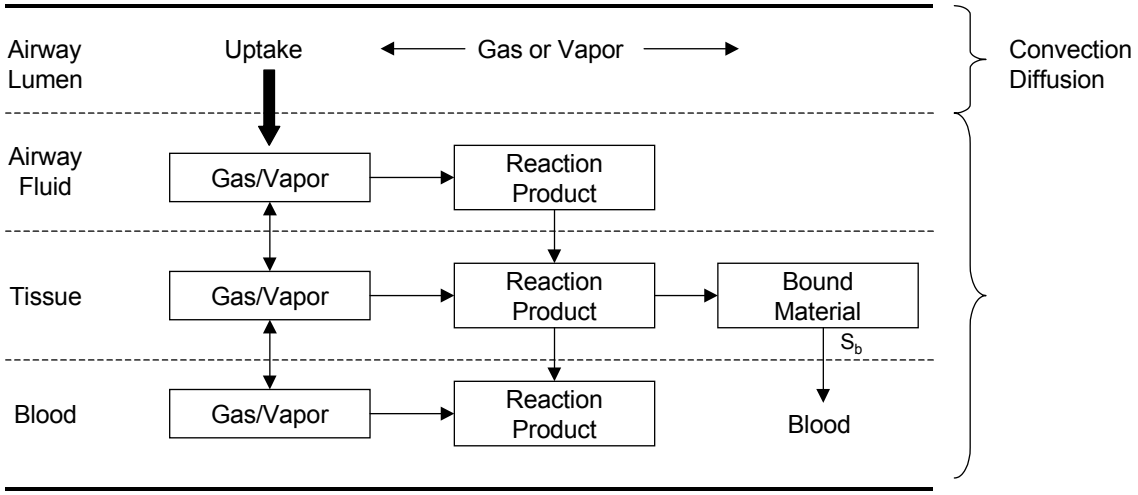
Table 3-5. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity[a]

	3 mo	1 yr	5 yr	10 yr			15 yr		Adult	
				Male	Female	Both	Male	Female	Male	Female
Resting (sleeping); Maximal workload 8%										
Breathing parameters:										
V_T(L)[b]	0.04	0.07	0.17	—	—	0.3	0.500	0.417	0.625	0.444
B(m^3h^{-1})[b]	0.09	0.15	0.24	—	—	0.31	0.42	0.35	0.45	0.32
f_R(min^{-1})[b]	38	34	23	—	—	17	14	14	12	12
Sitting awake; Maximal workload 12%										
Breathing parameters:										
V_T(L)	N/A	0.1	0.21	—	—	0.33	0.533	0.417	0.750	0.464
B(m^3h^{-1})	N/A	0.22	0.32	—	—	0.38	0.48	0.40	0.54	0.39
f_R(min^{-1})	N/A	36	25	—	—	19	15	16	12	14
Light exercise; Maximal workload 32%										
Breathing parameters:										
V_T(L)	0.07	0.13	0.24	—	—	0.58	1.0	0.903	1.25	0.992
B(m^3h^{-1})	0.19	0.35	0.57	—	—	1.12	1.38	1.30	1.5	1.25
f_R(min^{-1})	48	46	39	—	—	32	23	24	20	21
Heavy exercise; Maximal workload 64%										
Breathing parameters:										
V_T(L)	N/A	N/A	N/A	0.841	0.667	—	1.352	1.127	1.923	1.364
B(m^3h^{-1})	N/A	N/A	N/A	2.22	1.84	—	2.92	2.57	3.0	2.7
f_R(min^{-1})	N/A	N/A	N/A	44	46	—	36	38	26	33

[a]See Annex B (ICRP 1994b) for data from which these reference values were derived
[b]V_T = Tidal volume, B = ventilation rate, f_R = respiration frequency

h = hour; L = liter; m = meter; min = minute; mo = months; N/A = not applicable; yr = year(s)

Figure 3-9. Reaction of Gases or Vapors at Various Levels of the Gas-Blood Interface



Source: ICRP 1994b

Table 3-6. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part A

Clearance rates for insoluble particles

Pathway	From	To	Rate (d^{-1})	Half-time[a]
$m_{1,4}$	AI_1	bb_1	0.02	35 days
$m_{2,4}$	AI_2	bb_1	0.001	700 days
$m_{3,4}$	AI_3	bb_1	0.0001	7,000 days
$m_{3,10}$	AI_3	LN_{TH}	0.00002	No data
$m_{4,7}$	bb_1	BB_1	2	8 hours
$m_{5,7}$	bb_2	BB_1	0.03	23 days
$m_{6,10}$	bb_{seq}	LN_{TH}	0.01	70 days
$m_{7,11}$	BB_1	ET_2	10	100 minutes
$m_{8,11}$	BB_2	ET_2	0.03	23 days
$m_{9,10}$	BB_{seq}	LN_{TH}	0.01	70 days
$m_{11,15}$	ET_2	GI tract	100	10 minutes
$m_{12,13}$	ET_{seq}	LN_{ET}	0.001	700 days
$m_{14,16}$	ET_1	Environment	1	17 hours

See next page for Part B

Table 3-6. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract (*continued*)

Part B

Partition of deposit in each region between compartments[b]

Region or deposition site	Compartment	Fraction of deposit in region assigned to compartment[c]
ET_2	ET_2	0.9995
	ET_{seq}	0.0005
BB	BB_1	0.993-f_s
	BB_2	f_s
	BB_{seq}	0.007
bb	bb_1	0.993-f_s
	bb_2	f_s
	bb_{seq}	0.007
AI	AI_1	0.3
	AI_2	0.6
	AI_3	0.1

[a]The half-times are approximate since the reference values are specified for the particle transport rates and are rounded in units of d^{-1}. A half-time is not given for the transport rate from AI_3 to LN_{TH}, since this rate was chosen to direct the required amount of material to the lymph nodes. The clearance half-time of compartment AI_3 is determined by the sum of the clearance rates from it.
[b]See paragraph 181, Chapter 5 (ICRP 1994) for default values used for relating f_s to d_{ae}.
[c]It is assumed that f_s is size-dependent. For modeling purposes, f_s is taken to be:

$$f_s = 0.5 \text{ for } d_{ae} \le 2.5\sqrt{\rho/\chi}\ \mu m \text{ and}$$

$$f_s = 0.5e^{0.63(d_{ae}\sqrt{\rho/\chi}-2.5)} \text{ for } d_{ae} > 2.5\sqrt{\rho/\chi}\ \mu m$$

where

f_s	=	fraction subject to slow clearance
d_{ae}	=	aerodynamic particle diameter/(μm)
ρ	=	particle density (g/cm^3)
χ	=	particle shape factor

AI = alveolar-interstitial region; BB = bronchial region; bb = bronchiolar region; BB_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchial region; bb_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchiolar region; d = day(s); ET = extrathoracic region; ET_{seq} = compartment representing prolonged retention in airway tissue of small fraction of particles deposited in the nasal passages; LN_{ET} = lymphatics and lymph nodes that drain the extrathoracic region; LN_{TH} = lymphatics and lymph nodes that drain the thoracic region

Source: ICRP 1994b

of the compartments, expressed as a fraction per day and also as half-time. ICRP (1994b) also developed modifying factors for some of the parameters, such as age, smoking, and disease status. Parameters of the clearance model are based on human evidence for the most part, although particle retention in airway walls is based on experimental data from animal experiments.

The clearance of particles from the respiratory tract is a dynamic process. The rate of clearance generally changes with time from each region and by each route. Following deposition of large numbers of particles (acute exposure), transport rates change as particles are cleared from the various regions. Physical and chemical properties of deposited material determine the rate of dissolution, and as particles dissolve, absorption rates tend to change over time. By creating a model with compartments of different clearance rates within each region (e.g., BB_1, BB_2, BB_{seq}), the ICRP model overcomes problems associated with time-dependent functions. Each compartment clears to other compartments by constant rates for each pathway.

Particle transport from all regions is toward both the lymph nodes and the pharynx, and a majority of deposited particles ultimately are swallowed. In the front part of the nasal passages (ET_1), nose blowing, sneezing, and wiping remove most of the deposited particles. Particles remain here for about a day. For particles with AMADs a few micrometers or greater, the ET_1 compartment is probably the largest deposition site. A majority of particles deposited at the back of the nasal passages and in the larynx (ET_2) are removed quickly by the fluids that cover the airways. In this region, particle clearance is completed within 15 minutes.

Ciliary action removes deposited particles from both the bronchi and bronchioles. Though it is generally thought that mucocilliary action rapidly transports most particles deposited here toward the pharynx, some of these particles are cleared more slowly. Evidence for this is found in human studies. For humans, retention of particles deposited in the lungs (BB and bb) is apparently biphasic. The “slow” action of the cilia may remove as many as half of the bronchi- and bronchiole-deposited particles. In human bronchi and bronchiole regions, mucus moves more slowly the closer to the alveoli it is. For the faster compartment, it has been estimated that it takes about 2 days for particles to travel from the bronchioles to the bronchi and 10 days from the bronchi to the pharynx. The second (slower) compartment is assumed to have approximately equal fractions deposited between BB_2 and bb_2, both with clearance half-times estimated at 20 days. Particle size is a primary determinant of the fraction deposited in this slow thoracic compartment. A small fraction of particles deposited in the BB and bb regions is retained in the airway wall for even longer periods (BB_{seq} and bb_{seq}).

If particles reach and become deposited in the alveoli, they tend to stay imbedded in the fluid on the alveolar surface or move into the lymph nodes. The one mechanism by which particles are physically resuspended and removed from the AI region is coughing. For modeling purposes, the AI region is divided into three subcompartments to represent different clearance rates, all of which are slow.

Particle clearance from the alveolar-interstitial region has been measured in humans. The ICRP model uses two half-times to represent clearance: about 30% of the particles have a 30-day half-time, and the remaining 70% are given a half-time of several hundred days. Over time, AI particle transport falls and some compounds have been found in lungs 10–50 years after exposure.

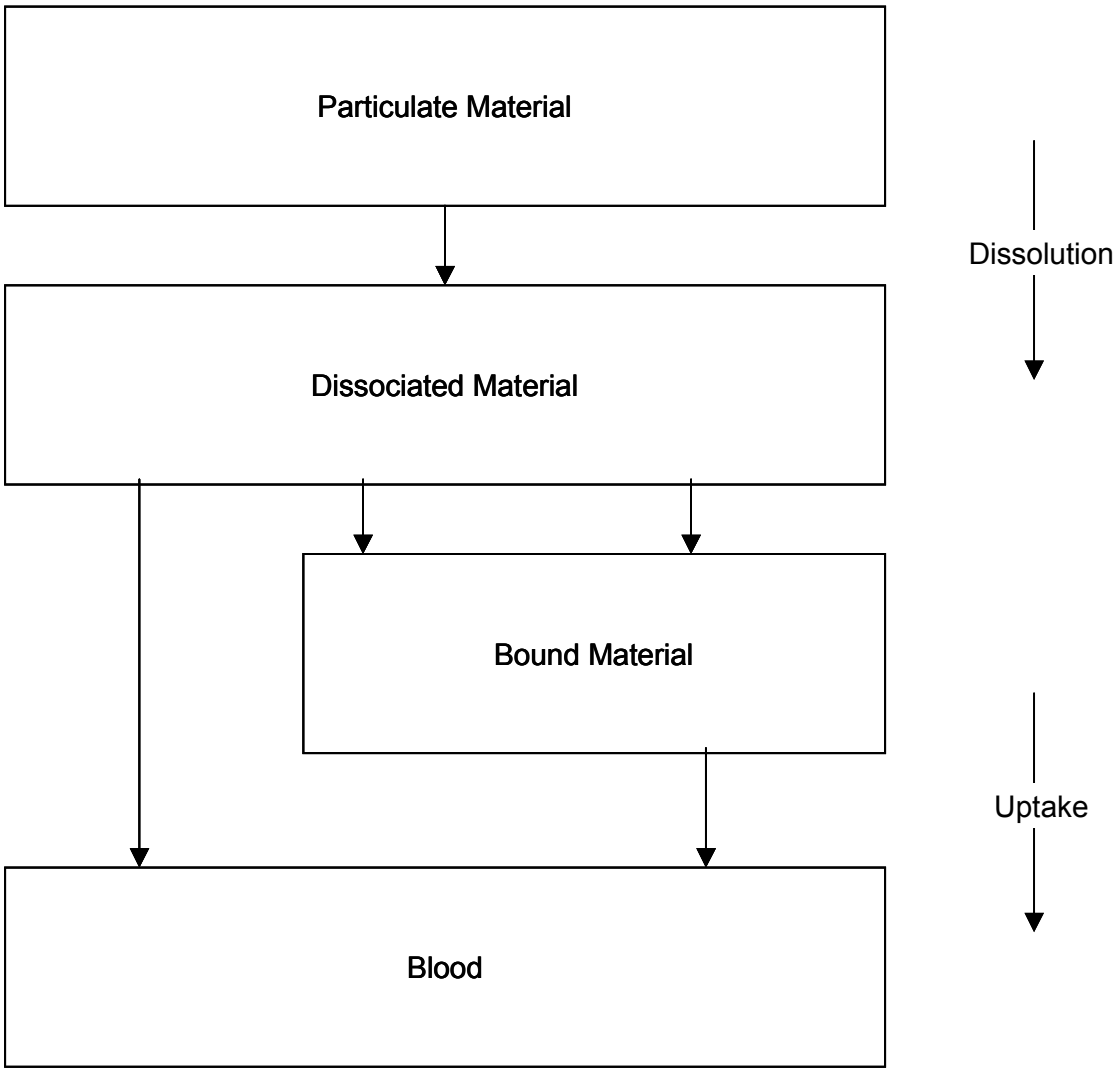
Absorption into Blood. The ICRP model assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages (ET_1), where no absorption occurs. It is essentially a 2-stage process, as shown in Figure 3-10. First, there is a dissociation (dissolution) of particles; then the dissolved molecules or ions diffuse across capillary walls and are taken up by the blood. Immediately following dissolution, rapid absorption is observed. For some elements, rapid absorption does not occur because of binding to respiratory-tract components. In the absence of specific data for specific compounds, the model uses the following default absorption rate values for those specific compounds that are classified as Types F (fast), M (medium), S (slow), and V (instantaneous):

- For Type F, there is rapid 100% absorption within 10 minutes of the material deposited in the BB, bb, and AI regions, and 50% of material deposited in ET_2. Thus, for nose breathing, there is rapid absorption of approximately 25% of the deposit in ET and 50% for mouth breathing. Type F iodine compounds include molecular iodine (I_2) and particulate aerosols of silver iodide and sodium iodide. For Type M, about 70% of the deposit in AI reaches the blood eventually. There is rapid absorption of about 10% of the deposit in BB and bb, and 5% of material deposited in ET_2. Thus, there is rapid absorption of approximately 2.5% of the deposit in ET for nose breathing, and 5% for mouth breathing. ICRP (1995) does not identify any Type M iodine compounds.

- For Type S, 0.1% is absorbed within 10 minutes and 99.9% is absorbed within 7,000 days, so there is little absorption from ET, BB, or bb, and about 10% of the deposit in AI reaches the blood eventually. ICRP (1995) does not identify any Type S iodine compounds.

- For Type V, complete absorption (100%) is considered to occur instantaneously. Methyl iodide is classified as a Type V compound (ICRP 1995).

Figure 3-10. The Human Respiratory Tract Model: Absorption into Blood



Source: ICRP 1994b

EPA (2002) Iodine Biokinetics Models

Description of the models.

EPA (2002a) developed PBPK models of the kinetics of ingested or injected iodide in rats and humans. The models were developed simultaneously with models of perchlorate biokinetics. When combined, the iodide and perchlorate models simulate the acute competitive inhibition of iodide transport by perchlorate in thyroid and other tissues that have NIS activity. The adult rat model has been extended to include pregnancy and maternal-fetal transfer of iodide, and lactation and maternal-pup iodide transfer through milk.

The adult rat and human models have the same structure and differ only in values for physiological and some of iodide parameters (Figure 3-11, Table 3-7). Both models simulate eight tissue compartments: blood, kidney, liver, skin, stomach, thyroid, fat, other slowly perfused tissues, and other richly perfused tissues. Uptakes from blood into the vascular compartments of the tissues are simulated as flow-limited processes. Distributions within blood, skin, stomach, and thyroid are simulated as diffusion-limited processes with first-order clearance terms. Transport of iodide within tissues that have NIS activity are simulated with tissue-specific affinity constants and maximum transport velocities. This includes uptake of iodine into thyroid follicle cells and secretion of iodide into the follicle lumen. Active transport of iodide into the stomach lumen and in skin is also simulated in the models. Excretion is simulated with a first-order clearance term for transfer of iodide from the kidney into urine.

Extensions of the adult rat model to simulate iodide kinetics during pregnancy include the addition of two additional compartments representing the mammary gland and placenta. Uptake of iodide into the mammary gland tissue from the mammary tissue vascular space is simulated as an affinity- and capacity-limited transport process, representing the activity of NIS in this tissue. Uptake of iodide into the placenta from blood is simulated as a flow-limited process. Exchanges of iodide between the placenta and fetus are simulated with first order clearance terms. The fetal model is identical in structure to the adult (non-pregnant) model, with adjustments in the physiological and iodide parameters to reflect the fetus.

The lactating rat model includes a milk compartment in mammary tissue and a first-order clearance term for describing secretion of iodide form mammary tissue into milk. Transfer of iodide from milk to the neonate is simulated as a first-order clearance process. The neonate model is identical in structure to the

Table 3-7. Chemical-specific Parameters for the Adult Male Rat and Human PBPK Models for Iodide[a]

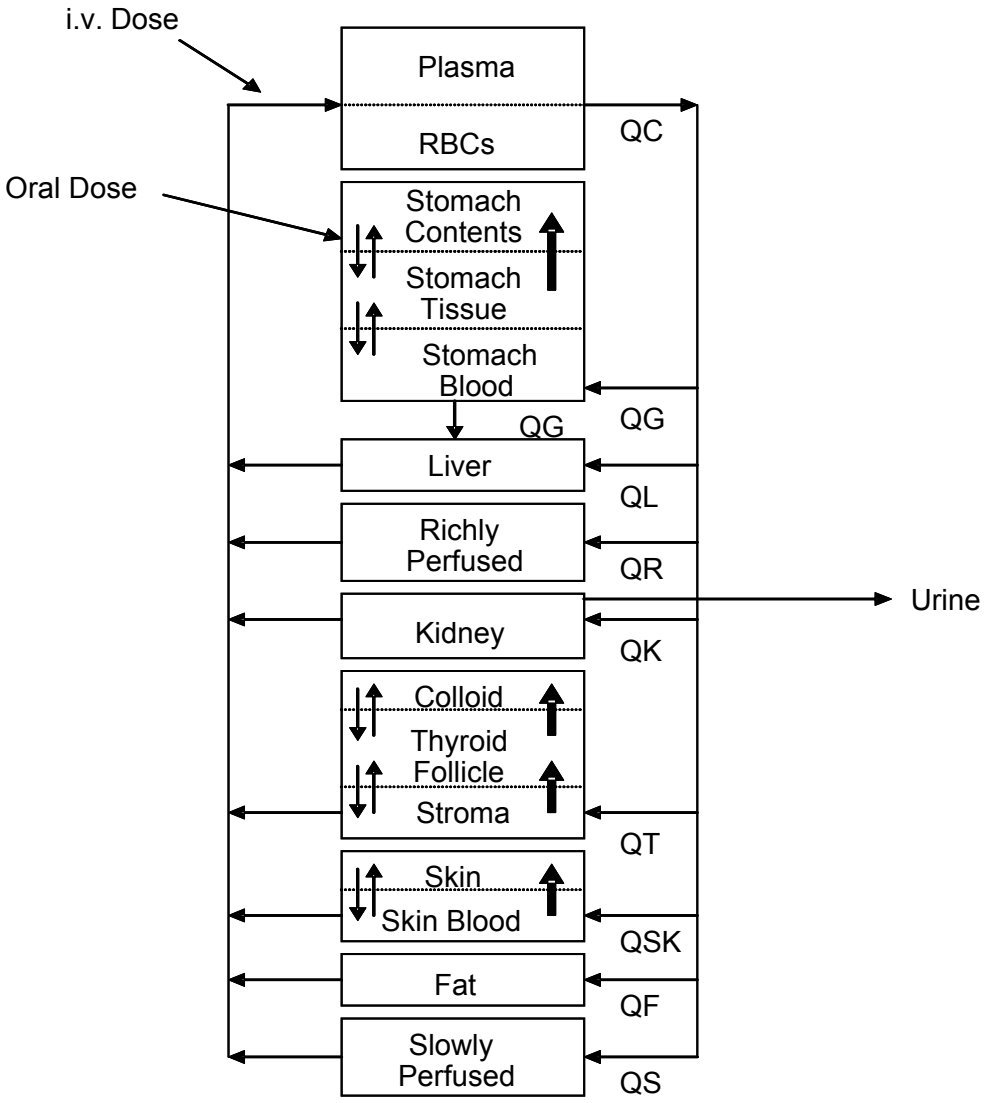
Partition Coefficients (unitless)	Rat	Human
Slowly Perfused/Plasma PS_	0.21	0.21
Richly Perfused/Plasma PR_	0.40	0.40
Fat/Plasma PF_	0.05	0.05
Kidney/Plasma PK_	1.09	0.05
Liver/Plasma PL_	0.44	0.44
Gastric Tissue/Gastric Blood PG_	1.40	0.50
Gastric Juice/Gastric Tissue PGJ_	3.00	3.50
Skin Tissue/Skin Blood PSk_	0.70	0.70
Thyroid Tissue/Thyroid Blood PT_	0.15	0.15
Thyroid Lumen/Thyroid Tissue PDT_	7.00	7.00
Red Blood Cells/Plasma	1.00	1.00
Max Capacity, Vmaxc (ng/hr-kg)		
Thyroid Colloid Vmaxc_DT	$4.0x10^{-7}$	$1.0x10^{8}$
Thyroid Follicle Vmaxc_T	$5.5x10^{4}$	~$1.5x10^{5}$
Skin Vmaxc_S	$5.0x10^{-5}$	$7.0x10^{5}$
Gut Vmaxc_G	$1.0x10^{6}$	9.010^{5}
Plasma Binding Vmaxc_Bp	–	–
Affinity Constants, Km (ng/L)		
Thyroid Lumen Km_DT	$1.0x10^{9}$	1.010^{9}
Thyroid km_T	$4.0x10^{6}$	$4.0x10^{6}$
Skin Km_S	$4.0x10^{6}$	4.010^{6}

Table 3-7. Chemical-specific Parameters for the Adult Male Rat and Human PBPK Models for Iodide[a]

Partition Coefficients (unitless)	Rat	Human
Gut Km_G	$4.0x10^{6}$	4.010^{6}
Plasma BInding km_B	–	–
Permeability Area Cross Products (L/hr-kg)		
Gastric Blood to Gastric Tissue PAGc_	0.10	0.20
Gastric Tissue to Gastric Juice PAGJc_	0.10	2.00
Skin Blood to Skin Tissue PASkc_	0.10	0.06
Plasma to Red Blood Cells PARBCc_	1.00	1.00
Follicle to Thyroid Follicle PATc_	$1.0x10^{-4}$	$1.0x10^{-4}$
Lumen to Thyroid Follicle PADTc_	$1.0x10^{-4}$	$1.0x10^{-4}$
Clearance Values (L/hr-kg)		
Urinary excretion CLUc_	0.05	0.1
Plasma unbinding Clunbc_	–	–

[a]Source: EPA 2002a

Figure 3-11. Structure of EPA (2002) PBPK Model of Iodine in Adult Male Humans and Rats



Thick arrows within tissue compartments indicate transfers that are affinity- and capacity-limited (e.g., NIS). Thin arrows within tissue compartments are diffusion limited transfers. Q indicates flow for flow-limited transfers.

adult (nonpregnant) model, with adjustments to the physiological and iodide parameter values to reflect the neonate.

Validation of the model.

The rat iodide model has been evaluated for predicting serum and thyroid iodine concentrations in adult rats that received acute intravenous injection of radioiodine (EPA 2002a). Model predictions corresponded reasonably well with observations. The model also predicted reasonably well the inhibition of radioiodine uptake in the thyroid produced by an acute intravenous dose of perchlorate; however, the model under-predicted thyroid iodide uptake in rats that received perchlorate in drinking water for 14 days at doses >1 mg/kg/day. Thus, the model simulated a greater inhibition of thyroid uptake of iodide in animals that received repeated doses of perchlorate than was actually observed. The inability of the model to accurately predict the effect of repeated exposures to perchlorate on thyroid iodide uptake is not surprising, since the model does not simulate the hormonal regulation of NIS activity and organification of iodide in the thyroid. In animals that received repeated exposures to perchlorate, induction of NIS and thyroid hormone production are likely to have occurred secondary to elevations in serum TSH (EPA 2002a; Uyttersprot et al. 1997). Such a response could have partially restored thyroid iodide uptake to higher levels than would be predicted if induction is not taken into account.

The adult human model also predicted reasonably well radioiodine in serum, thyroid, gastric contents, and urine in subjects who received an intravenous dose of radioiodine (Hays and Solomon 1965), when model parameters were calibrated to achieve good correspondence to the observations. Similarly, model predictions of thyroid radioiodine uptake in subjects who received oral doses of perchlorate agreed with observations when the kinetic parameters for iodide in the thyroid (i.e., maximum transport into the thyroid follicle) were adjusted to achieve good correspondence to the observations (EPA 2002a). When the model was calibrated by adjusting the maximum transport rate for iodide into the thyroid follicle, it accurately predicted the observed time course for radioiodine uptake in a Graves' disease patient who received a single tracer dose of radioiodine (Stanbury and Wyngaarden 1952); however, the model substantially over predicted iodine uptake after the same patient received a dose of perchlorate. Here again, the error in predictions of the effect of perchlorate on iodine uptake may reflect humoral regulation of iodide transport and organification mechanisms or the response to perchlorate in Graves' disease patients that is not simulated in the model.

The rat maternal/fetal models were evaluated by comparing predictions of radioiodine concentrations in mammary gland and placenta, and maternal and fetal serum and thyroid following single intravenous

injections of radioiodine, with or without concurrent injection of perchlorate or exposure to perchlorate in drinking water (EPA 2002a; Versloot et al. 1997). Model predictions were in reasonable agreement with observations for rats that received single injections of iodide with or without single injections of perchlorate; however, the model under-predicted maternal thyroid iodide levels in animals that received repeated oral exposures to perchlorate.

Similar outcomes occurred in evaluations of the lactating dam/neonate model (EPA 2002a). The model accurately predicted serum and thyroid iodine concentrations in the dam and neonate following single intravenous injections of radioiodine, with or without concurrent injection of perchlorate. However, the model under predicted maternal iodide levels in dams that received repeated exposures to perchlorate in drinking water.

Risk assessment.

The rat and human models have been used to calculate human equivalent exposure levels for perchlorate that would be expected to produce the same degree of inhibition of iodide uptake into the thyroid gland (EPA 2002a). These estimates have been used to extrapolate dose-response relationships for perchlorate observed in rats to humans.

Target tissues.

The models are designed to calculate iodine concentrations in serum and thyroid.

Species extrapolation.

The models are designed for applications to rat or human dosimetry and cannot be applied to other species without modification.

Interroute extrapolation.

The models are designed to simulate intravenous or oral exposures to radioiodine and cannot be applied to other routes of exposure without modification.

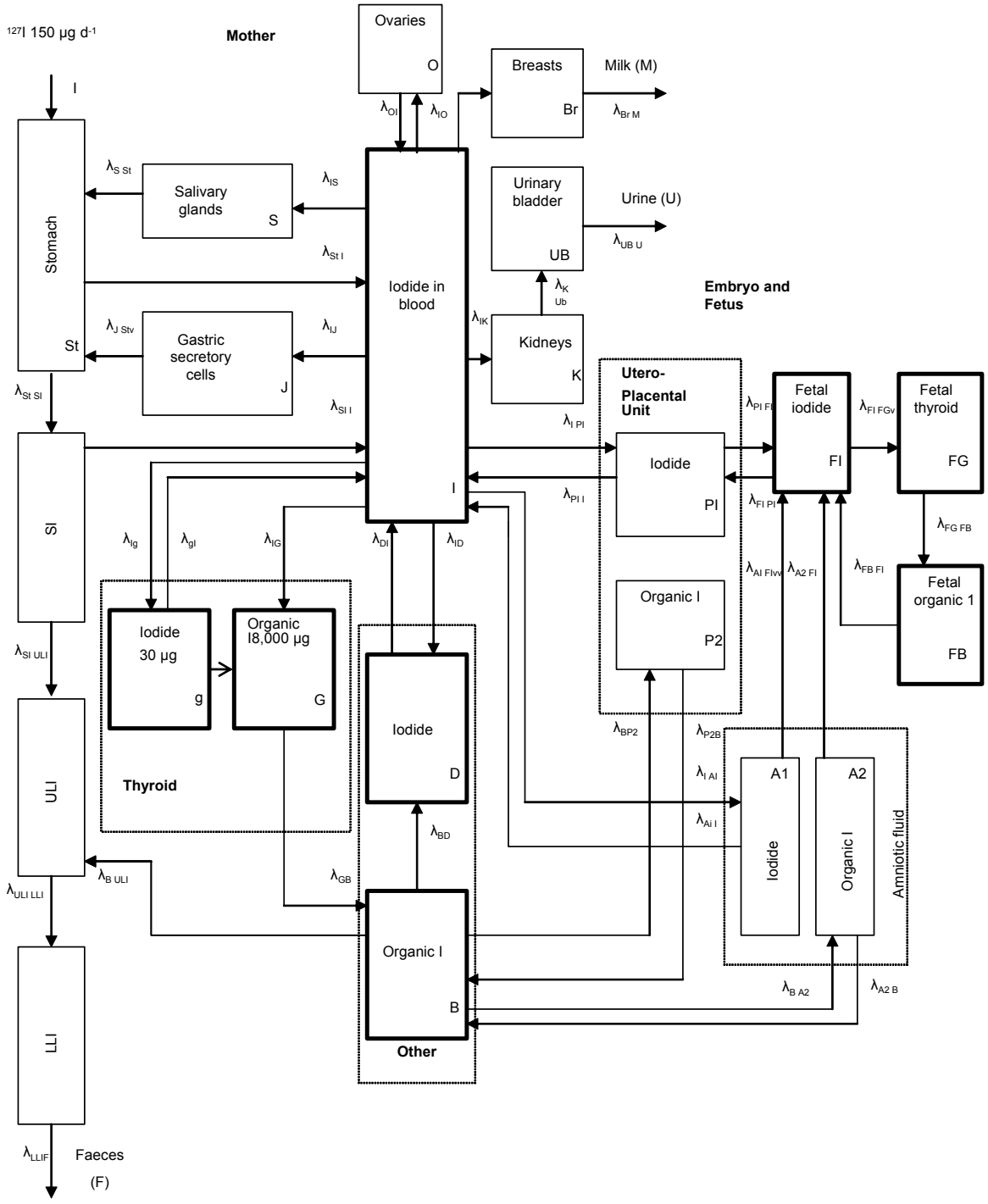
Berkovski (2002) Iodine Biokinetics Model

Description of the model.

Berkovski (1999a, 1999b) developed compartmental models of the biokinetics of iodine in the pregnant and lactating human female (Figure 3-12). The most recent description of the models (Berkovski 2002) is the basis for the ICRP (2002) iodine model. The models simulate the transfer of iodine from the pregnant woman to the fetus and to breast milk, during lactation. The maternal model simulates the gastrointestinal cycling of iodine, including absorption to blood from the stomach (slow) and small intestine (fast), secretion into the stomach, secretion into salivary glands (the latter transfers to the stomach), and secretion of organic iodine from other tissues into the large intestine (e.g., biliary transfer; the latter transfers to feces). Iodide in the central blood compartment distributes to the breasts, kidney (to urinary bladder), ovaries, thyroid gland, and other tissues. The model includes pathways for cycling of iodine into and out of the organic iodine (e.g., thyroid hormones) pool. This includes the thyroid gland, which has subcompartments for iodide and organic iodine (e.g., thyroid hormone and precursors). The thyroidal iodide compartment exchanges with the blood compartment; the organic iodine compartment receives input from blood and delivers organic iodine to the other tissue compartment. In the other tissue compartment, organic iodine is deiodinated and the resulting iodide pool exchanges with the iodide in the blood compartment. The model predicts, for a euthyroid adult who ingests 150 μg iodide/day, equilibrium contents of approximately 21 μg iodide in blood, 30 μg iodide and 8,000 μg organic iodine in the thyroid gland, 57 μg iodide and 1,350 μg organic iodine in other tissues, and 21 μg iodide in blood. The resulting ratio of total iodine in thyroid to that in blood is approximately 400.

The pregnancy model extends the maternal model with additional compartments representing the uterus and placenta, amniotic fluid compartment, and fetus. Iodide in the maternal blood compartment exchanges with iodide in the placental/uterine and amniotic fluid compartments. Organic iodine in the maternal other tissues compartment exchanges with organic iodine in the placental and amniotic fluid compartments. The fetal compartment includes three subcompartments representing cycling of fetal iodide into thyroid and extra-thyroidal iodine pools. Iodide can enter the fetal compartment from exchange with iodide in the placental/uterine compartments or from transfer from the amniotic fluid (i.e., fetal ingestion of amniotic fluid). Transfer coefficients vary through gestation to account for changes in maternal and fetal iodine biokinetics associated with growth of the placenta and fetus, initiation of fetal thyroid iodine accumulation and hormone production (approximately 12 weeks of gestation), and increased maternal renal clearance of iodide.

Figure 3-12. Berkovski (2002) Metabolic Model for Iodine



Adapted from Berkovski 1999a

The lactation model includes an additional compartment for breast milk, which receives iodide from the breast compartment.

Validation of the model.

Berkovski (1999a, 1999b, 2002) presents comparisons of model predictions and observations made in humans. The model predictions agree well with the observed kinetics of elimination of ^{131}I from amniotic fluid after intravenous injection of ^{131}I. The model also simulates, with good agreement, observed fetal thyroid radioiodine uptakes and elimination at various stages of gestation.

Risk assessment.

The Berkovski (2002) model is the basis for the ICRP (2002) model, which is used to establish radiation dose equivalents (Sv/Bq) of various ingested radioactive isotopes of iodine.

Target tissues.

The model is designed to calculate radioiodine intake limits based on radiation dose to all major organs that concentrate iodine (relative to blood), including the thyroid gland, salivary glands, ovaries, and fetus.

Species extrapolation.

The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Interroute extrapolation.

The model is designed to simulate oral exposures to radioiodine; however, it has been applied to simulating the biokinetics of intravenous injections of iodide and could be applied other routes of exposure with modification to include simulations of the absorption from these routes to blood.

ICRP (1989) Iodine Biokinetics Model

Description of the model.

ICRP (1989) developed a compartmental model of the kinetics of ingested iodine in humans with parameter values that are applicable to infants, children, adolescents, and adults. The model is a

modification and expansion of a similar model described in ICRP (1979; Riggs 1952). Ingested iodine is assumed to be completely absorbed. Absorbed iodine is assumed to distribute to three compartments: blood, thyroid gland, and extrathyroid tissues (Figure 3-13). Of the iodine entering the transfer compartment, 30% is assumed to be transferred to the thyroid gland; the remaining 70% is excreted in urine. All iodine eliminated from the thyroid gland is assumed to be transferred to the extrathyroidal tissues compartment as organic iodine (e.g., iodothyronines). Twenty percent of the iodine eliminated from extrathyroidal tissues is assumed to be excreted in feces; the remaining 80% is transferred to blood. Elimination half-times of iodine from thyroid, and extrathyroidal tissues are age-dependent, while that from blood is independent of age (Figure 3-13). The modifications made in this model from ICRP (1979) include: (1) 20%, rather than 10% of the of iodine eliminated from extrathyroidal tissues is assumed to be excreted in feces; (2) age-dependent elimination half-times for iodine, which allows the model to be applied to infants, children, adolescents, and adults; and (3) the extrathyroidal iodine pool is assumed to be 0.1 of the thyroid pool and the thyroid iodine pool is allowed to be variable, reflecting geographic variation or other sources of variation in intake.

Validation of the model.

The extent to which the ICRP model has been validated is not described in ICRP (1989).

Risk assessment.

The model has been used to establish radiation dose equivalents (Sv/Bq) of ingested various radioactive isotopes of iodine (ICRP 1989, 1993).

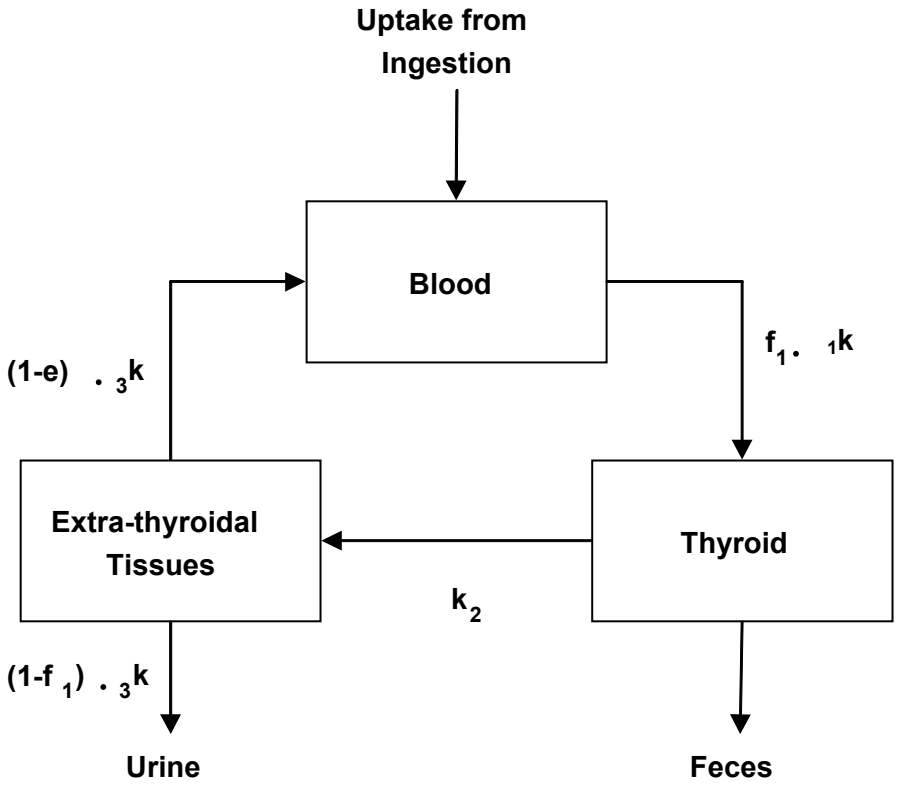
Target tissues.

The model is designed to calculate radioiodine intake limits based on radiation dose to all major organs, including the thyroid gland.

Species extrapolation.

The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Figure 3-13. International Commission on Radiological Protection (ICRP) (1989) Metabolic Model for Iodine



ICRP (1989) Metabolic Model for Iodine

Age	f_1	Thyroid uptake (%)	Fecal excretion (%)	Biological half-time[a] (d)			Apparent half-time[b] (d)
				Blood T_1	Thyroid T_2	Extrathyroidal T_3	Thyroid
3 months	1	30	20	0.25	11.2	1.12	15
1 year	1	30	20	0.25	15	1.5	20
5 years	1	30	20	0.25	23	2.3	30
10 years	1	30	20	0.25	58	5.8	70
15 years	1	30	20	0.25	67	6.7	80
Adult	1	30	20	0.25	80	12	91

[a] $\ln 2/k_i$
[b] 2–16 days after uptake

Interroute extrapolation.

The model is designed to simulate oral exposures to radioiodine and cannot be applied to other routes of exposure without modification.

Killough and Eckerman (1986) Iodine Biokinetics Model

Description of the model.

Killough and Eckerman (1986) developed a 2-compartment modification of the 3-compartment model as described by Riggs (1952, the basis for the ICRP 1979 model). In the Killough and Eckerman (1986) model, the compartment representing the extrathyroidal organic iodine pool in Riggs (1952) has been eliminated and transfer into the thyroid gland is represented with a first-order rate constant (rather than a deposition fraction). This change provides for simulation of the short-term kinetics of uptake of iodine into the thyroid (rather then only maximal uptakes), enabling such observations to be incorporated into model calibration efforts (Killough and Eckerman 1986). Values for the transfers of iodine into and out of the thyroid are age-dependent, which is the basis for age-dependence of the biokinetics simulated in the model.

Validation of the model.

The extent to which the Killough and Eckerman model has been validated is not described in Killough and Eckerman (1986).

Risk assessment.

The model has been used to establish radiation doses to the thyroid for 4,216 patients administered ^{131}I for clinical diagnostic purposes (Killough and Eckerman 1986).

Target tissues.

The model is designed to calculate thyroid gland radiation doses associated with administered activities of radioiodine.

Species extrapolation.

The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Interroute extrapolation.

The model is designed to simulate biokinetics of iodine after the delivery of iodine to the central *transfer compartment* (irrespective of the route of absorption). Oral, inhalation, or other routes exposures to radioiodine could be simulated with modification to include simulations of the absorption from these routes.

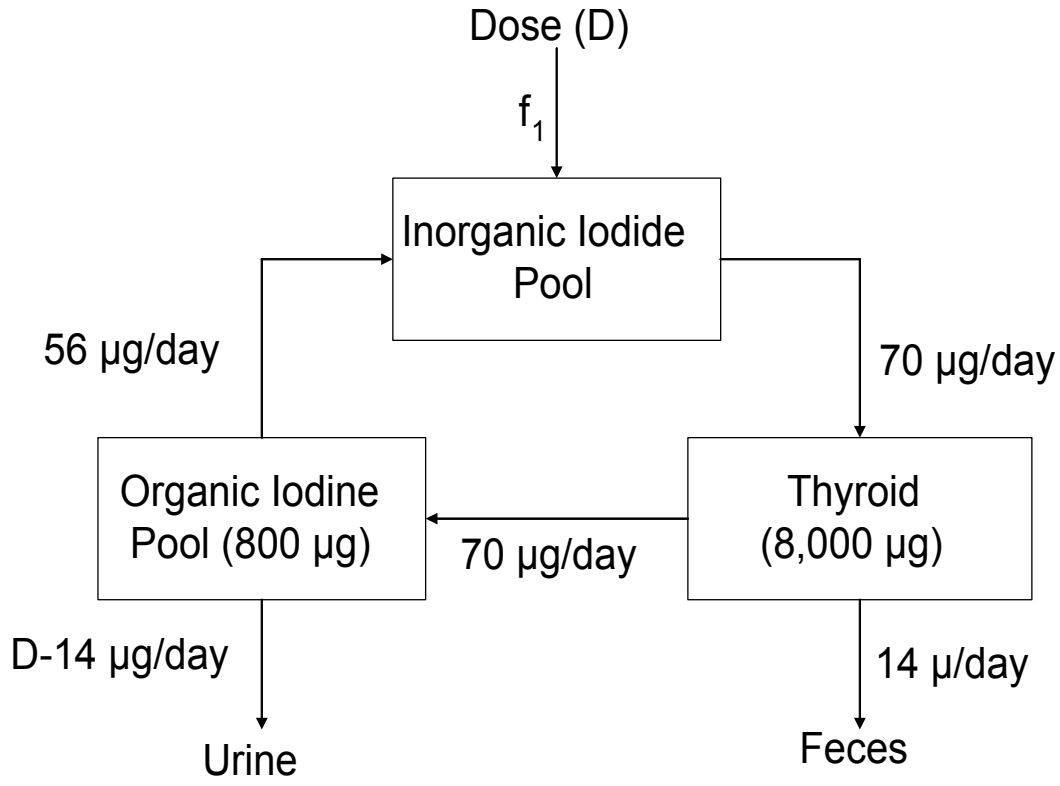
NRPB-UK Model

Description of the model.

The National Radiological Protection Board of the United Kingdom (NRPB-UK) developed a compartmental model of ingested iodine in human adults and children (Stather and Greenhalgh 1983). The model has three compartments representing the thyroid gland, an inorganic iodide pool that includes all inorganic iodide in the body with the exception of that in the thyroid gland, and an organic iodine pool, exclusive of organic iodine in the thyroid gland (Figure 3-14). Iodide that enters the gastrointestinal tract from ingestion is assumed to be completely absorbed into the inorganic iodide pool. Of the iodine entering the inorganic iodide pool, 25% is transferred to the thyroid gland where it resides with an elimination half-time of 79 days; the rest is excreted in urine. The thyroid gland is assumed to have a steady state iodine content of 8 mg. All iodine eliminated from the thyroid gland is assumed to be transferred to the organic iodine pool where it resides with an elimination half-time of 8 days. Twenty percent of the iodine eliminated from the organic iodine pool is assumed to be excreted in feces; the remaining 80% enters the inorganic iodide pool.

Models for 1-year-old infants and 10-year-old children are also described in Stather and Greenhalgh (1983). The models are essentially the same as the adult model with one change; the elimination half-time for iodine in the thyroid gland is assumed to be 17 days for 1-year-old infants and 72 days for 10-year-old children.

Figure 3-14. National Radiological Protection Board of the United Kingdom Metabolic Model for Iodine



Source: Stather and Greenhalgh 1983

Validation of the model.

The extent to which the NRPB-UK model has been validated is not described in Stather and Greenhalgh (1983).

Risk assessment.

The model was developed for calculating radiation doses to populations in the United Kingdom following release of iodine isotopes into the environment. The extent to which the model has been used for this purpose is not described in Stather and Greenhalgh (1983).

Target tissues.

The model is designed to calculate intake and exposure limits, based on radiation dose to the NRPB-UK model thyroid gland.

Species extrapolation.

The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Interroute extrapolation.

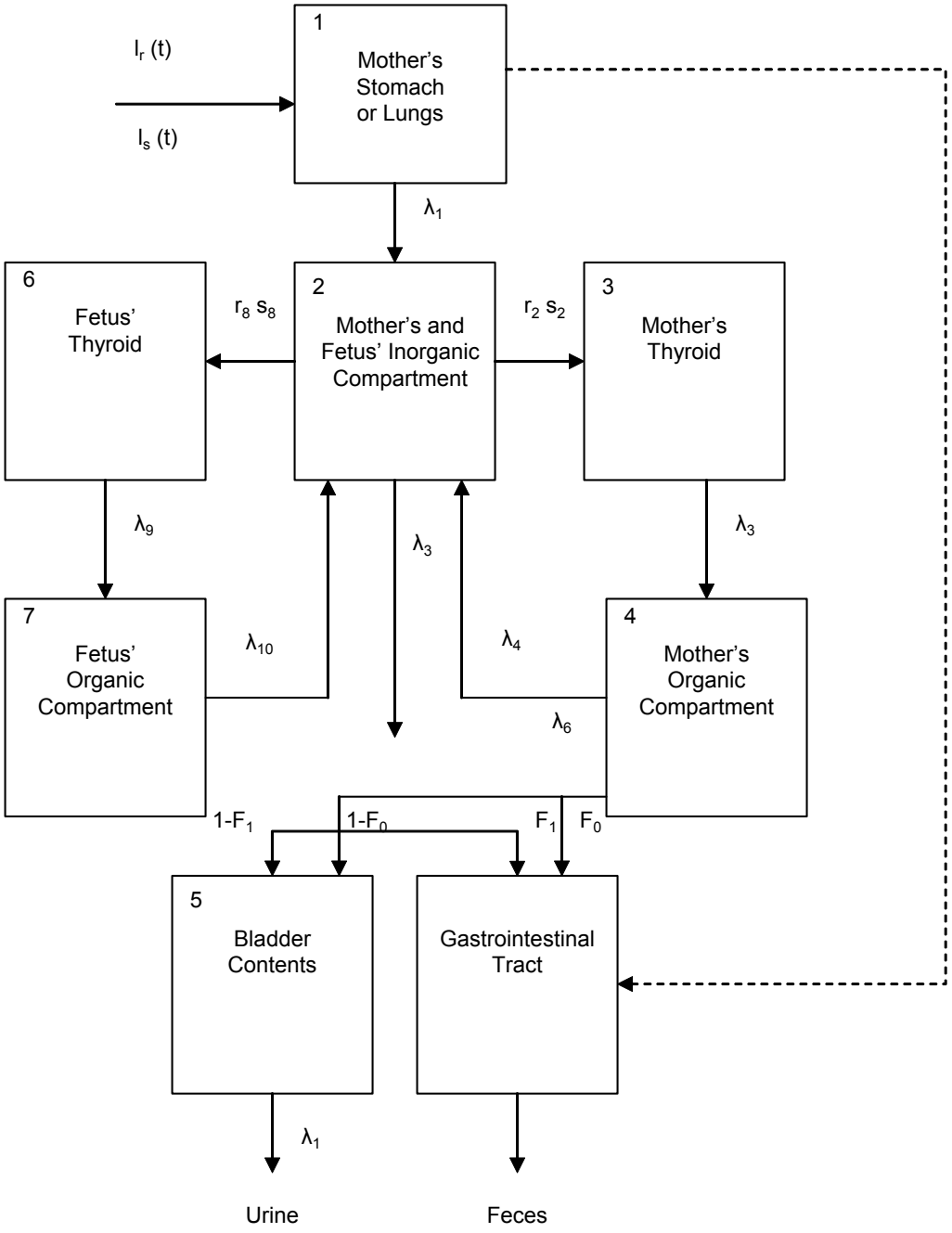
The model is designed to simulate oral exposures to radioiodine and cannot be applied to other routes of exposure without modification.

Johnson (1982) Model

Description of the model.

Johnson (1982, 1986) described a compartmental model of iodine biokinetics in humans that included parameters for simulating pregnancy. The structure of the maternal model is similar to the Stather and Greenhalgh (1983) model in that it has three compartments representing the thyroid gland, an extra-thyroidal inorganic iodide pool, and an organic iodine pool, exclusive of organic iodine in the thyroid gland (Figure 3-15). Iodide that enters the gastrointestinal tract from ingestion or the lungs from inhalation is assumed to be absorbed into the inorganic iodide pool. From the inorganic iodide pool, iodide is transferred to the thyroid gland (at a rate equal to loss of thyroidal iodine to the organic iodine

Figure 3-15. Johnson (1982) Metabolic Model for Iodine



Adapted from Johnson 1986

pool), or is excreted in urine and feces. All iodine eliminated from the thyroid gland is assumed to be transferred to the organic iodine pool, from which it can renter the extra-thyroidal inorganic iodine pool. Daily thyroid iodide uptakes vary with thyroid gland mass. Thyroid gland growth and mass are age- and gender-dependent, which are the bases for age- and gender dependence of the biokinetics in the model.

The pregnancy model includes fetal thyroid and fetal organic iodine compartments. Iodide cycles from the maternal extrathyroidal iodide pool, to the fetal thyroid pool, to the fetal organic iodine pool, from where it can return to the maternal extrathyroidal iodide pool.

Validation of the model.

The extent to which the Johnson (1982, 1986) model has been validated is not described in either publication.

Risk assessment.

The model was developed for calculating radiation doses to populations following release of iodine isotopes into the environment. The extent to which the model has been used for this purpose is not described in Johnson (1982, 1986).

Target tissues.

The model is designed to calculate intake and exposure limits, based on radiation dose to the thyroid gland.

Species extrapolation.

The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Interroute extrapolation.

The model is designed to simulate oral and inhalation exposures to radioiodine; however, it could be applied to other routes of exposure with modifications to include simulations of the absorption from these routes to the extrathyroidal inorganic iodide pool.

Oddie et al. Model

Description of the model.

Oddie et al. (1955) described a compartmental model of absorbed iodine human adults and infants (Fisher et al. 1962) for predicting 24-hour radioiodine uptake by the thyroid gland in clinical procedures. The model has two compartments representing the thyroid gland and a central iodide pool that includes all inorganic iodide in the body with the exception of that in the thyroid gland. An organic iodine pool is not included in the model. Although this would preclude the model from accurately simulating radioiodide levels in extrathyroidal tissues, including blood, it was not considered necessary for simulating the initial uptake of iodide by the thyroid following a single dose of radioiodine, prior to significant release of organic iodine from the thyroid gland. Iodide that enters the inorganic iodide pool is assumed to be transferred either to the thyroid gland, represented as a first order rate constant k_1, or to the kidney for urinary excretion, represented by a rate constant k_2, usually corrected for loss of iodide in sweat, feces, and uncollected urine (Oddie and Fisher 1967). In a study of 20 healthy adults, k_1 was estimated to be $60x10^{-5}$/minute in subjects who ingested a tracer dose of radioiodine (Fisher et al. 1965). In this same study, the value of k_1 was $49x10^{-5}$ after 13 weeks of daily ingestion of 252 µg iodide/day and $35x10^{-5}$, after 13 weeks of daily ingestion of 1,000 µg iodide/day. The estimate of k_2 from this study was $300x10^{-5}$ $minute^{-1}$. Values for k_1 estimated in various populations have ranged from 67 to $134x10^{-5}$ $minute^{-1}$ (Oddie and Fisher 1967). The volume of the iodide space was estimated to be 2.1 L (Fisher et al. 1965).

The same model has been used to predict thyroid uptakes of iodine in infants. Values for k_1 and k_2 were estimated from studies in which 24-hour thyroid uptakes of iodine were measured in 26 euthyroid newborn infants (Fisher et al. 1962). The values for k_1 and k_2 were $2.4x10^{-3}$ $minute^{-1}$ and $1.1x10^{-3}$ $minute^{-1}$, respectively. The iodide space was estimated to be approximately 0.4 L in newborn infants.

Validation of the model.

The model has been shown to predict 24-hour iodine uptakes in the thyroid in adults who received single doses of radioiodine. Predicted 24-hour thyroid uptakes of radioiodine were compared to observed estimates in 1,573 euthyroid subjects reported from various studies; the difference between observed and predicted estimated for eight studies ranged from 0.7 to 2.1%, with the observed uptakes ranging from 21 to 37% (Oddie and Fisher 1967).

Risk assessment.

The model was developed for predicting the 24-hour uptake of radioiodine in the thyroid after single doses of radioiodine are given in the clinical setting for assessing thyroid function. It has been evaluated in terms of its predictive value in detecting abnormal thyroid conditions that affect iodide uptake into the gland (Oddie et al. 1960). The extent to which the model has been used for risk assessment could not be ascertained from the available literature.

Target tissues.

The model is designed to predict 24-hour uptakes of radioiodine into the thyroid gland.

Species extrapolation.

The model is designed for applications to humans and cannot be applied to other species without modification.

Interroute extrapolation.

The model is designed to simulate oral ingestion or parenteral injection (e.g., intramuscular in infants) of radioiodine and cannot be applied to other routes of exposure without modification.

3.6 MECHANISMS OF ACTION

3.6.1 Pharmacokinetic Mechanisms

Absorption. The mechanism(s) by which iodide is absorbed from the gastrointestinal tract is not known. Based on the study conducted by Small et al. (1961), absorption appears to occur primarily in the small intestine in humans. This study measured iodine in the saliva of healthy human subjects who ingested 0.25 g of potassium iodide (0.19 g iodide) together with a radioopaque suspension of barium sulfate that allowed the emptying of the stomach to be imaged with a fluoroscope. In five subjects, iodine was not detected in saliva until 2–3 minutes after the first appearance of the barium sulfate in the duodenum; the actual time of appearance relative to the oral dose of iodide ranged from 15 to 40 minutes. An intravenous dose of probanthine, which delays gastric emptying time, given just prior to the oral dose of potassium iodide, substantially delayed the time of appearance of iodine in saliva to 114–133 minutes;

however, in each of three subjects, iodine was detected in saliva 3–4 minutes after the first appearance of the radioopaque marker in the duodenum. When iodide was instilled directly into the duodenum together with the radioopaque marker (two subjects), iodine was detected in saliva 3–4 minutes after the dose was administered. These observations suggest that the absorption of iodide in humans occurs primarily in the small intestine and that the stomach may play a minor role in iodide absorption. The mechanisms by which iodide is transported across the intestinal epithelium are not known. Iodide may be transported by mechanisms that also transport chloride such as the Cl^-/HCO_3^- antiport (Dalmark 1976; Lambert and Lowe 1978) or Cl^- channels (Katayama and Widdicombe 1991).

While the above studies implicate the small intestine as the major site of absorption of iodide in humans, studies in rats and dogs indicate that 14–30% of an oral dose of iodide may be absorbed in the stomach in these species (Small et al. 1961; Cohn 1932)

Distribution.

Iodide Transport. Uptake of iodide into the thyroid is facilitated by a membrane carrier in the basolateral membrane of the thyroid follicle cell (Carrasco 1993; Levy et al. 1998a; Shen et al. 2001). The carrier, or NIS, catalyzes the simultaneous transfer Na^+ and I^- across the basolateral membrane (Chambard et al. 1983; Iff and Wilbrandt 1963; Nilsson et al. 1990). The stoichiometry of transfer reaction is $(2)Na^+/(1)I^-$, which confers to the NIS a net positive charge and, therefore, a sensitivity to transmembrane voltage (Eskandari et al. 1997; O'Neill et al. 1987). In the presence of an inward-directed electrochemical gradient for Na^+, the NIS can transfer I^- into the cell against a pronounced outward-directed electrochemical gradient for I^- (Takasu et al. 1984; Williams 1969; Woodbury and Woodbury 1963). This enables the follicle cell to achieve intracellular/extracellular concentration ratios of 10–50 for iodide (Andros and Wollman 1991; Bagchi and Fawcett 1973; Shimura et al. 1997; Vroye et al. 1998; Weiss et al. 1984b; Wolff 1964).

The NIS has been studied extensively in several *in vitro* preparations, including isolated plasma membrane vesicles of mammalian thyroid (O'Neill et al. 1987), FRTL-5 cells, a cell line derived from normal rat thyroid (Weiss et al. 1984b), *Xenopus lavis* oocytes transformed by intracellular injection of FRTL-5 RNA to express NIS (Eskandari et al. 1997), and other mammalian cells cultures transformed to express NIS (Levy et al. 1997; Nakamura et al. 1990; Smanik et al. 1996; Yoshida et al. 1997). The apparent K_m for I^- transport in cell systems is approximately 30–40 μM, which is considerably higher than the serum iodide concentration of 0.04–0.08 μM (5–10 μg/L) (Eskandari et al. 1997; Weiss et al. 1984b). The relatively high K_m enables the iodide transport rate to be highly sensitive to changes in plasma I^-

concentration. Iodide transport by the NIS is inhibited by other anions, most notably, thiocyanate (SCN^-) and perchlorate (ClO_4^-) (Carrasco 1993; Wolff 1964). Thiocyanate is one of several anions other than I^- that can be transported by the NIS, including $SeCN^-$, NO_3^-, ClO_3^-, Br^-, BF_4^-, IO_4^-, and BrO_3^- (Eskandari et al. 1997). Perchlorate, on the other hand, does not appear to be transported by NIS (Eskandari et al. 1997; Yoshida et al. 1997). Thus, thiocyanate and perchlorate, which both inhibit iodide uptake in thyroid *in vivo*, do so by different mechanisms; thiocyanate is a competitive substrate for transport, whereas perchlorate appears to block I^- binding to the NIS.

Synthesis of NIS is regulated by the pituitary hormone, TSH, which stimulates iodide uptake into the thyroid. The mechanism involves both increased transcription of the NIS gene and increased translation of mRNA for NIS (Kogai et al. 1997; Levy et al. 1997; Ohno et al. 1999; Pekary et al. 1998). Both responses to TSH follow binding of TSH to a receptor on the basolateral membrane and activation of the enzyme adenylate cyclase by GTP binding protein G_α (Akamizu et al. 1990; Chazenbalk et al. 1990; Kogai et al. 1997; Parmentier et al. 1989; Perret et al. 1990; Raspe and Dumont 1995). In FRTL-5 cells grown in the absence of TSH, NIS activity declines to a minimum level and can be restored by the addition of TSH to the medium or by treating the cells with dibutryl-cAMP or other agents that increase the intracellular concentration of cAMP (Pekary et al. 1998; Weiss et al. 1984a, 1984b). Thus, the actions of TSH appear to involve the activation of adenylate cyclase and subsequent increase in the intracellular concentration of cAMP. TSH also appears to mediate post-transcriptional regulation of NIS, including increasing the intracellular elimination half-time of the NIS protein and stimulating the incorporation of the NIS protein into the thyrocyte cell membrane (Riedel et al. 2001).

Synthesis of NIS also appears to be regulated by plasma iodide concentration through a mechanism that does not directly involve TSH. In rats exposed to drinking water containing 500 mg/L I as sodium iodide, expression of mRNA for the NIS in the thyroid decreased by 45% after 1 day of exposure and 60% after 6 days of exposure compared to controls that ingested water without added iodide. Serum iodide concentrations were 150–200-fold higher in the exposed rats compared to controls, whereas the serum TSH concentrations were not different between control and treated groups (Eng et al. 1999). A similar observation was made in dogs made hypothyroid by treatment with propylthiouracil (an inhibitor of iodination of thyroglobulin) and perchlorate (Uyttersprot et al. 1997). The hypothyroid state elevated TSH concentrations in serum; nevertheless, a single injection of 0.3 mg potassium iodide (0.23 mg I) resulted in decreased expression of NIS in the thyroid within 24–48 hours after the dose, without a change in TSH concentrations in serum. Both iodide and T_3 depress the expression of NIS mRNA and iodide uptakes in rat thyroid follicle cells grown in culture (Sptizweg et al. 1999).

The exact mechanisms by which the NIS gene transcription is regulated have not been determined. The gene in humans and rats has been sequenced, enabling studies of the mechanisms of gene transcription regulation (Dai et al. 1996; Smanik et al. 1996). The human gene resides on chromosome 19 (Smanik et al. 1997). Mutations in the gene sequence have been associated with hypothyroidism, goiter, and abnormally low thyroid uptake of injected iodide (Fujiwara et al. 1997, 1998, 2000; Kosugi et al. 1998, 2002; Levy et al. 1998c; Pohlenz and Refetoff 1999; Pohlenz et al. 1997). The 5'-flanking region of the rat NIS gene has been shown to contain one or more promoter regions; however, their role in regulation of the NIS transcription is not completely understood (Endo et al. 1997; Kogai et al. 2001; Ohno et al. 1999; Schmitt et al. 2000, 2001; Tong et al. 1997). A promoter region in the rat NIS gene appears to respond to a rise in intracellular cAMP, most likely by binding a cAMP-inducible or cAMP-activated transcription factor (Chun and Di Lauro 2001; Ohno et al. 1999). NIS expression in FRTL-5 cells is increased in response to extracellular adenosine, possibly through a mechanism that is independent of cAMP (Harii et al. 1999). A promoter region in the rat NIS gene responsive to thyroid transcription factor 1 (TTF-1) has also been described (Endo et al. 1997). Tong et al. (1997) found evidence for a promoter region in the rat NIS gene that could be suppressed in cell cultures that were transformed with the oncogene PTC1. This may provide a mechanism for the decreased expression of the NIS gene in thyroid papillary carcinomas and the decreased iodide uptake of some thyroid carcinomas (Smanik et al. 1996, 1997).

Several tissues in humans, other than thyroid, actively express NIS and accumulate iodide; these include the mammary gland, salivary glands, and gastric mucosa (Brown-Gant 1961; Lacroix et al., 2001; Smanik et al. 1997; Spitzweg et al. 1998, 1999; Wolff 1983). These tissues can achieve intracellular/extracellular and/or transepithelial concentration ratios for I^- concentrations of 20–40. Transport of iodide in these tissues is inhibited by thiocyanate and perchlorate; however, transport activity is not responsive to TSH. Clinical cases of genetic absence or impaired iodide uptake in the thyroid coupled with low uptakes in saliva and gastric fluid suggest an involvement of an NIS mechanism in these tissues (Fujiwara et al. 1997, 1998; Kosugi et al. 1998; Leger et al. 1987; Pohlenz and Refetoff 1999; Pohlenz et al. 1997; Wolff 1983). Further evidence for extrathyroidal NIS comes from studies of mammary gland. The NIS gene is expressed in the mammary gland of the human, rat, and many strains of mice (Levy et al. 1997; Perron et al. 2001; Rillema et al. 2000b; Smanik et al. 1997; Spitzweg et al. 1998; Tazebay et al. 2000). In the rat, expression of the NIS, or a structurally similar membrane protein, increases during nursing and decreases after weaning (Cho et al. 2000; Levy et al. 1998a). In the mouse and rat, the induction of NIS appears to

be stimulated by prolactin (Cho et al. 2000; Rillema and Rowady 1997; Rillema et al. 2000b). The NIS gene is also expressed in human kidney and placenta (Bidart et al. 2000; Spitzweg et al. 2001).

Studies in animals have revealed other tissues that actively secrete or accumulate iodide transport by a mechanism that is inhibited by perchlorate and thiocyanate, suggestive of an active NIS. These include choroid plexus, ciliary body of the eye, small intestine (ileum), ovary, placenta, and skin in mammals; and avian salt gland in marine birds (Brown-Grant 1961). In humans, the NIS gene is expressed in mammary gland, salivary glands, and gastric mucosa (Lacroix et al. 2001; Smanik et al. 1997; Spitzweg et al. 1998).

An iodide transporter that is distinct from NIS has been characterized in the apical membrane of the thyroid follicle cell (Royaux et al. 2000; Taylor et al. 2002; Yoshida et al. 2002). This transporter may function in the facilitated transfer of iodide from the follicle cell in the follicle lumen. Mutations in the gene coding for the apical transporter occur in Pendred syndrome, an autosomal recessive disorder characterized by hearing loss, thyroid iodide organification deficits goiter (Scott et al. 2000).

Iodothyronine Transport. Uptake of T_4 and T_3 into tissues occurs by a saturable, energy-dependent carrier transport system. Evidence for active transport derives from a variety of observations. The rate of uptake of T_3 into the perfused rat liver is proportional to the concentration of free T_3 in the perfusate and is not related to the total concentration or bound concentration (Mendel et al. 1988). The free cytosolic concentration of T_3 in the *in vivo* rat liver and heart muscle exceeds that of the simultaneous free concentration in plasma, suggesting uptake of T_3 into these tissues against a chemical gradient for T_3 (Oppenheimer and Schwartz 1985). T_3 uptake into confluent cultures of human or rat hepatoma cells is saturable, stereoselective for the active L enantiomer, temperature dependent, and inhibited by metabolic and membrane transport inhibitors, including phloretin (Movius et al. 1989; Topliss et al. 1989). Saturable, stereoselective, temperature-dependent, and energy-dependent uptake of T_3 and T_4 has also been observed in cultures of human fibroblasts and of T_3 in *in vitro* preparations of rat skeletal muscle (Centanni and Robbins 1987; Docter et al. 1987).

Metabolism.

Iodination in the Thyroid Gland. Iodination of thyroglobulin is catalyzed by thyroid peroxidase, a hemoprotein in the apical (luminal) membrane of thyroid follicle cells (Dunn and Dunn 2001). Thyroid peroxidase catalyzes both the iodination of tyrosine residues in thyroglobulin and the coupling of the iodinated residues to form the thyroid hormones, T_4 and T_3, and diiodotyrosine. The iodination reaction involves the oxidation of iodide (I^-) to a reactive species having a sufficiently high oxidation potential to

iodinate the aromatic ring of tyrosine. The oxidizing agent in the reaction is hydrogen peroxide, which is generated at the apical membrane of follicle cells by an NADPH oxidase (Deme et al. 1994; Dupuy et al. 1991). Although the exact mechanism of the iodination reaction is not completely understood, three species are suspected as being candidates for the reactive iodinating species: a free radical (I⓪), iodinium (I^+), or an enzyme-bound hypoiodite ($[EOI]^-$) (Taurog 1996). Human thyroglobulin contains 134 tyrosyl residues, of which approximately 20 undergo iodination to yield approximately 2–4 molecules of T_4 or T_3 per molecule of thyroglobulin. The coupling reaction occurs within thyroglobulin, rather than as a reaction between free iodinated tyrosines. In the formation of T_4, two molecules of diiodotyrosine are coupled, whereas the formation of T_3 is a coupling of monoiodotyrosine and diiodotyrosine residues. The reaction is catalyzed by thyroid peroxidase with hydrogen peroxide serving as the oxidizing agent in the formation of a reactive intermediate of the contributing diiodotyrosine residue, possibly a free radical species (Taurog et al. 1994). Specificity of iodination and coupling of tyrosine residues within thyroglobulin is conferred, in part, by the specificity of thyroid peroxidase and, in part, by the structure of thyroglobulin (Taurog 1996).

The gene for human thyroid peroxidase has been isolated and sequenced (Kimura et al. 1987; Libert et al. 1987; Magnusson et al. 1987). Transcription of the gene is stimulated by TSH, possibly through a mechanism involving cAMP (McLachlan and Rapoport 1992).

Deiodination of Iodothyrones in Peripheral Tissues. Deiodination serves both as an important mechanism for the production of extrathyroidal T_3 and for the deactivation of the thyroid hormones, T_4 and T_3. The deiodination reactions are catalyzed by selenium-dependent deiodinase enzymes (selenodeiodinases). Three selenodeiodinases have been described that differ in substrate preference, reaction products, response to inhibitors (propylthiouracil, gold), and response to T_3 (Table 3-8). Full activity of each enzyme requires selenocysteine in the amino acid sequence of the active site, which is the basis for deiodination activity being responsive to nutritional selenium status (Larsen and Berry 1994; see Section 3.10).

Excretion.

Urinary Excretion of Iodide. Urinary excretion normally accounts for >97% of the elimination of absorbed iodine. The renal plasma clearance of iodine has been measured in human subjects during continuous intravenous infusions of radioiodide (Bricker and Hlad 1955). Under these conditions, only a negligible amount of radioiodine in the plasma was associated with protein and >98% was ultrafilterable; thus, the renal clearance of radioiodine can be assumed to reflect that of radioiodide (Bricker and Hlad

Table 3-8. Properties of Human Iodothyronine Selenodeiodinases

Parameter	Type 1	Type 2	Type 3
Physiological role	Plasma T_3 production, deactivate T_3 and T_4, degrade rT_3	Plasma and intracellular T_3 production	Deactivate T_3 and T_4
Tissue location	Liver, kidney, thyroid, central nervous system, pituitary	Central nervous system, pituitary, brown fat, placenta, thyroid, skeletal muscle, heart	Central nervous system, placenta, skin
Substrate preference	$rT_3>>T_4>T_3$	$T_4\$rT_3$	$T_3>T_4$
Molecular weight (D)[a]	29,000	35,000	31,500
Apparent K_m (M)	~10^{-7} (rT_3) ~10^{-6} (T_4)	10^{-9} (T_4) ~10^{-8} (rT_3)	~10^{-9} (T_3) ~10^{-8} (T_4)
Deiodination site	Outer and inner ring	Outer ring	Inner ring
Apparent K_i (M)			
Propylthiouracil	$2x10^{-7}$	$4x10^{-3}$	10^{-3}
Gold	~$5x10^{-9}$	~$2x10^{-6}$	$5x10^{-6}$
Response to T_3	Increase	Decrease	Increase

[a]Monomer

T_3 = 3,5,3ℕ-triiodo-L-thyronine; T_4 = 3,5,3ℕ,5ℕ-tetraiodo-L-thyronine (thyroxine); rT_3 = reverse T_3

Source: Larsen et al. 1998

1955; Walser and Rahill 1965). Under steady-state conditions with respect to the serum radioiodine concentration, the renal plasma clearance of radioiodine was approximately 30% of the glomerular filtration rate, suggesting that filtered iodide is reabsorbed in the renal tubule (Vadstrup 1993). Measurements of the steady-state renal clearance of radioiodide in dogs have provided additional evidence for tubular reabsorption of iodide (Beyer et al. 1981; Walser and Rahill 1965). The mechanism of renal tubular reabsorption of iodide has not been elucidated, although studies to examine mechanisms have been largely limited to clearance studies. NIS mRNA is expressed in human kidney and NIS immunoreactivity has been observed in the human kidney proximal and distal tubules; however, its role in iodine transport in the kidney has not been elucidated (Spitzweg et al. 2001). In humans, iodide clearance as a fraction of the glomerular filtration rate (C_I/GFR) increases in response to an acute increase in GFR and decreases in response to an acute decrease in GFR; however, C_I/GFR is relatively unaffected by large acute increases in the plasma concentration of radioiodine at a constant GFR (Bricker and Hlad 1955). This suggests a sensitivity of tubular reabsorption to both filtered load of iodide and tubular flow rate. C_I/GFR can be increased to near unity during mannitol-induced diuresis (Bricker and Hlad 1955). Although the inability to detect an apparent saturation of tubular reabsorption at high filtered loads of iodide and the sensitivity of tubular reabsorption to tubular flow rate are consistent with a passive, paracellular, component to iodide reabsorption, these observations do not rule out the existence of facilitated transport of iodide in the nephron. In humans, C_I/GFR, whole body clearance of radioiodine is increased during diuresis induced by furosemide and hydrochlorothiazide, two clinical diuretics that decrease sodium and chloride reabsorption in the in the loop of Henle and distal convoluted tubule, suggesting the possibility of reabsorption of iodide in distal segments of the nephron (Seabold et al. 1993). This observation is further supported by steady-state clearance measurements in dogs, in which C_I/GFR was found to increase in response to hydrochlorothiazide-induced diuresis, and to be lower, near that of C_{Cl}/GFR, in dogs that had been maintained on a sodium deprivation diet (Beyer et al. 1981; Walser and Rahill 1965). The latter observation would suggest that adaptations to sodium deprivation that result in greater reabsorption of sodium in the late distal nephron also give rise to increased reabsorption of iodide.

3.6.2 Mechanisms of Toxicity

The mechanism by which excess iodide produces hypothyroidism is not completely understood. Iodide excess inhibits the iodination of thyroglobulin in the thyroid gland and inhibits the release of T_4 and T_3 from the gland (Pisarev and Gärtner 2000). Both effects could contribute to stimulation of release of TSH from the pituitary gland and to the increase in serum concentration of TSH and hypertrophy of the thyroid

gland that has been shown to accompany iodide-induced thyroid gland suppression (see Section 3.2.2.2, Endocrine). The mechanism by which iodide suppresses iodination and thyroid hormone release appears to involve inhibition of adenylate cyclase. The stimulatory actions of TSH on the thyroid gland, which include increased iodide transport and increased iodination of thyroglobulin and production and release of T_4 and T_3, occur in response to a rise in intracellular cAMP levels that follow binding of TSH to TSH receptors on thyroid gland follicle cells. Iodide inhibits adenylate cyclase in thyroid gland follicle cells and decreases the TSH-induced rise in intracellular cAMP. However, the effect of iodide on adenylate cyclase can be prevented by inhibitors of iodination, such as propylthiouracil. This has led to the suggestion that the ultimate active inhibitor is an endogenous iodinated species that is produced in a reaction requiring thyroid peroxidase. Candidates for the endogenous inhibitor are one or more iodinated lipids (Filetti and Rapoport 1983; Pereira et al. 1990; Pisarev and Gärtner 2000). The synthesis of NIS also appears to be regulated by plasma iodide concentration, through a mechanism that does not directly involve TSH. In rats and dogs, expression of mRNA for the NIS in the thyroid decreased when serum iodide concentrations were increased by ingestion or injection of iodide, even when serum TSH concentrations were unchanged (Eng et al. 1999; Uyttersprot et al. 1997).

Excess iodide intake may be a contributing factor in the development of autoimmune thyroiditis in people who are susceptible (Brown and Bagchi 1992; Foley 1992; Rose et al. 1997; Safran et al. 1987). In certain inbred strains of rats and mice, exposure to iodide has been shown to increase the incidence of lymphocytic thyroiditis (Allen and Braverman 1990; Allen et al. 1986; Noble et al. 1976; Rasooly et al. 1996). The mechanism by which iodide stimulates autoimmunity is not completely understood. In the inbred mouse strain, NODh2^{h4}, both $CD4^+$ and $CD8^+$ T cells are required for iodine-induced acceleration of autoimmunity (Hutchings et al. 1999). Highly iodinated thyroglobulin may be an antigen in susceptible animals (or humans) (Dai et al. 2002; Rose et al. 1997; Saboori et al. 1998a, 1998b, 1999; Sundick et al. 1987). Other proposed mechanisms include effects of iodine on the regulation of major histocompatibility complex class I and increased expression of thyroid gland TNF-α (Schuppert et al. 2000; Roti and Vagenakis 2000; Ruwhof and Drexhage 2001; Verma et al. 2000). Thyroid autoimmunity may produce hypothyroidism by stimulating thyroid cell apoptosis (Huang and Kukes 1999; Phelps et al. 2000; Stassi et al. 2000).

Excess iodide can, under certain circumstances, induce hyperthyroidism and thyrotoxicosis; this has been observed most often after iodine supplementation of iodine-deficient populations (Braverman and Roti 1996; Fradkin and Wolff 1983; Leger et al. 1984; Paschke et al. 1994). The mechanism by which iodide induces hyperthyroidism is not completely understood. Chronic iodine deficiency results in thyroid gland

proliferation, which may increase the fixation of mutations in the gland and promote the development of autonomous nodules that are less responsive or unresponsive to regulation in response to serum TSH concentrations. Iodine excess, under these conditions, could result in increased and unregulated thyroid hormone production (Corvilain et al. 1998; Dremier et al. 1996; Roti and Uberti 2001).

Extremely high acute doses of iodine in the form of tinctures containing iodine and sodium triiodide have resulted in deaths (Finkelstein and Jacobi 1937). The mechanism of toxicity is not understood, although direct chemical injury to the gastrointestinal tract and related secondary consequences, including fluid and electrolyte loss, massive acute extracellular fluid volume contraction, and cardiovascular shock, may contribute to the widespread systemic effects that have been observed in lethal or near-lethal poisonings.

3.6.3 Animal-to-Human Extrapolations

The principal health effects of iodine in humans have been characterized in experimental, clinical, and epidemiological studies of humans. Animal models remain useful for exploring mechanisms, and where relevant, these studies have been described; for example, the use of inbred rat strains to study iodine-induced autoimmune thyroiditis (see Section 3.2.2.2, Endocrine). The major features of the toxicokinetics of iodine in humans, particularly following oral exposures, have been characterized in experimental and clinical studies of humans. A substantial amount of experience exists in the application of biomarkers for assessing human exposures to iodine (e.g., urinary iodine excretion and thyroid scintillation scan) and health effects in humans (e.g., serum thyroid hormone, TSH, and thyroid antibodies). Thus, the assessment of health effects and health risks associated with exposures to iodine or radioiodine can be based soundly on human studies rather than on extrapolations from animal studies.

3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate terminology to describe such effects remains controversial. The terminology endocrine disruptors, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and

Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning endocrine disruptors. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as hormonally active agents. The terminology endocrine modulators has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Iodine is an endocrine disruptor in that the principal direct effects of excessive iodine ingestion are on the thyroid gland and on the regulation of thyroid hormone production and secretion. As discussed in Section 3.2.2.2, Endocrine Effects, the effects of iodine on the thyroid gland include hypothyroidism, hyperthyroidism, and thyroiditis. The above three types of effects can occur in children and adults, and in infants exposed *in utero* or during lactation. Adverse effects on the pituitary and adrenal glands derive secondarily from disorders of the thyroid gland. A wide variety of effects on 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 (Braverman and Utiger 2000).

3.8 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential

effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and in vitro models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Children are highly vulnerable to radioiodine toxicity and related thyroid cancers (NRC 1999). Radioiodine is secreted into milk in humans, cows, and goats, and infants and children ingest a larger amount of milk per unit of body mass than adults; they also absorb ingested iodine as avidly as adults. As a result, children exposed to milk that has been contaminated with radioiodine may receive a larger internal dose of radioiodine than similarly exposed adults. This larger absorbed iodine dose per unit of body mass is concentrated in a smaller thyroid mass in infants and children (Aboul-Khair et al. 1966; Kay et al. 1966; Mochizuki et al. 1963), which can result in a higher radiation dose per unit of thyroid mass.

In addition to a smaller thyroid mass, thyroid iodine uptakes, expressed as a fraction of absorbed dose, are 3–4 times higher during the first 10 days of postnatal life compared to adult uptakes and decline to adult levels after approximately age 10–14 days (Fisher et al. 1962; Kearns and Phillipsborn 1962; Morrison et al. 1963; Ogborn et al. 1960; Van Middlesworth 1954). As a result, newborn infants will be particularly vulnerable to high radiation doses from internal exposure to radioiodine. NCI (1997) estimated that the radiation dose (rad) to the thyroid gland resulting from ingestion of 1 μCi of ^{131}I activity would increase with decreasing age in children from approximately 1.5 rad/μCi in adults, to approximately 6.6 rad/μCi at 5 years, 12 rad at 1 year, and 33 rad in newborn infants. Another important factor that contributes to higher vulnerability of children is that children under 15 years of age appear to be more susceptible to developing thyroid tumors from thyroid irradiation (Wong et al. 1996). 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 (Ron et al. 1995). An age-dependence has been found for solid tumors of other organs and external radiation dose (Thompson et al. 1994). 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.

Evidence for vulnerability of infants and children to radioiodine toxicity derive from studies of populations that have been exposed to radioiodine fall-out as a result of thermonuclear bomb tests and nuclear reactor accidents. Several epidemiological studies have examined thyroid gland disorders in residents of the Marshall Islands who were exposed to radioiodine from atmospheric fallout after an atmospheric nuclear bomb test (so-called BRAVO test, see Section 3.3.2 for a more detailed discussion of exposures from the Marshall Islands BRAVO test). The exposures occurred as a result of an unexpected change in the wind direction after the bomb detonation. Residents of several islands near and downwind from the test site on Bikini Atoll (e.g., Ailingnae, Rongelap, Utrik) were exposed to both internal radioiodine and external gamma radiation from fallout during the 2 days prior to their evacuation. The estimated gamma radiation dose on these islands ranged from 69 to 175 rad (0.7–1.75 Gy) or approximately 10–50% of the estimated thyroid dose (Conard 1984; Hamilton et al. 1987; Howard et al. 1997; Takahashi et al. 1999). Cases of thyroid gland disorders began to be detected in the exposed population in approximately 10 years after the exposure, particularly in persons who were exposed as children; these included cases of apparent growth retardation, myxedema, and thyroid gland nodules and neoplasms (Conard et al. 1970). In 1981, health screening of children on Rongelap revealed an 83% prevalence of elevated serum concentrations of TSH (>5 mU/L) 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 (15 Gy). Prevalence of elevated serum TSH decreased with exposure age and/or thyroid dose: 25% for ages 2–10 years (800–1,500 rad, 8–15 Gy) and 9% for ages $10 years (335–800 rad, 3.3–8 Gy). A similar age-related prevalence of thyroid abnormalities occurred after radioiodine release from the fire at the Chernobyl nuclear power plant in the Ukraine. Clinical records from the Republics of Belarus and Ukraine show an increase in the incidence of thyroid nodules and thyroid cancers in children and adolescents, which became apparent approximately 4 years after the release of radioactive materials from the Chernobyl nuclear power plant in April 1986 (Astakhova et al. 1998; Cherstvoy et al. 1996; Drobyshevskaya et al. 1996; Tronko et al. 1996) (see Section 3.3.2 for a more detailed discussion of exposures from the Chernobyl accident). A comparison of thyroid cancers diagnosed in children in the Belarus-Ukraine region after the Chernobyl fire with thyroid cancers diagnosed in children in France and Italy during the same period revealed a striking age difference (Pacini et al. 1997). Most the Belarus-Ukraine cancers were diagnosed at age ≤5 years, whereas most of the cases in France and Italy were diagnosed after age 14 years. This observation is consistent with a radioiodine contribution to the Belarus-Ukraine cancers and a higher vulnerability of infants to radioiodine toxicity.

Nutritional factors can affect the toxicokinetics of iodine in children and adults. The most important factor is dietary iodine. Chronic iodine deficiency triggers homeostatic mechanisms to increase iodide uptake into the thyroid gland in order to sustain adequate thyroid hormone levels to regulate metabolism (Delange and Ermans 1996). These mechanisms include induction of iodide transport activity and iodination activity in the thyroid gland, as well as hypertrophy of the gland (i.e., goiter). As a result, exposures to radioiodine that occur during a state of deficiency can be expected to result in a larger fraction of the radioiodine dose being deposited in the thyroid gland, which could result in a higher radiation dose and risk.

Another nutritional factor that could potentially affect iodine biokinetics in infants and children is selenium deficiency. Selenium is a cofactor in the iodothyronine deiodinases that are important for the synthesis of the thyroid hormone, T_3, in extrathyroidal tissues. Iodine deficiency, in conjunction with selenium deficiency, has been associated with goiter and cretinism, a developmental impairment related to prenatal hypothyroidism (Goyens et al. 1987; Vanderpas et al. 1990). In this state, in which the thyroid gland is responding to a deficiency in T_3 production by increasing iodide transport and iodination activity in the thyroid gland, infants and children (as well as adults) may experience a higher thyroid uptake of absorbed iodine, and possibly a higher radiation dose to the thyroid when exposed to radioiodine.

As previously discussed in Section 3.5.2.2, exposure to iodine can begin *in utero* with maternal exposure and, as a result, the fetus is vulnerable to the potential toxic effects of maternal iodine exposures that occur during pregnancy. Maternal exposures to excess iodine have been shown to produce thyroid enlargement and hypothyroidism in neonates (Coakley et al. 1989; Hassan et al. 1968; Iancu et al. 1974; Martin and Reno 1962; Penfold et al. 1978; Vicens-Colvet et al. 1998). Deaths have occurred in neonates as a result of tracheal compression from thyroid gland enlargement (Galina et al. 1962). The vulnerability of the fetal thyroid gland has a toxicokinetic basis. Radioiodine uptake in the fetal thyroid commences in humans at approximately 70–80 days of gestation and precedes the development of thyroid follicles and follicle colloid, which are generally detectable at approximately 100–120 days of gestation (Book and Goldman 1975; Evans et al. 1967). Fetal iodide uptake activity increases with the development of the fetal thyroid and reaches its peak at approximately 6 months of gestation, at which point, the highest concentrations in the thyroid are achieved, approximately 5% of the maternal dose/g fetal thyroid (approximately 1% of the maternal dose) (Aboul-Khair et al. 1966; Evans et al. 1967). Fetal radioiodine concentrations 1–2 days following a single oral maternal dose of radioiodine generally exceed the concurrent maternal thyroid concentration by a factor of 2–8, with the highest fetal/maternal ratios occurring at approximately 6 months of gestation (Book and Goldman 1975). Following exposure to ^{131}I

from maternal ingestion of medically administered radioiodine or from repeated exposure to radioactive fallout, the fetal/maternal ratio for thyroid radioiodine concentration has been estimated to be approximately 2–3 (Beierwaltes et al. 1963; Book and Goldman 1975; Eisenbud et al. 1963).

Dermal exposures to iodine, in particular topical antiseptics containing povidone-iodine, can expose the fetus to iodine. For example, increases in iodine concentration in maternal urine and umbilical cord blood have been observed in pregnant women who received dermal or vaginal applications of povidone-iodine prior to delivery for disinfection of the skin and fetal scalp electrodes, suggesting that absorption of iodine occurs with these uses of povidone-iodine as well (l'Allemand et al. 1983; Bachrach et al. 1984). Consistent with this are observations that topical application of iodine preparations (i.e., povidone-iodine) during labor has produced thyroid gland suppression in newborns (l'Allemand et al. 1983; Novaes et al. 1994). Infants can also absorb iodine when such iodine preparations are applied topically. Use of povidone-iodine for topical and surgical wound disinfection in infants has been shown to induce transient hypothyroidism or hyperthyroidism (Brown et al. 1997; Chabrolle and Rossier 1978a, 1978b).

Nursing infants can be exposed to iodine in breast milk (Dydek and Blue 1988; Hedrick et al. 1986; Lawes 1992; Morita et al. 1998; Robinson et al. 1994; Rubow et al. 1994; Spencer et al. 1986). The level of exposure will depend not only on the maternal exposure, but also on the physiologic status of the maternal thyroid. A larger fraction of the absorbed dose is excreted in breast milk in the hypothyroid state compared to the hyperthyroid state; in the hypothyroid state, excretion of radioiodine into breast milk can be 10 times higher (e.g., 25% of the dose) than in euthyroid or hyperthyroid states (Hedrick et al. 1986; Morita et al. 1998; Robinson et al. 1994).

Iodine is not stored in skeletal tissue or fat to any significant degree and thus, mobilization of these tissues during pregnancy, for production of the fetal skeleton or breast milk, would not be expected to contribute to fetal or infant exposure. There is no evidence that iodine metabolism would be appreciably different in children compared to adults. It is possible that the conjugation of iodothyronines with glucuronic acid could be limited in newborns as a result of the normal development of glucuronyltransferase activity in the newborn and infant; however, there is no evidence for an effect on iodine toxicokinetics. In the Gunn rat, which is a strain of rat that is deficient in glucuronyltransferase activity, glucuronic acid conjugates of iodothyronines are formed and biliary excretion of iodothyronines is impaired; however, normal circulating levels iodothyronine appear to be maintained (Curran and DeGroot 1991). This would suggest that the thyroid gland may not increase uptake of iodine in response to an impairment in glucuronyl-transferase activity.

Models of the biokinetics of iodine in infants, children, adolescents, and adults have been developed by ICRP (1989, 1994a, 1995). Models have also been developed that predict, with reasonably high accuracy, the accumulation of radioiodide in the thyroid gland of infants and children exposed to single doses of radioiodine for clinical procedures (Fisher et al. 1962).

3.9 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to iodine are discussed in Section 3.9.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly

adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by iodine are discussed in Section 3.9.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.11 "Populations That Are Unusually Susceptible".

3.9.1 Biomarkers Used to Identify or Quantify Exposure to Iodine

Urinary iodine excretion provides a reliable biomarker of steady state iodine intake. Under steady state conditions, in which exposure to iodine has been reasonably constant for at least 6 months, daily iodine will approximate the 24-hour urinary iodine excretion. The basis for this relationship is that ingested iodide is nearly completely absorbed in the gastrointestinal tract and that urine is the principal route of excretion of the absorbed iodide (see Sections 3.5.1.2 and 3.5.4.2). The use of urinary iodide as a biomarker of iodide exposure is supported by studies in which 24-hour urinary iodide was measured before and after supplementation. For example, 31 patients received oral supplements of 382 µg I/day for 6 months. Prior to the supplementation, the mean 24-hour urinary iodide excretion rate was 36 µg/day (range, 13–69), whereas after 6 months of iodide supplementation, the mean 24-hour urinary iodide excretion rate was 415 µg/day (Kahaly et al. 1998). The difference between these two values, 379 µg/day, is nearly identical to the supplemental dose of 382 µg/day.

Exposure to ^{123}I, ^{124}I, and ^{131}I can be detected directly from external measurements of gamma radiation emanating from the thyroid gland. The basis for this is that approximately 90% of the iodine in the body is in the thyroid gland and absorbed iodine is rapidly taken up into the thyroid gland. The measurement procedure is known as a thyroid scintillation scan. A scintillation detector device usually consists of a shielded sodium iodide crystal connected to a collimator and spectrometer. The detector is placed over the thyroid gland and the spectrometer is tuned to collect gamma emissions having peak energies of the target isotope (e.g., 0.159, 0.511, or 0.364 MeV for ^{123}I, ^{124}I, or ^{131}I, respectively). Events are corrected for attenuation by overlying tissue by counting a neck phantom containing a gamma source of known activity. Because of the relatively short radioactive decay half-times of ^{123}I (13 hours), ^{124}I (4.2 days), and ^{131}I (8 days), thyroid scans must be conducted soon after exposure in order to detect the iodine in the thyroid gland.

The thyroid scintillation scan is also used in medical practice to identify disease of the thyroid, and can reflect either idodie excess or deficiency.

3.9.2 Biomarkers Used to Characterize Effects Caused by Iodine

The thyroid gland is the primary and most sensitive target for both chemical and radioiodine toxicity. As a result, biomarkers of iodine effects are those that allow the detection of preclinical and clinical suppression or stimulation of the thyroid gland. Effects on the thyroid gland can be classified into three types: hypothyroidism, hyperthyroidism, and thyroiditis. Hypothyroidism refers to a state of diminished production of thyroid hormones leading to clinical manifestations of thyroid insufficiency and can occur with or without goiter, a functional hypertrophy of the gland in response to suppressed hormone production and elevated serum thyroid stimulating hormone (TSH, also known as thyrotropin) concentrations. Typical biomarkers of hypothyroidism are depressions in the circulating levels of thyroxine (T_4) and/or triiodothyronine (T_3) below their normal ranges. This is always accompanied by an elevation of the pituitary hormone, TSH, above the normal range. Typical normal ranges are for hormone levels are shown in Table 3-9. 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. Thyroid autoimmunity can be detected as a presence of IgG antibodies to thyroglobulin and thyroid peroxidase in serum antibodies (Table 3-9). In addition to the above measurements, physical examination, ultrasound and thyroid scintillation scanning can reveal nodules and other normal or abnormal variations in thyroid gland structure and function. Examples of the use of these measurements in assessing iodine-induced effects on the thyroid gland are presented in Section 3.2 of the profile.

Table 3-9. Typical Reference Ranges for Serum Thyroid Hormones and TSH in Humans

	Reference range	
Hormone	Metric	SI unit
Total T_4	4–11 µg/dL	60–140 nM[a]
Free T_4	0.7–2.1 ng/dL	10–25 pM[a]
Total T_3	75–175 ng/dL	1.1–2.7 nM[a]
Free T_3	0.2–0.5 ng/dL	3–8 pM
Reverse T_3	15–45 ng/dL	0.2–0.7 nM
TSH	0.3–4.0 mU/L[b,c]	1–15 pM
Thyroid peroxidase antibodies (TPA)	<10 IU/mL	No data
Thyroglobulin autoantibodies (Tg-ab)	<10 IU/mL	No data

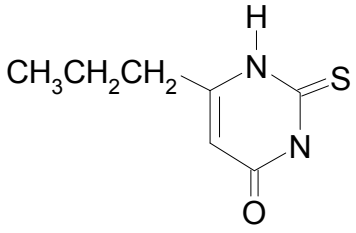
[a]Children may be higher
[b]Assumes a biologic potency of 7–15 mU/mg
[c]Higher in neonates (de Zegher et al. 1994)

T_3 = 3,5,3ℕ-triiodo-L-thyronine; T_4 = 3,5,3ℕ,5ℕ-tetraiodo-L-thyronine (thyroxine); TSH = thyroid stimulating hormone

Source: Stockigt (2000) and Marcocci and Chiovato (2000)

3.10 INTERACTIONS WITH OTHER CHEMICALS

Thioureylenes and Thionamides. Several of thionamide compounds that contain a thioureylene chemical group have been shown to increase the accumulation of iodide in the thyroid gland and to decrease the production of iodothyronines (Green 1996):



Propylthiouracil

These include several drugs used in the treatment of thyrotoxicosis and other hyperthyroid states, (carbimazole, methimazole, and propylthiouracil); as well as the antibiotic, ethionamide; the cancer chemotherapy agent, 6-mercaptopurine; and goitrin, a natural constituent of the plant genus Brassicae (rutabaga, turnip, and cabbage). The thionamides exert their effects by inhibiting the iodination of tyrosine and monoiodotyrosine in the thyroid gland and the coupling of iodotyrosines to form iodothyronines. The mechanisms for these effects are not completely understood; however, at least two mechanisms are needed to explain the reversible and irreversible inhibition of iodothyronine production that is characteristic of these agents. Thionamides agents may act reversibly by reducing I^+ or some other reactive intermediate of iodine required in the iodination reaction, and also through a mechanism that involves a direct, irreversible reaction with thyroid peroxidase.

Thiouracil and propylthiouracil, and related thioureylenes, are also inhibitors of iodthyronine deoidinase (Leonard and Koehrle 1996). The mechanism of inhibition involves the formation of a covalent complex with deiodinase enzymes. Inhibitory potency is highest for Type 1 deiodinase (Table 3-8). The result of inhibition is a decreased metabolic clearance of iodothyronines.

Analine Derivatives. As a class, para-substituted aminobenzenes have activity similar to that of the thionamides in that they increase the accumulation of iodide in the thyroid gland and decrease production of iodothyronines, although possibly not through the same mechanisms (Green 1996). The group

includes several drugs (and drug classes), amphenone B, carbutamide, amino-glutethimide, p-aminosalicylic acid, and the sulfonamides.

Substituted Phenols. Various substituted phenols that have hydroxyl groups in the meta positions have been shown to increase thyroid iodide accumulation and to inhibit iodothyronine production in the thyroid. These include resorcinol, 2,4-dihydroxybenzoic acid, and 2,4-dihydroxyphenol. These compounds exert their activity by producing an irreversible inhibition of thyroid peroxidase (Green 1996).

Hydroxypyridines. Hydroxypyridines, including 3-hydroxypyridine and 3,4-dihydroxypyridine, have been shown to increase thyroid iodide accumulation and to inhibit iodothyronine production in the thyroid (Green 1996).

Perchlorate and Related Complex Anions. A variety of complex inorganic anions have been shown to decrease the uptake of iodide in the thyroid gland. When given at high enough dosages, these agents can induce hypothyroidism and goiter (Green 1996). The complex anions include, in order of potency: perchlorate (ClO_4^-), perrhenate (ReO_4^-), pertechnetate (TcO_4^-), and tetrafluorborate (BF_4^-). The mechanism for their activity is competitive inhibition of the NIS (Carrasco 1993; Eskandari et al. 1997; Wolf 1964). These agents may also be transported by the NIS to varying degrees. Perchlorate does not appear to be transported by NIS (Eskandari et al. 1997; Yoshida et al. 1997). These anions can also affect accumulation and/or secretion of iodide in other tissues that have an active iodide transporter, including the choroid plexus, gastric mucosa, mammary gland, placenta, salivary gland, and sweat gland (Brown-Gant 1961).

Thiocyanate. Thiocyanate (SCN^-) is a potent inhibitor of iodide uptake in the thyroid gland and iodination of thyroglobulin. The mechanism for the effect on iodide uptake is primarily related to competitive inhibition of iodide transport by the $Na+/I^-$ symport in thyroid gland; however, thiocyanate may also accelerate iodide efflux from the thyroid by being a substrate with iodide for an anion exchange mechanism on the basolateral membrane of thyroid follicle cells (Eskandari et al. 1997; Yoshida et al. 1997). Thiocyanate inhibits iodination, apparently by its actions as a competitive oxidation substrate for thyroid peroxidase (Virion et al. 1980). Unlike other complex anion inhibitors of iodide transport, thiocyanate is not accumulated in the thyroid gland.

Thiocyanate is a product of the metabolism of cyanide (ATSDR 1997) to which humans are exposed when they smoke cigarettes, which has prompted interest in the potential effects of smoking on thyroid

iodine metabolism and thyroid disease (Bertelsen and Hegedus 1994). Thiocyanate is a metabolite of nitroprusside, a drug used in the treatment of acute hypertensive emergencies and cardiac failure. Impairment of thyroid function in patients on nitroprusside has been reported (Bodigheimer et al. 1979; Nourok et al. 1964).

Microsomal Enzyme Inducers. Agents that induce hepatic microsomal enzymes increase the activity of phenolic glucuronyl transferases that catalyze the conjugation of iodothyronines with glucuronic acid (Curran and DeGroot 1991; Visser 1990). Induction of glucuronyltransferase increases the metabolic clearance of iodothyronines and, if sufficiently accelerated, can stimulate TSH release and goiter. Such effects have been observed in rats and other experimental animal models in response to exposures to 2,4-benzopyrene, chlordane, DDT and DDD, 3-methylcholanthrene, PCBs, chlorinated dibenzodioxins (CDDs), and toxaphene. A variety of drugs have also been shown to exert effects on glucruonide conjugation of iodothyronines, including the sedative, phenobarbital; the anticonvulsants, phenytoin and carbamazepine; and the antibiotic, rifampin.

Polychlorinated Biphenyls (PCBs). Depending on dose and duration, PCBs can disrupt the production and disposition of thyroid hormones at a variety of levels and thereby may potentially interact with iodine in impairing the thyroid gland. The major findings include (1) histological changes in the thyroid gland indicative of both stimulation of the gland (e.g., similar to that induced by TSH or a hypothyroid state) and disruption of the processing of follicular colloid needed for normal production and secretion thyroid hormone; (2) depression of serum T_4 and T_3 levels, which may effectively create a hypothyroid state (in some studies, low doses resulted in elevated serum T_4 levels while depressed levels occurred at higher PCB doses); (3) increased rates of elimination of T_4 and T_3 from serum; (4) increased activities of T_4-UDP-glucuronyl transferase (UDP-GT) in liver, which is an important metabolic elimination pathway for T_4 and T_3; (5) decreased activity of iodothyronine sulfotransferases in the liver, which are also important in the metabolic elimination of iodothyronines; (6) decreased activity of iodothyronine deiodinases, including brain Type-2 deiodinase, which provide the major pathways for the production of the active thyroid hormone, T_3; and (7) decreased binding of T_4 to transthyretin, an important transport protein for both T_4 and T_3 (ATSDR 2000b).

Selenium. Selenium is essential for the activity of the glutathione peroxidases and iodothyronine deiodinases. In humans, concurrent selenium and iodine deficiency have been associated with goiter and cretinism, a developmental impairment related to prenatal hypothyroidism (Goyens et al. 1987; Vanderpas et al. 1990). Supplementation of individuals deficient in both iodine and selenium with

selenium produces a further decrease in thyroid function, but if selenium supplementation is preceded by normalization of iodine levels, then normal thyroid function is restored (Contempré et al. 1991, 1992). Selenium intake has been reported to affect thyroid hormone levels in humans; these effects include decreases in serum T_3 and T_4 levels and increases in serum TSH levels, suggesting suppression of thyropid hormone production (Brätter and Negretti De Brätter 1996; Duffield et al. 1999; Hagmar et al. 1998; Hawkes and Keim 1995). In experimental animals, selenium deficiency produces in decreased metabolic clearance of iodothyronines and decreased extrathyroidal production of T_3, as a result of decreased iodothyronine deiodinase activity, which can be restored to normal by selenium repletion (Arthur and Beckett 1994; Behne and Kyriakopolous 1993). Selenium deficiency also results in decreases in thyroid iodine concentrations. The latter effect is thought to involve direct and indirect effects on thyroid hormone production and secretion. The direct effect is thought to result from decreased activity of glutathione peroxidase in the thyroid and increased availability of hydrogen peroxide for utilization in the production of iodothyronines in the thyroid, which can then be exported from the gland. The indirect effect may involve increased release of TSH from the pituitary gland in response to a decrease in plasma concentration of T_3, resulting from inhibition of deiodination of T_4.

Amiodarone. The more serious side effects of the use of the antiarrythmia drug, amiodarone, are effects on the thyroid, including hypothyroidism, hyperthyroidism, and thyroditis (Bogazzi et al. 2001; Meier and Burger 1996). Although the exact mechanisms for these effects are not completely understood, amiodarone contains a large quantity of iodine and has been shown to inhibit the deiodination of iodothyronines; in particular, the production of T_3 from T_4, most likely as a result of inhibition of Type 1 deiodinase (Table 3-8). A metabolite of amiodarone, desethyamiodarone, has been shown to inhibit binding of T_3 to thyroid hormone receptors in a variety of tissues (Green 1996). As a thyroid receptor antagonist, amiodarone (or its metabolite) also stimulates the release of TSH from the pituitary gland.

Lithium. Hypothyroidism and goiter have been associated with chronic therapy with lithium carbonate for management of bipolar disease (Green 1996; Spaulding et al. 1972). The mechanism for these effects is not understood, although it has been suggested that lithium may inhibit the coupling reaction in the synthesis of iodothyronines and may inhibit thyroid hormone secretion.

Propranolol. Propranolol is a drug used in the treatment of hypertension, angina, and other cardiovascular disorders as well as for the symptomatic treatment of thyrotoxicosis. Although the basis for its use in treatment of thyrotoxicosis is to counteract the cardiovascular symptoms of the disorder, the drug is also an inhibitor of iodothyronine deiodination (Meier and Burger 1996). The effect is unrelated

to its activity as a β-adrenergic receptor antagonist, as both the L- and D-isomer (devoid of β-receptor antagonist activity) inhibit the deiodination of T_4. The mechanism for this action is not understood.

Dexamethasone. Although the corticosteroids exert multiple effects on the physiological regulation of thyroid hormone release (e.g., decreased TSH release from the pituitary), these agents also have appreciable activity as inhibitors of iodothyronine deiodinase and can decrease the metabolic clearance of iodothyronines (Meier and Burger 1996).

Iodinated Drugs. A variety of iodine-containing drugs have been shown to inhibit iodothyronine deiodination and thereby decrease the metabolic clearance of iodothyronines. These include the antiarrhythmic agent, amiodarone (previously discussed), and several radiographic contrast agents used for cholecystography such as iopanoic acid, sodium ipodae, and tyropanoate (Meier and Burger 1996).

3.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to iodine than will most persons exposed to the same level of iodine in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of iodine, or compromised function of organs affected by iodine. Populations who are at greater risk due to their unusually high exposure to iodine are discussed in Section 6.7, Populations With Potentially High Exposures.

People who consume diets deficient in iodine may be more vulnerable to the toxic effects of exposure to radioiodine. At very low intakes, representing iodine deficiency (e.g., 20 µg/day), uptake of iodide into the thyroid gland is increased (Delange and Ermans 1996). This response is mediated by TSH, which stimulates iodide transport and iodothyronine production in the thyroid gland (see Section 3.6.1). If exposure to radioiodine was to occur in an individual who is iodine-deficient, a larger fraction of the absorbed radioiodine may be taken up by the thyroid gland and a larger radiation dose to the thyroid gland may be received. Iodine deficiency has been suggested to be a possible contributing factor to the increase in thyroid cancer incidence observed in Belarus after the Chernobyl reactor accident (Gembicki et al. 1997; Robbins et al. 2001).

People who have multinodular goiter or thyroid gland adenomas can have foci of thyroid gland tissues that produce and secrete thyroid hormone autonomously from control of the gland by TSH. The

mechanisms for thyroid tissue autonomy appear to involve clonal expansion of follicle cells that have a either a modified TSH receptor or receptor coupling mechanism, or that overexpress growth factors (Corvilain et al. 2000; Derwahl and Studer, 2001; Krohn et al. 2000). Autonomous nodules can give rise to hyperthyroidism (e.g., toxic nodular goiter, toxic adenoma). Iodine deficiency and goiter appear to be risk factors in the development of autonomous nodules (Aghini-Lombardi et al. 1999). People who have the autonomous nodules appear to be more vulnerable to iodide-induced hyperthyroidism (Braverman and Roti 1996; Ermans and Camus 1972). This may, in part, explain the increased incidence of hyperthyroidism that sometimes accompanies the introduction of iodide supplements into the diet of iodine-deficient populations (Connolly 1971b; Corvilain et al. 1998; Delange et al. 1999). In experimental studies, supplemental doses of 75–150 µg I/day for 1–2 weeks have induced hyperthyroidism in euthyroid patients who had autonomous thyroid adenoma (Livadas et al. 1977). Patients with certain types of thyroid autoimmunity may be more susceptible to developing hyperthyroidism when exposed to excess iodine (Braverman and Roti 1996; Braverman et al. 1971a; Roti and Uberti 2001).

Populations with diets that are deficient in selenium may be more susceptible to iodine toxicity. Selenium is a cofactor in the iodothyronine deiodinases that are important for the synthesis of the thyroid hormone, T_3, in extrathyroidal tissues. Iodine deficiency, in conjunction with selenium deficiency, has been associated with goiter and cretinism, a developmental impairment related to prenatal hypothyroidism (Goyens et al. 1987; Vanderpas et al. 1990). In this state, in which the thyroid gland is responding to a deficiency in T_3 production by increasing iodide transport and iodination activity in the thyroid gland, infants and children (as well as adults) may experience a higher thyroid uptake of absorbed iodine and possibly a higher radiation dose to the thyroid when exposed to radioiodine.

People who have $-thalassemia, an inherited disorder of hemaglobin production that can lead to anemia, may be more sensitive to developing hypothyroidism when exposed to excess iodide (Alezandrides et al. 2000).

3.12 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to iodine. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to iodine. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for

medical advice. The following text provides specific information about treatment following exposures to iodine:

Braverman LE, Utiger RD. 2000. *Werner and Ingbar's The thyroid: A Fundamental and Clinical Text.* Philadelphia, PA: Lippincott-Raven.

Treatment of toxicity from exposure to excess iodine is directed at lowering exposure and, if clinical hypothyroidism or hyperthyroidism persists, correcting the thyroid dysfunction. Treatment of clinical hypothyroidism includes the administration of thyroid hormone. Treatment of hyperthyroidism involves administering thyroid hormone synthesis inhibitors.

Treatment of toxicity from exposure to radioiodine is also directed at lowering thyroid gland uptakes of absorbed iodine, for example, by administration of potassium iodide (see Section 3.12.2). If the exposure produces persistent hypothyroidism or hyperthyroidism, the treatment strategies for the clinical abnormalities are the same as those for exposure for nonradioactive iodine.

3.12.1 Reducing Peak Absorption Following Exposure

No information was located on methods to reduce peak absorption following exposure. Mitigation of toxic effects following exposure to radioiodine is directed at reducing the uptake of absorbed iodine in the thyroid gland (see Section 3.12.2).

3.12.2 Reducing Body Burden

Approximately 90% of the iodine in the human body is contained in the thyroid gland. The thyroid gland is also the major toxicity target of radioiodine. Therefore, methods for reducing the uptake and accumulation of radioiodine in the thyroid gland can reduce the radioiodine body burden, the absorbed radiation dose to the thyroid gland and body, and the toxic effects of exposure to radioiodine. Iodine uptake into the thyroid gland is highly sensitive to the iodide intake. At very high intakes of iodine, representing an intake excess (e.g., >1 mg/day), iodine uptake into the thyroid gland decreases, primarily as a result of decreased iodothyronine synthesis (Wolff-Chaikoff effect) and iodide transport into the gland (Nagataki and Yokoyama 1996; Saller et al. 1998). A single oral dose of 30 mg iodide (as sodium iodide) decreases the 24-hour thyroid uptake of radioiodine by approximately 90% in healthy adults (Ramsden et al. 1967; Sternthal et al. 1980). The inhibition of uptake was sustained with repeated oral

doses of sodium iodide for 12 days, with complete recovery to control (presodium iodide) uptake levels within 6 weeks after the last sodium iodide dose (Sternthal et al. 1980), or within 8 days after a single dose (Ramsden et al. 1967). Repeated oral doses of 1.5–2.0 mg iodide/m^3 of surface area produced an 80% decrease in thyroid uptake of radioiodine in children (Saxena et al. 1962). Inhibition of radioiodine uptake by the thyroid gland that occurs when large doses of iodide are administered results in more rapid urinary excretion of radioiodine and decreased iodine body burden (Ramsden et al. 1967). The administration of iodide as prophylaxis for reducing thyroid uptake of radioiodine after accidental releases of radioiodine has been recommended by the FDA and NCRP (FDA 1978, 2001b; NCRP 1977). Recommendations regarding the distribution and administration of potassium iodide in the event of a nulcear accident have been provided by the National Research Council (NRC 2004). Doses of 50 mg (infants <1 year of age) or 100 mg (adults) I, as potassium iodide, just before or at the time of exposure, have been found to be effective for blocking (>90%) thyroid uptake of radioiodine (Verger et al. 2001). The dose of potassium iodide that is effective for achieving this level radioiodine uptake block will depend on the time of dosing, relative to the exposure, as well as the dietary iodide status; higher doses of potassium iodide may be needed under conditions of low dietary iodide intake (Zanzonico and Becker 2000). The FDA (2001b) has recommended that potassium iodide be administered at the following doses, daily doses, until the risk of exposure from inhalation or ingestion no longer exists:

Receptor (years)	Predicted thyroid radiation dose (cGy, rad)	Dose (mg KI/day)	Dose (mg I/day)
Adults >40 years	$500		
Adults >18–40 years	$10	130	100
Pregnant or lactating women	$5		
Adolescents >12–18 years*		65	50
Children >3–12 years	$5		
Infants <1 month–3 years		32	24
Infants <1 month		16	12

* Adolescents $70 kg should receive adult dose (130 mg/day)

3.12.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanisms of action of excess iodine in producing goiter, hypothyroidism, hyperthyroidism, or thyroiditis involve direct interactions between iodide and physiological elements involved in thyroid hormone synthesis and release, and iodine transport. Therefore, the principal strategy for reducing toxic effects is to decrease iodine intake or uptake into the thyroid gland (see Section 3.12.2). Numerous cases of reversal of iodine-induced hypothyroidism or hyperthyroidism after reduction of iodide intake have been reported and are described in this profile (see Section 3.2.2.2, Endocrine Effects). The principal

clinical strategy for managing permanent hypothyroidism is the administration of T4 (Brent and Larsen 2000). The principal clinical strategies for managing permanent hyperthyroidism is the administration of agents that inhibit iodination of thyroglobulin, such as propylthiouracil or methimazole, or that inhibit thyroid uptake of iodine, such as perchlorate, or the destruction of the thyroid gland with radiation. The latter is usually accomplished by administering a cytotoxic dose of ^{131}I. β-Adrenergic antagonists are also used to manage some of the symptoms of thyrotoxicosis (Cooper 2000). Cases of massive acute, near-lethal poisoning from ingestion of tinctures of iodine (mixtures of molecular iodine and sodium triiodide) have included fluid and electrolyte replacement to manage cardiovascular shock (Finkelstein and Jacobi 1937).

The sulfhydryl compound, amifostine, has been found to reduce the toxic effects of high exposures to ^{131}I in patients who undergo ablative therapy with ^{131}I for thyroid cancers (Bohuslavizki et al. 1996, 1998a, 1998b, 1999). The mechanism for the protective effect appears to be accumulation of amifostine in the salivary gland and scavenging of free radicals formed as a result of interactions of ionizing radiation from ^{131}I with tissues.

3.13 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of iodine is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of iodine.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.13.1 Existing Information on Health Effects of Iodine

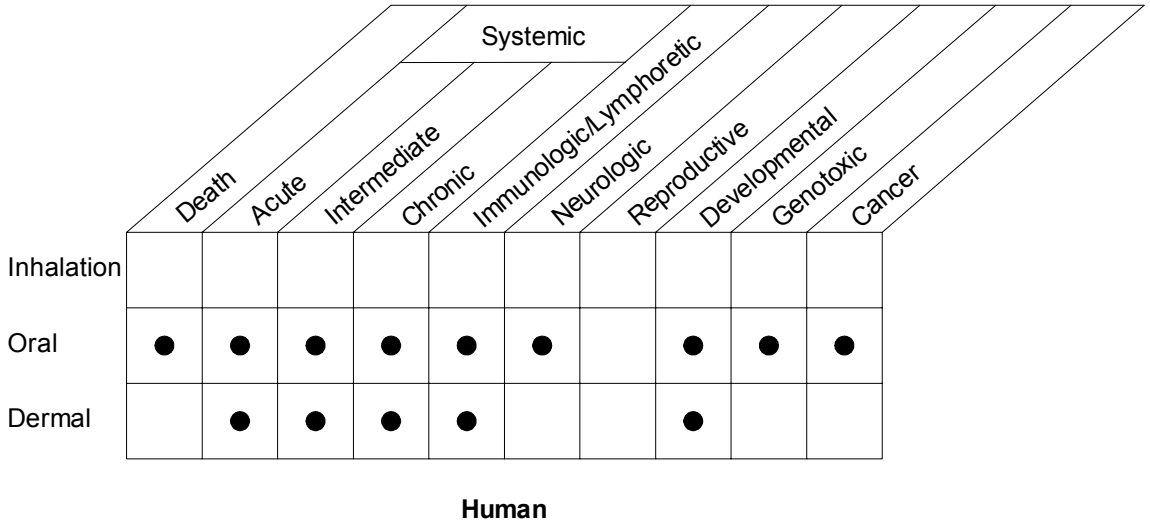
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to iodine are summarized in Figures 3-16 and 3-17. The purpose of this figure is to illustrate the existing information concerning the health effects of iodine. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

3.13.2 Identification of Data Needs

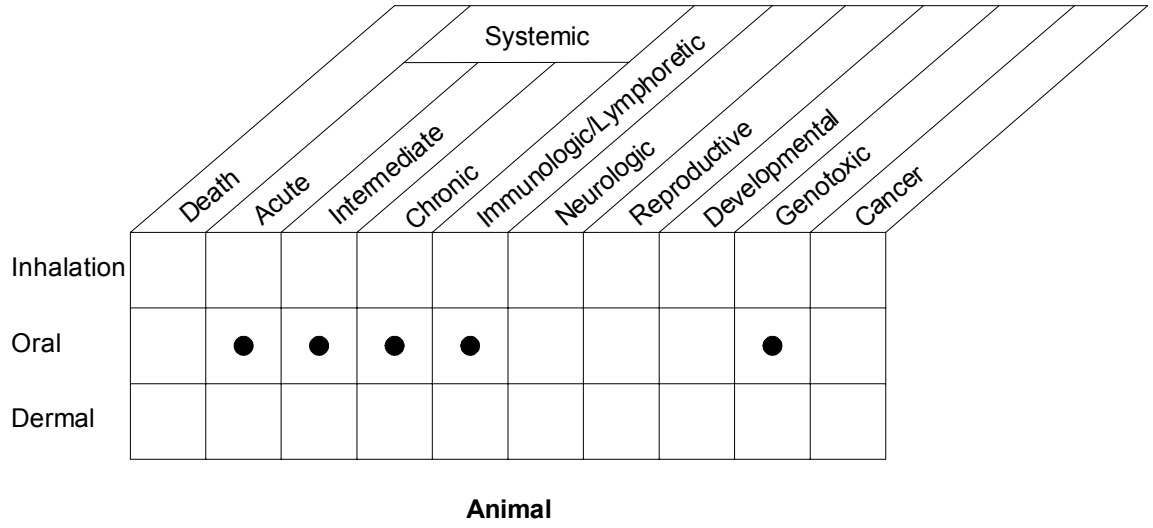
Acute-Duration Exposure. The primary effect of acute exposures to excess iodine in humans is hypothyroidism. This effect has been studied extensively in experimental studies of humans and is also well documented in the clinical case literature. Reported NOAELs for iodine-induced hypothyroidism in humans vary widely for reasons that are not completely understood. Acute exposures to excess iodine produce allergic reactions in people. The mechanisms for sensitivity and the reactions are not completely understood.

The effects of acute exposures to radioiodine (primarily ^{131}I) have been extensively studied in humans. An enormous amount of epidemiological and case literature derives from the clinical use of ^{131}I in diagnostic procedures and in treatment of thyroid gland enlargement and thyrotoxicosis. Epidemiology studies have also examined health effects resulting from accidental environmental exposures due to nuclear bomb detonations (e.g., Marshall Islands) and releases from nuclear power plants (e.g., Chernobyl). These studies collectively and convincingly identify the thyroid gland as the primary target of radioiodine. Other tissues that are either near the thyroid gland, such as the parathyroid gland, or that accumulate iodine, such as the salivary gland, also are affected by exposures to ^{131}I; however, these effects occur at absorbed radiation doses that are clearly cytotoxic to the thyroid gland. Breast tissue expresses NIS and appears capable of accumulating ^{131}I and transferring it to mammary milk; therefore, it is a potential target of ^{131}I. However, epidemiology studies reported to date have not found a significant risk of breast cancer even after cytotoxic exposures to ^{131}I.

Figure 3-16. Existing Information on Health Effects of Stable Iodine



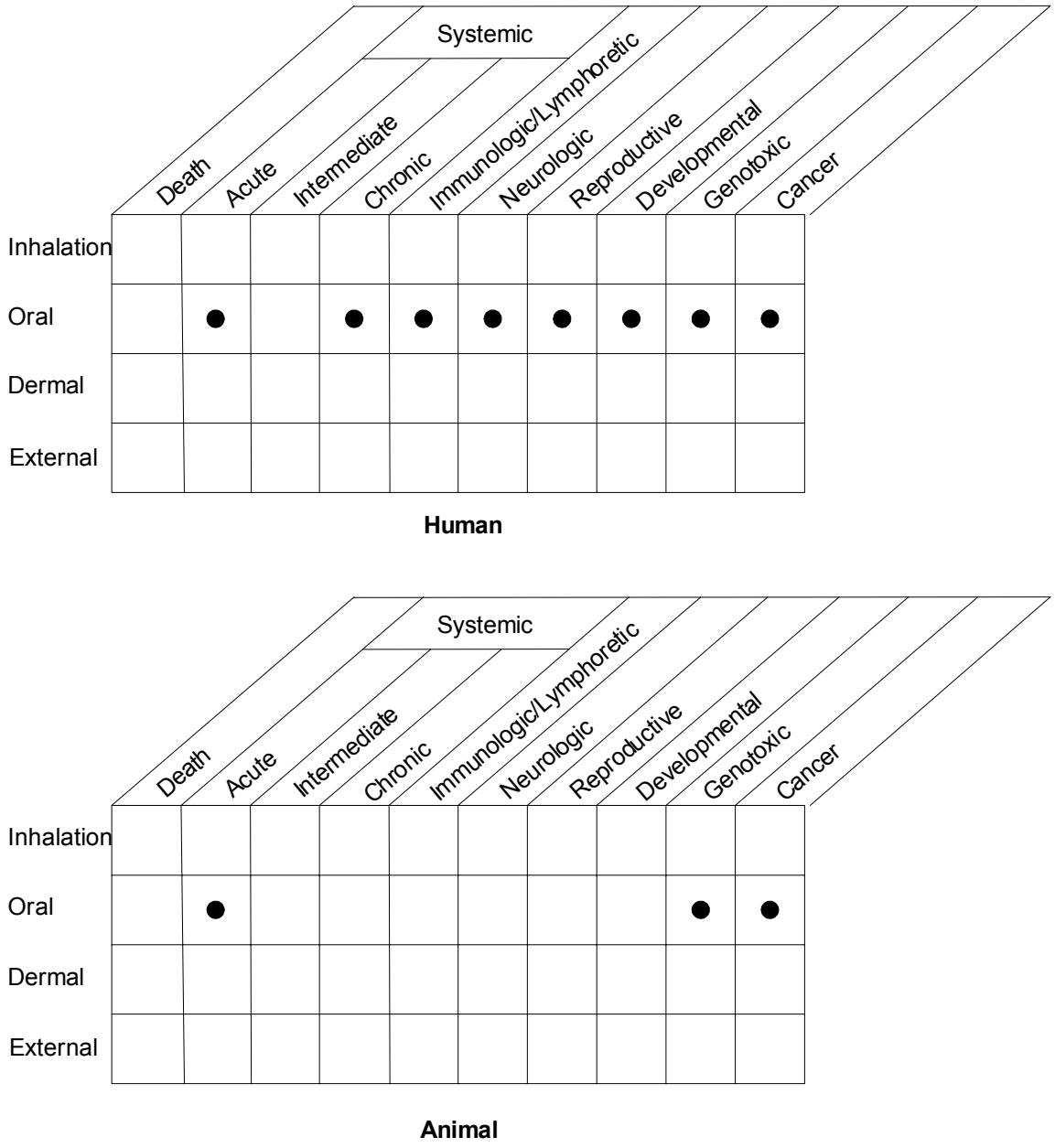
Human



Animal

● Existing Studies

Figure 3-17. Existing Information on Health Effects of Radioactive Iodine



Intermediate-Duration Exposure. The primary effect of intermediate-duration exposures to excess iodine in humans is hypothyroidism. This effect has been studied extensively in humans and is well documented in the clinical case literature. Reported LOAELs for iodine-induced hypothyroidism in euthyroid humans, without goiter, fall within a reasonably narrow range, and are higher than those for people who are iodine deficient, suggesting a higher sensitivity in these subjects. The mechanisms for this are not completely understood. Intermediate-duration exposure has also been shown to induce hyperthyroidism in people who have nontoxic goiter. Here again, the mechanisms are not completely understood, although clonal expansion of autonomous follicle cells and autoimmunity are suspected contributors. Intermediate-duration exposures to excess iodine produce allergic reactions in people. The mechanisms for sensitivity and the reactions are not completely understood.

Chronic-Duration Exposure and Cancer. Epidemiological studies and clinical case literature identify the thyroid gland as the principal target of chronic exposure to excess iodine. Goiter, hypothyroidism, hyperthyroidism, and/or thyroid autoimmunity are the main outcomes of chronic exposure to excess iodine. Which effect occurs appears to be related to the pre-existing iodine intake (e.g., deficient or replete) and the presence or absence of possibly pre-existing autoimmunity and/or thyroid gland enlargement (or nodularity).

Genotoxicity. Stable iodine has been tested for genotoxicity in a variety of eukaryotic cell systems and has been found to be without mutagenic activity. The genotoxicity of radioactive iodine (^{131}I) has been extensively studied in clinical studies of patients who received ^{131}I for therapy of thyroid cancer and thyrotoxicosis and in people who were exposed to radioiodine from nuclear power plant accidents (e.g., Chernobyl).

Reproductive Toxicity. Several studies of reproductive effects of exposures to ^{131}I have been reported. These studies indicate that relatively high exposures to radioiodine (i.e., that are cytotoxic to the thyroid gland) can produce impairment of testicular function. The mechanism for this is not understood, but the observation of these effects suggests a possible exposure of the testes to ^{131}I. The testis is not presently known to express NIS; however, studies of the uptake of radioiodine in testes were not located.

Developmental Toxicity. Developmental toxicity of iodine and radioiodine related to effects on the fetal/neonatal thyroid gland has been well documented in the clinical case literature. The primary effect is congenital hypothyroidism and associated sequelae.

Immunotoxicity. The epidemiological and clinical case literature has identified thyroid autoimmunity and allergic reactions as the primary immunologic effects of exposure to excess iodine. Thyroid autoimmunity is an extremely important mechanism of thyroid gland disease. The mechanisms by which iodine induces thyroid autoimmunity are not completely understood. The production of antibodies to highly iodinated thyroglobulin has been proposed as a possible contributor.

Neurotoxicity. The primary target of iodine toxicity is the thyroid gland. A large amount of clinical literature exists on the neurological sequelae of thyroid gland disorders.

Epidemiological and Human Dosimetry Studies. The epidemiological literature on iodine- and radioiodine-related health effects is very substantial and provides information on exposures associated with the primary effect, thyroid gland dysfunction. There remain certain complications in the interpretation of the major epidemiology studies of environmental exposures to iodine and radioiodine. These relate to the magnitude of the contribution of iodine deficiency and autoimmunity in the observed thyroid gland outcomes (e.g., hypothyroidism, hyperthyroidism, thyroid gland nodularity, and cancers).

Studies of human dosimetry of ^{131}I are extensive, in large part, because of the extensive use of ^{131}I in diagnostic and treatment procedures that require highly certain estimates of the radiation dose delivered to the thyroid gland. The clinical information has been incorporated into reconstructions of thyroid doses experienced by the general public.

Biomarkers of Exposure and Effect.

Exposure. The use of urinary iodide for assessing steady state iodine intakes is well substantiated in the clinical and epidemiological literature and is supported by toxicokinetics studies in humans. Similarly, the use of external scintillation spectrometry to estimate radioiodine doses to the thyroid gland also has a substantial clinical history.

Effect. The clinical literature on thyroid gland disorders extensively documents the major biomarkers of thyroid gland dysfunction that are relevant to iodine toxicity.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of iodine in humans has been substantially explored and characterized in experimental studies and clinical cases. Radioiodine toxicity is most likely in tissues that can transport and accumulate iodide. Studies of the expression of

NIS and factors that alter expression of NIS can further advance our understanding of which tissues are at risk and what factors, including genetic factors, might affect sensitivity to radioiodine in humans.

Comparative Toxicokinetics. The extensive information on the toxicokinetics of iodine in humans makes extrapolations from animals less important in assessing the health effects of iodine in humans. Studies of interindividual variability in humans are valuable for identifying sensitive subpopulations.

Methods for Reducing Toxic Effects. The principal method for preventing the toxic effects of radioiodine is dosing with stable iodine, which decreases the thyroid gland uptake of radioiodine and the absorbed radiation dose to the gland. The mechanistic basis and effectiveness of this approach is well established from experimental and clinical studies.

Children's Susceptibility. Higher susceptibility of the fetus and infants to iodine and radioiodine toxicity is substantiated by the epidemiological and clinical case studies. The toxicokinetic basis for the susceptibility of infants and children to iodine exposure is understood. Uncertainties in assessing the potential health effect of iodine exposures are largely related to estimating exposures, in particular, the pathways by which environmental releases result in radioiodine uptake into the fetal or infant thyroid gland (see Section 6.8.1).

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.13.3 Ongoing Studies

Ongoing studies pertaining to iodine have been identified and are shown in Table 3-10.

Table 3-10. Ongoing Studies on Health Effects of Radioactive Iodine

Investigator	Affiliation	Title	Sponsor
Baker JR	University of Michigan at Ann Arbor	Characterization of thyroid autoantibodies and antigens	NCRR
Brent GA	University of California, Los Angeles	Regulation of the sodium/iodine symporter in breast	NCI
Burek CL	John Hopkins University	Immunotoxic effects of iodine	NIH—National Institute of Diabetes and Digestive and Kidney Diseases
Burek CL	John Hopkins University	Nod h2h4 mice as a sentinel model for autoimmune thyroid	NIEHS
Carrasco N	Yeshiva University	Characterization of the thyroid Na +/I-symporter	NIH—National Institute of Diabetes and Digestive and Kidney Diseases
Degroot LJ	University of Chicago	Pathogenesis and therapy of autoimmune thyroid disease	NIH—National Institute of Diabetes and Digestive and Kidney Diseases
Kong Y-CM	Wayne State University	T cell recognition—repertoire in autoimmune thyroiditis	NIH—National Institute of Diabetes and Digestive and Kidney Diseases
Naylor EW	Neo Gen Screening, Inc.	Simplified population screening for adult hypothyroidism	NIH—National Institute of Diabetes and Digestive and Kidney Diseases
Refetoff SS	University of Chicago	Regulation and mechanisms of hormone action	NIH—National Institute of Diabetes and Digestive and Kidney Diseases
Refetoff SS	University of Chicago	Screening for inherited thyroid defects	NCRR
Sgouros G	Sloan-Kettering Institute for Cancer	Modeling and dosimetry for radiolabeled antibody therapy	NCI
St Germain DL	Dartmouth College	Regulation of thyroid hormone metabolism	NIH—National Institute of Diabetes and Digestive and Kidney Diseases
St Germain DL	Dartmouth College	The role of the Type 3 deiodinase in development	NIH—National Institute of Diabetes and Digestive and Kidney Diseases

Table 3-10. Ongoing Studies on Health Effects of Radioactive Iodine

Investigator	Affiliation	Title	Sponsor
Weintraub BD	University of Maryland, Baltimore Professional School	Structure/function relationships of human thyrotrophin	NIH—National Institute of Diabetes and Digestive and Kidney Diseases

NCI = National Cancer Institute; NCRR = National Center for Research Resources; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institute of Health/National Institute of General Medical Sciences

Source: CRISP 2001; National Institutes of Health; Central Repository of Incidents, Solutions, and Problems

4. CHEMICAL, PHYSICAL, AND RADIOLOGICAL INFORMATION

4.1 CHEMICAL IDENTITY

Iodine is a nonmetallic element belonging to the halogen family in Group VIIA of the periodic table. Iodine is found in nature as iodide (i.e., I^-) in brines or in molecular compounds with other elements (e.g., iodate or IO_3^-). The chemical information for elemental iodine and some of its compounds is listed in Table 4-1. Radioactive isotopes of iodine (e.g., see Section 4.2) are an additional cause of concern with regard to human health (see Chapter 3).

4.2 PHYSICAL, CHEMICAL, AND RADIOLOGICAL PROPERTIES

The physical properties of iodine and selected iodine compounds are listed in Table 4-2. The percent occurrence of iodine isotopes and radiological properties of iodine isotopes is listed in Table 4-3.

Iodine can exist in several oxidation states: -1, 0, +1, +3, +5, and +7. Under normal environmental conditions, the -1, 0, and +5 oxidation states are the most important. There are 36 isotopes of iodine having masses between 108 and 143 (Chu et al. 1999); 14 of these yield significant radiation. The only naturally-occurring isotopes of iodine are ^{127}I and ^{129}I, which are stable and radioactive, respectively. Isotopes of mass less than 127 are produced in particle accelerators (common examples are ^{123}I and ^{125}I), while those >127 are formed in neutron generators such as nuclear reactors and atomic bombs (common examples are ^{129}I and ^{131}I). A total of 72% of uranium fissions and 75% of plutonium fissions leads directly or by beta decay of precursors, to iodine isotopes. For example, 2.89% of ^{235}U and 3.86% of ^{239}Pu fission atoms lead to the formation of a series of isobar 131 isotopes, including ^{131}In, ^{131}Sn, ^{131}Sb, ^{131}Te, ^{131}I, and ^{131}Xe. Each isotope can be formed as an initial fission product and, once formed, each isotope decays by beta-ray emission to the right on the sequence, through ^{131}I, and with stable ^{131}Xe. The process can be displayed as:

$$^{235}U + {}^{1}n \dashrightarrow {}^{131}In \xrightarrow{0.28\ s} {}^{131}Sn \xrightarrow{56\ s} {}^{131}Sb \xrightarrow{23.0\ m} {}^{131}Te \xrightarrow{25.0\ m} {}^{131}I \xrightarrow{8.02\ d} {}^{131}Xe$$

Table 4-1. Chemical Identity of Iodine and Iodine Compounds

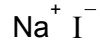
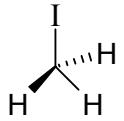
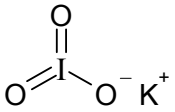
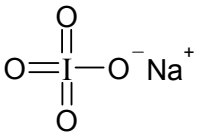
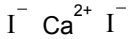
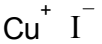
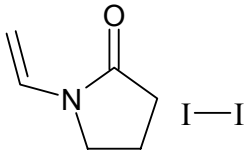
Property	Iodine	Hydrogen iodide	Sodium iodide	Potassium iodide	Methyl iodide	Cesium iodide
Chemical formula	I_2	HI	NaI	KI	CH_3I	CsI
Chemical structure						
Synonyms	Actomar; diiodine; eranol; iodine-127; molecular iodine	Hydroiodic acid	Sodium monoiodide; sodium Iodine	Hydroiodic acid, potassium salt; PIMA; SSK; iodide of potash	Monoiodo-methane; iodomethane	No data
Trade names	None	None	None	None	Halon 10001	No data
Identification numbers						
CAS registry	7553-56-2	10034-85-2	7681-82-5	7681-11-0	74-88-4	7789-17-5
NIOSH RTECS	NN1575000	MW3760000	WB6475000	TT2975000	PA9450000	No data
EPA hazardous waste	None	None	None	None	U138	None
OHM/TADS	None	None	None	None	None	None
DOT/UN/NA/ IMO shipping	UN 1759; UN 1760	UN 2197; UN 1787 Corrosive material/ IMO 8.0; IMO 2.0	None	None	UN 2644 Poison/ IMO 6.1	None
HSDB	34	2155	750	5040	1336	None
NCI	42355	None	None	77362	9366	None
STCC	None	None	None	None	None	None

Table 4-1. Chemical Identity of Iodine and Iodine Compounds

Property	Potassium iodate	Sodium periodate	Calcium iodide	Copper (I) iodide	Povidone iodine
Chemical formula	KIO3	NaIO4	CaI_2	CuI	$C_6H_9I_2NO$
Chemical structure					
Synonyms	Iodic acid, potassium salt	Sodium metaperiodate	Calcium diiodide; calcium iodide hydrate	Copper monoiodide; natural marshite; cuprous iodide	Poly(1-(2-oxo-1-pyrrolidinyl)-ethylene)iodine complex; betadine; efodine; Iodopoly(vinyl pyrrolidinone); isobetadyne; isodine; poly(vinylpyrrolidinone) iodide; ultradine
Trade names	None	None	None	None	None
Identification numbers					
CAS registry	7758-05-6	7790-28-5	10102-68-8	7681-65-4	25655-41-8
NIOSH RTECS	NN1350000	None	None	None	TR1579600
EPA hazardous waste	None	None	None	None	None
OHM/TADS	None	None	None	None	None
DOT/UN/NA/ IMO shipping		None	None	None	None
HSDB	1231	None	None	271	6831
NCI		None	None	None	26245
STCC	None	None	None	None	None

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances; STCC = Standard Transportation Commercial Code

Source: HSDB 2001; Lide 2000

Table 4-2. Physical and Chemical Properties of Iodine and Iodine Compoundsa

Property	Iodine	Hydrogen iodide	Sodium iodide	Potassium iodide
Molecular weight, g/mole	253.809[a]	127.91[a]	149.89[a]	166.02[a]
Color	Bluish-black[a]	Colorless[a]	White	Colorless or white[a]
Physical state	Solid; scales or plates[a]	Gas[a]	Solid; crystals or granules	Solid; crystals, granules, or powder[a]
Melting point	113.60 EC[a]	-50.8 EC[a]	651 EC[a]	680 EC[a]
Boiling point	185.24 EC[a]	-35.1 EC[a]	1,304 EC[d]	1,323 EC[d]
Density, g/cm^3 (25 EC)	4.93[a]	5.23[a]	3.67[a]	3.12[a]
Odor	Characteristic[a]	No data	Odorless[a]	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility (25 EC):				
Water	330 mg/L[a]	2,340 g/L (10 EC)[a]	2,000 g/L[a]	1,429 g/L[a]
Organic solvents(s)	141 g/kg benzene[a]	Soluble[a]	500 g/L alcohol[a]	13 g/L acetone[a]
Partition coefficients:				
Log K_{ow}	2.49[b]	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure (25 EC)	0.305 mm Hg[a]	5,940 mm Hg[c]	1 mm Hg (767 EC)[c]	No data
Henry's Law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	Non-flammable	No data	No data
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Iodine and Iodine Compounds[a]

Property	Methyl iodide	Cesium iodide	Potassium iodate	Sodium periodate
Molecular weight, g/mole	141.94[a]	259.81[a]	214.02[a]	213.892[d]
Color	Colorless[a]	Colorless[d]	White[a]	White[d]
Physical state	Liquid[a]	Solid; crystals, or powder[a]	Solid, crystals[a]	Solid; crystals[d]
Melting point	-66.5 EC[a]	621 EC[a]	560 EC[a]	Decomposes ~300 EC
Boiling point	42.5 EC[a]	ca. 1,280 EC[a]	No data	No data
Density, g/cm^3 (25 EC)	2.28 (20 EC)[a]	4.5[a]	3.98[c]	3.86[d]
Odor	Pungent, ether-like[c]	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility (25 EC):				
Water	13.9 g/L (20 EC)[c]	Miscible[a]	9.16 g/100 g[c]	Soluble[d]
Organic solvents(s)	Miscible[a]	Soluble in alcohol; insoluble in acetone[a]	No data	No data
Partition coefficients:				
Log K_{ow}	1.51[c]	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure (25 EC)	405 mm Hg	No data	No data	No data
Henry's Law constant	0.00526 atm-cu m/mole	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Iodine and Iodine Compounds[a]

Property	Calcium iodide	Copper (I) iodide	Povidone iodine
Molecular weight, g/mole	293.89[a]	190.45[a]	364.95[c]
Color	Yellow[a]	Red-brown[a]	Yellow-brown[c]
Physical state	Solid; lumps or powder[a]	Solid; powder or crystals[a]	Solid; powder[c]
Melting point	740 EC	588–606 EC[a]	300 EC[e]
Boiling point	1,100 EC	~1,290 EC[a]	No data
Density, g/cm^3 (25 EC)		5.63[a]	
Odor	No data	No data	Slight characteristic[c]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility (25 EC)			
Water	Very soluble[a]	80 mg/L (18 EC)[c]	Soluble[c]
Organic solvents(s)	Very soluble in alcohol, acetone[a]	Insoluble[a]	Insoluble[c]
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's Law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Explosive limits	No data	No data	No data

[a]Budavari et al. 1998
[b]Hansch and Leo 1995
[c]HSDB 2000
[d]Lide 2000

Source: Chemfinder 2001, unless otherwise specified

Table 4-3. Percent Natural Occurrence and Radioactive Properties of Isotopes of Iodine

Isotope	CAS registry number	Natural abundance (%)	Beta energies, MeV[a] (intensity)	Gamma energies, keV[a]	Half-life	Activity, Ci/gram[c]
^{123}I	15715-08-9	No data	1.08 (97.0%)	158.97	13.3 hours	1.92×10^{6}
^{124}I	14158-30-6	No data	EC[b]	602.7 722.8 1691.0	4.18 days	2.52×10^{5}
^{125}I	14158-31-7	No data	EC[b]	35.5	59.4 days	1.76×10^{4}
^{126}I	14158-32-8	No data	EC[b]	388.6 666.3 753.8	13.11 days	7.91×10^{4}
^{127}I	7553-56-2	<100	No data	No data	Stable	No data
^{129}I	15046-84-1	1×10^{-13} to 1×10^{-10}	0.154	29.5 29.8 33.6	1.57×10^{7} years	1.77×10^{-4}
^{131}I	10043-66-0	No data	0.334 (7.3%) 0.606 (89.9%)	284.3 364.5	8.04 days[d]	1.24×10^{5}
^{132}I	14683-16-0	No data	0.74 (13.0%) 0.96 (8.2%) 1.18 (18.8%) 1.61 (12.6%) 2.14 (19.0%)	667.7 772.6 954.6	2.30 hours	1.03×10^{7}
^{133}I	14834-67-4	No data	0.54 (87.0%) 0.88 (4.5%)	529.9 875.3	20.8 hours	1.13×10^{6}
^{134}I	14914-27-3	No data	1.31 (30.4%) 1.59 (16.2%) 1.82 (11.0%) 2.44 (12.5%)	847.0 884.1	52.5 minutes	2.67×10^{7}
^{135}I	14834-68-5	No data	679.7 (8.0%) 856.8 (8.8%) 969.9 (21.9%) 1,082.7 (8.0%) 1,387.6 (23.8%)	546.6 836.8 1,038.8 1,131.5	6.57 hours	3.53×10^{6}

[a]Not all gamma and beta energies are included in summary; see Chu et al. (1999) for a complete listing
[b]EC = electron capture decay
[c]Activity = $(N_A \ln 2)/(M_w t_{½})$
[d]Lide 2000

Source: Chu et al. 1999

The same process occurs for ^{129}I ($t_{1/2}$=1.6x107 years) and includes mass 129 isobars beginning with ^{129}Cd and ending with ^{129}Xe. Iodine isotopes above ^{127}I decay by emitting beta and gamma radiation, whose combined energies are unique to each iodine isotope. ^{131}I, for example, decays by beta particle emission, and 0.96 MeV of energy is shared between the beta particle and the gamma ray. At least seven possible beta/gamma combinations occur. In 90.4% of the decays, a 0.61 MeV beta particle is emitted. The remaining excess energy is emitted as either a 0.364 MeV gamma ray for 85.3% of the time, or a pair of 0.284 and 0.080 MeV gamma rays for the other 5.1% of the time. The following is the decay scheme for ^{131}I (Cember 1996):

$$^{131}I \dashrightarrow {}^{131}Xe\ (\text{stable}) + \beta^- (0.61\ \text{MeV}; 85.3\%) + \gamma (0.36\ \text{MeV})$$
$$+ \beta^- (0.61\ \text{MeV}; 5.1\%) + \gamma (0.284\ \text{MeV}) + \gamma (0.080\ \text{MeV})$$
$$+ \beta^- (0.81\ \text{MeV}; 0.6\%) + \gamma (0.16\ \text{MeV})$$
$$+ \beta^- (0.47\ \text{MeV}; 0.3\%) + \gamma (0.50\ \text{MeV})$$
$$+ \beta^- (0.47\ \text{MeV}; 0.2\%) + \gamma (0.33\ \text{MeV}) + \gamma (0.2\ \text{MeV})$$
$$+ \beta^- (0.33\ \text{MeV}; 6.9\%) + \gamma (0.64\ \text{MeV})$$
$$+ \beta^- (0.25\ \text{MeV}; 1.6\%) + \gamma (0.72\ \text{MeV})$$

Isotopic masses of iodine <127 can be produced using a beam of high energy protons generated using a linear accelerator. Proton beams tuned at fixed energies up to 30 MeV produce isotopes, such as ^{123}I, by interaction of the proton beam with a target of high atomic mass.

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Iodine, a halogen, occurs in low concentrations in nature in the form of iodides mainly in sea water, although there are a number of major sources iodine including the underground waters from certain deep-well boring and mineral springs (i.e., brines) and natural deposits of sodium nitrate ore (i.e., caliche) found in the northern part of Chile. Only a few marine organisms contain iodine in relatively large quantities including seaweeds, sponges, and corals. The different production processes for recovering iodine are based on the raw materials used. Approximately 54% of the iodine consumed in the world is obtained from Chile as a coproduct from surface mineral deposits used to produce nitrate fertilizers (USGS 2002). About 43% of the iodine consumed in the world comes from brines processed in Japan, the United States, and the former Soviet Union. The primary production process for recovery of iodine from brines is the blow-out process. The blow-out process for brines can be divided into brine clean-up, iodide oxidation followed by air blowing and recovery, and iodine finishing. In 2001, iodine was recovered from brines by the blow-out process by three companies operating in Oklahoma, which accounted for 100% of the U.S. elemental iodine production. These three companies are IOCHEM Corporation (Dewey County, Oklahoma), North American Brine Resources (Dover, Oklahoma), and Woodward Iodine Corporation (Woodward County, Oklahoma). Production of iodine in the United States has remained steady ranging from 1,270 to 1,620 metric tons between the years 1996 and 2000 (Lauterbach and Ober 1995; USGS 1998, 2002).

After World War II, the U.S. government began stockpiling iodine for defense applications. By 1968, the DOD had acquired 3,700 metric tons of iodine. In 1992, Congress determined that the stockpile was unnecessary, reduced the stockpile goal to zero, and authorized the sale of all excess material. As of September 30, 2001, the uncommitted inventory of stockpile-grade iodine was 1,629 metric tons (USGS 1998, 2002).

The only naturally occurring isotopes of iodine are ^{127}I and ^{129}I, which are stable and radioactive, respectively. Other radioactive iodine isotopes (e.g., ^{131}I) do not occur in nature; they are the direct result of anthropogenic activity. As discussed in Chapter 4, ^{129}I and ^{131}I are produced by nuclear fission. Nearly all of the ^{129}I and ^{131}I generated in the United States is present in spent nuclear reactor fuel rods. These fuel rods are currently located at commercial reactor facilities or at Department of Energy (DOE)

facilities across the United States. The cumulative yield of ^{129}I is about 1% of all fission products. Thus, ^{129}I represents only a very small fraction of the total fission product inventory in the nuclear fuel cycle. A limited amount of ^{123}I, ^{125}I, and ^{131}I will be produced for industrial, scientific, and medicinal applications by International Isotopes Inc. (Denton, Texas) using a linear accelerator (DOE 1996d; International Isotopes 2001; USGS 1998).

5.2 IMPORT/EXPORT

In 2000, 77% of the apparent consumption of iodine in the United States (6,320 metric tons) was imported. Of the 4,790 metric tons of iodine imported in 2000, approximately 67% was imported from Chile, 21% from Japan, and 11% from Russia. Exports of iodine have decreased from 2,410, 2,760, and 2,790 metric tons in 1996, 1997, and 1998, respectively, to 1,130 and 900 metric tons in 1999 and 2000, respectively (USGS 1998, 2002).

5.3 USE

End uses for iodine in 1999 were estimated from a United States Geological Survey (USGS) canvass of consumers as follows (by percentage): sanitation (45%); animal feed (27%); pharmaceutical (10%); heat catalyst (8%); stabilizers (5%); and other (5%) (USGS 1999). Other smaller uses included inks and colorants, photographic chemicals, laboratory reagents, production of batteries, high-purity metals, motor fuels, and lubricants. Hydrogen iodide (i.e., HI) is used in the manufacture of hydroiodic acid and organic iodo compounds, and to remove iodine from iodo compounds. Potassium iodide (i.e., KI) is used in animal feeds, catalysts, photographic chemicals, for sanitation, and for treatment of radioiodine poisoning resulting from nuclear accidents. Sodium iodide (i.e., NaI) is used in photography and for the production of organic chemicals. Methyl iodide (i.e., CH_3I) is used as a methylation agent in organic synthesis, in microscopy, as an embedding material for examining diatoms, and in testing for pyridine. Potassium iodate (i.e., KIO_3) is used in salt iodization, as an oxidizing agent in analytical chemistry, and as a maturing agent and dough conditioner (Lauterbach and Ober 1995; USGS 1998).

Radioactive iodine has been used successfully for the treatment of cancer of the thyroid. The radioactive isotope ^{123}I is considered the agent of choice for brain, thyroid, and renal imaging and uptake measurements. ^{125}I is used as a cancer therapeutic, and as a brain, blood, and metabolic function diagnostic. ^{131}I is used as a brain, pulmonary, and thyroid diagnostic (Lauterbach and Ober 1995; USGS 1998).

5.4 DISPOSAL

Most nonradioactive iodine minerals, iodine compounds, and iodine-containing materials do not require special disposal or handling requirements. However, some chemical forms may be classified as hazardous materials if the compound is chemically reactive, flammable, or toxic. Care should be taken to read and understand all of the hazards, precautions, and safety procedures for each specific chemical form. In addition, all federal, state, and local laws and regulations should be investigated and subsequently followed with regard to disposal and handling of the specific chemical form of the iodine compound or material.

Radioactive iodine does require special disposal and handling requirements and is regulated by the Nuclear Regulatory Commission. Radioactive waste-containing radioactive iodine can be grouped into three categories: low-level waste (LLW); high-level waste (HLW) and spent nuclear fuel; and mixed waste. As defined by the Nuclear Waste Policy Act, high-level radioactive waste is "the highly radioactive material resulting from the reprocessing of spent nuclear fuel, including liquid waste produced directly in reprocessing and any solid material derived from such liquid waste that contains fission products in sufficient concentration." However, most classifications of HLW also include spent nuclear fuel. Most HLW was generated from the production of plutonium. A small fraction is related to the recovery of enriched uranium from naval reactor fuel. This waste typically contains highly radioactive, short-lived high activity fission by-products as well as other long-lived isotopes, hazardous chemicals, and toxic heavy metals. Radioiodine contamination is only a small fraction of the activity of HLW. Liquid HLW is typically stored in large underground tanks of either stainless steel or carbon steel depending on whether they are acid or alkaline solutions. There are about 100 million gallons of high-level liquid waste stored in underground tanks in Washington, South Carolina, Idaho, and New York. These tanks contain a variety of radioactive liquids, solids, and sludges. Some of the liquid wastes have been solidified into glass, ceramic slag, salt cakes, and sludges (DOE 1996a; Murray 1994).

Spent nuclear fuels, such as fuel elements and irradiated targets used in nuclear reactors, are currently disposed of at the commercial nuclear power plants and DOE facilities where they were produced. Spent fuel is highly radioactive due to the large concentration of fission products and must be stored in special water-cooled pools that shield and cool the material. Most of the radioactive iodine remains trapped in the spent fuel rod matrix and is never released. Roughly all DOE spent fuel, about 3,000 metric tons, is stored at four sites: Hanford, Savannah River, Idaho National Engineering and Environmental Laboratory

(INEEL), and West Valley, New York. Commercial reactors have generated more than 30,000 metric tons of spent fuel. The spent fuel from these facilities is stored at the more than 100 commercial nuclear reactor sites around the United States. Since spent commercial nuclear reactor fuel is placed in on-site storage while awaiting off-site disposal, the only isotope of iodine remaining in the fuel matrix when it leaves the generating facility will be ^{129}I. The establishment of an HLW and spent fuel repository for both DOE and commercial waste is currently under construction at Yucca Flats, Nevada. It is not projected to be in operation until after the year 2010 (DOE 1996b, 2001d; Eisenbud 1987; Murray 1994). A temporary storage site for spent fuel rods has been proposed on the Goshute Indian Reservation in the Skull Valley of Utah (MHR 2001; NCSL 2002). However, as of 2003, the U.S. Nuclear Regulatory Commission (USNRC) as blocked the issuance of a license for the project (USNRC 2003).

Mixed waste contains both radioactive and chemically hazardous materials such as toxic, corrosive, flammable, or explosive materials. The radioactive component may be either HLW or LLW. All liquid HLW is mixed waste, usually in the presence of organic solvents or heavy metals in addition to radioactive components. Disposal of mixed wastes is regulated by the EPA under the Resource Conservation and Recovery Act (RCRA) and by the USNRC under the Atomic Energy Act. The EPA and the USNRC have developed special procedures on how to handle and dispose of this special category. The DOE operates an incinerator in Oak Ridge, Tennessee, which burns mixed hazardous radioactive wastes (DOE 1996a).

Low-level waste is all radioactive waste that cannot be classified as HLW, spent fuel, or mixed waste. Low-level does not necessarily mean low radioactivity or low environmental hazards. However, the bulk of LLW has relatively little radioactivity and practically no transuranic elements. Thus, LLW usually does not require shielding from radioactivity or heat removal equipment. Most LLW is acceptable for near surface land disposal. LLW types that may be contaminated with ^{129}I include both wet and dry wastes. Examples of the physical form of LLW are spent ion exchange resins, filter sludges, filter cartridges, evaporator bottoms, compactible trash, noncompactible trash, irradiated components, ashes produced from the incineration of combustible material, contaminated detergents or solvents, organic liquids, and discarded contaminated equipment or tools. Of the LLW generated today, approximately 64% of the volume and 70% of the radioactivity are generated as a result of nuclear power plant activities or supporting fuel cycle operations. Other sources of LLW are industrial, academic, government, and medical. Radioiodine contamination accounts for only a small fraction of the activity of LLW. LLW typically is packaged in drums or boxes and buried in shallow pits or trenches. Approximately 3 million cubic meters of LLW generated in the United States have been disposed of this way. LLW from DOE

sources is currently disposed of at several DOE facilities across the United States. Only three sites accept non-DOE LLW, Barnwell, South Carolina; Richland, Washington; and Envirocare of Utah, Inc. (Clive, Utah). Over half of the LLW in the eastern United States is disposed of at the Barnwell site. As required by the Federal LLRW (Low Level Radioactive Waste) Policy Act in 1980 and the 1985 amendments, states or interstate compacts are required to build facilities to contain LLW generated from sources within their boundaries. However, other than Barnwell, South Carolina; Richland, Washington; and Clive, Utah sites, no other facility in the United States is currently accepting LLW from non-DOE sources. Currently, many generators store LLW on-site until additional facilities can be constructed in the future (DOE 1996a; Eisenbud 1987; Envirocare 2001; Murray 1994).

Decay on-site is one method chosen in the medical community to handle their low level radioiodine waste. Contaminated clothing, food trays, linen, materials used to clean patients' rooms, furniture, and telephones are quarantined until levels of radioiodine are sufficiently low. A period of 10 half-lives may be adequate to reduce the radioactivity to safe levels to permit reuse of the materials without controls.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

The stable isotope of iodine, ^{127}I, and two of its radioactive isotopes, ^{129}I and ^{131}I, have been identified in at least 8, 3, and 6, respectively, of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for iodine is not known. The frequency of these sites can be seen in Figures 6-1, 6-2, and 6-3. All of these sites are located within the United States.

Iodine is a naturally occurring constituent of the earth's crust and is the least abundant of the halogen elements (Straub et al. 1966). The stable isotope iodine, ^{127}I, is ubiquitous throughout the earth's surface. The concentration of ^{127}I in the earth's crust is approximately 0.5 ppm; in the oceans, the concentration is 45–60 μg/L, and in the atmosphere, the concentration ranges from 10 to 20 ng/m^3. Concentrations of iodine in the environment throughout the United States vary depending on the proximity to the seacoast and the soil type. The concentration of iodine in bedrock varies between 0.5 and 380 ppm, depending on whether the rock is igneous or sedimentary.

Iodine exists in many chemical forms (e.g., molecular iodine, iodide, iodate, periodate) and can undergo oxidation-reduction as well as microbial alkylation (mostly methyl iodide). Iodine has nine radioisotopes, of which ^{123}I, ^{125}I, ^{129}I, and ^{131}I are commonly encountered in acute or chronic exposures to human populations, due either to the life-times of the radioisotope in the environment, their production, and/or their use in industry, medicine, and research.

^{129}I is the only naturally occurring iodine radioisotope. It is produced as a fission product of uranium and thorium in soils and oceans, and is also formed in reactions of xenon with high energy particles in the upper atmosphere and reactions of neutrons with ^{128}Te and ^{130}Te (Soldat 1976). ^{129}I has a half-life of 1.6×10^7 years and decays through β emission; ^{129}I has a mass/decay rate equivalency of 1 g ^{129}I=6.55 MBq (177 μCi) (Robkin and Shleien 1995). $^{129}I/^{127}I$ ratios from natural production of ^{129}I should be 3×10^{-14} in the environment, but with the introduction of ^{129}I from nuclear weapons testing and nuclear energy activities, the ratio is now 10^{-8} (Ballad et al. 1978). The estimated global inventory of ^{129}I is approximately 9,600 Ci (0.36 PBq or 5.4×10^7 g ^{129}I), of which 9,200 Ci (0.34 PBq or 5.2×10^7 g ^{129}I) is associated with igneous activity (DOE 1994).

Figure 6-1. Frequency of NPL Sites with Iodine Contamination

Figure 6-2. Frequency of NPL Sites with ^{129}I Contamination

Figure 6-3. Frequency of NPL Sites with ^{131}I Contamination

^{125}I and ^{131}I are produced in the fission of uranium and plutonium by neutron bombardment in reactors and/or heavy nuclei particles in accelerators. ^{125}I has a half-life of 60 days and decays through electron capture (EC) emitting a 35.5 keV gamma-ray and K-shell x-rays (27.4 keV, 112%; 31.4 keV, 24%). The specific activity of ^{125}I is 67.7 TBq/g or 18,277 Ci/g. ^{131}I has a half-life of 8.04 days and decays through β emission; ^{131}I has a specific activity of 457 TBq/g or 123,429 Ci/g. Unlike ^{129}I, ^{125}I and ^{131}I do not have long residency times in the environment due to their short half-lives and, thus, do not pose risks associated with an accumulation in the environment. However, in acute exposures to ^{125}I and ^{131}I, there is the potential for significant radiation exposure to the thyroid.

Releases of iodine into the environment occur from both natural sources and human activity. The natural sources include volatilization of iodine from the oceans, weathering of rock, and volcanic activity (Cohen 1985; Whitehead 1984). Sources of iodine from human activities include release of radioiodine from nuclear weapons testing and nuclear fuel reprocessing, waste stream effluent from municipal plants, and combustion of waste and fossil fuels (Likhtarev et al. 1993; Moran et al. 1999; NAS 1974; NCRP 1983; Stetar et al. 1993).

Iodine enters the atmosphere mainly through volatilization of methyl iodide and, to a lesser extent, molecular iodine from the ocean surface. ^{129}I is introduced naturally through the conversion of ^{129}Xe (xenon-129) to ^{129}I through the interaction with high energy particles in the upper atmosphere. ^{131}I was released through weapons production/utilization, nuclear fuel reprocessing, and energy production (AEC 1974; Likhtarev et al. 1993; Marter 1993; Moran et al. 1999; NCRP 1983; Robkin and Sheien 1995). In the atmosphere, iodine undergoes extensive photochemical changes and can exist as gaseous inorganic, gaseous organic, or particulate forms. These forms have an average residency time in the atmosphere of 10, 18, and 14 days, respectively (Whitehead 1984).

The gaseous inorganic and particulate forms of iodine are precipitated from the atmosphere through wet (rain, sleet, and snow) and dry (gravitational settling and wind turbulence) deposition processes (Whitehead 1984). Alkyl iodides, such as methyl iodide, have a low susceptibility to both wet and dry deposition. The deposition of iodine will depend on particle size and concentration, wind turbulence, and the chemical form of iodine. If precipitation occurs over land, iodine will be deposited onto plant surfaces or soil surfaces, or into surface waters. The average retention time of iodine on plant surfaces is 7.5–14 days due to weathering (AEC 1974; Heinemann and Vogt 1980; Kirchner 1994). Retention of iodine in the soil is influenced by a number of factors, including soil pH, soil moistness, porosity of soil,

and composition of organic and inorganic (e.g., aluminum and iron oxides) components (Sheppard et al. 1995; Whitehead 1984). Approximately 1% of iodine received through atmosphere-to-soil deposition is returned through volatilization of molecular iodine and methyl iodide; the remaining iodine is eventually returned to the oceans through surface water and groundwater (USNRC 1979; Whitehead 1984). The average residency time of iodine in the soil at 0.3- and 1-meter depths has been suggested to be 80 and 800 years, with only 1–3% of deposited iodine migrating to the 1-meter depth (DOE 1986).

Transport of iodine through surface water and groundwater is not greatly retarded by the soil, rock, and sediments over or through which these waters flow (USNRC 1981). The concentration of iodine in river water ranges between 0.1 and 18 μg/L, which parallels the concentration of iodine in rainwater of 0.1–15 μg/L (USNRC 1979). In groundwater, the mean concentration is 1 μg/L (Yuita 1994a). The concentration of iodine in river water often increases downstream of urban areas due to the discharge of waste streams from municipal treatment facilities. This is especially true for ^{131}I that enters sewage streams from patients undergoing radioiodine therapies (Tubiana 1982; UNSCEAR 2000). Slightly elevated concentrations of ^{129}I have been observed in surface water and groundwater near nuclear fuel reprocessing facilities (Beals and Hayes 1995; DOE 1994).

Iodine has been shown to bioaccumulate in many seawater and freshwater aquatic plants (Poston 1986). Freshwater plants (e.g., algae) contain 10^{-5}% by weight of iodine, whereas marine plants (algae) contain 10^{-3}% by weight (NCRP 1983). In freshwater fish, iodine concentrations in tissues range from 0.003 to 0.81 ppm, which gives concentration ratios (fish/water) of 0.9–810. In marine fish, the iodine concentrations range between 0.023 and 0.11 ppm, yielding concentration ratios of between 10 and 20 (Poston 1986). In terrestrial plants, iodine can be taken up through the roots, mainly as iodide and to a lesser extent, as iodate or iodine (Burte et al. 1991; Whitehead 1984). The average iodine concentration in terrestrial plants is 0.42 μg/g. The uptake is dependent on soil conditions and the use of fertilizers (Moiseyev et al. 1984). Distribution of iodine and iodide varies throughout the plant (Voigt et al. 1988). The uptake of iodine into terrestrial plants in combination with deposition of iodine onto the surfaces of plants plays an important role in the transfer of iodine through the soil-plant-cow-milk pathway. The efficiency through which iodine is transferred through this pathway is important in ascertaining the risk of radioiodine exposures in the general human population from continuous or accidental releases of ^{131}I and ^{129}I, especially in children (AEC 1974; Soldat 1976; Tubiana 1982; Voigt et al. 1989).

The iodine content of food has been studied extensively, with intakes of iodine typically ranging from 0.064 to 0.379 mg/day (FDA 1974; Pennington et al. 1984, 1986). The major sources of iodine intake

from food in a typical U.S. diet are added salt and food additives, followed by meat and meat products, milk and milk products, and green/yellow vegetables (FDA 1974). Other foods that can provide a high amount of iodine in the diet include seaweed, marine shellfish, and marine fish.

It is estimated that the intake of iodine through inhalation is $4x10^{-5}$ g/year (USNRC 1979). The average intake of iodine from drinking water, assuming an average iodine concentration of 3 μg/L, is estimated to be $1.5x10^{-3}$ g/year (USNRC 1979). If the average intake of iodine from food is assumed to be the recommended dietary allowance (RDA) for iodine of 150 mg/day, then the yearly intake of iodine would be approximately 55 g. Thus, the largest source of iodine in the average U.S. diet comes from food intake. The intake of iodine through food consumption can be increased greatly in diets high in marine fish (~800 μg/kg wet weight), shellfish (~800 μg/kg), and seaweed-based products (0.8–4.5 g/kg dry weight) (FDA 1974). Other sources of iodine intake are alternative medicines and nutritional supplements which, depending on the specific iodine content and dosage, can approach toxic levels (e.g., >6 g/day) (Cassileth 1999).

Currently, the intake of ^{129}I and ^{131}I by the general population through inhalation, drinking water, and food intake does not pose any significant risk, due to the extremely low levels of ^{129}I and ^{131}I in the general environment. However, there are certain populations of individuals who are at risk to potential exposures to high levels of iodine or acute/chronic levels of radioiodine. Individuals undergoing specific diagnostic or therapeutic procedures or receiving certain types of medications can significantly increase whole-body and thyroid burdens of iodine and ^{131}I (FDA 1989b; Tubiana 1982). Family members, especially children, of patients undergoing ^{131}I therapies can experience exposure to both the radioisotope and the radiation emitted from ^{131}I (Barrington et al. 1999; Jacobson et al. 1978). Likewise, medical personnel working with, or in proximity to, ^{131}I can also have elevated whole-body and thyroid burdens of this radioisotope and are at risk to exposure to the photon radiation emitted from ^{131}I (Blum and Liuzzi 1967; Mountford and O'Doherty 1999; Tubiana 1982). Workers in nuclear power plants or nuclear fuel reprocessing facilities are at risk for potentially high acute exposures of ^{129}I and ^{131}I (Bhat et al. 1973; Raghavendran et al. 1978). Laboratory workers who are involved in the iodination of chemicals or biologics with $^{125}I/^{131}I$ or the use of these radioiodinated materials also show increased thyroid burdens of these radioisotopes (Bogdanove and Strash 1975; de Groot 1979; Dunn and Dunscombe 1981; Jönsson and Mattsson 1998; Kivinitty et al. 1984; Krzesniak et al. 1979; Kwok and Hilditch 1982; Pomroy 1979).

6.2 RELEASES TO THE ENVIRONMENT

The stable isotope of iodine, ^{127}I, and two of its radioactive isotopes, ^{129}I and ^{131}I, have been identified in 8, 3, and 6, respectively, of 1,636 current or former NPL hazardous waste sites within a variety of environmental media (air, leachate, and groundwater) collected at these sites (HazDat 2004).

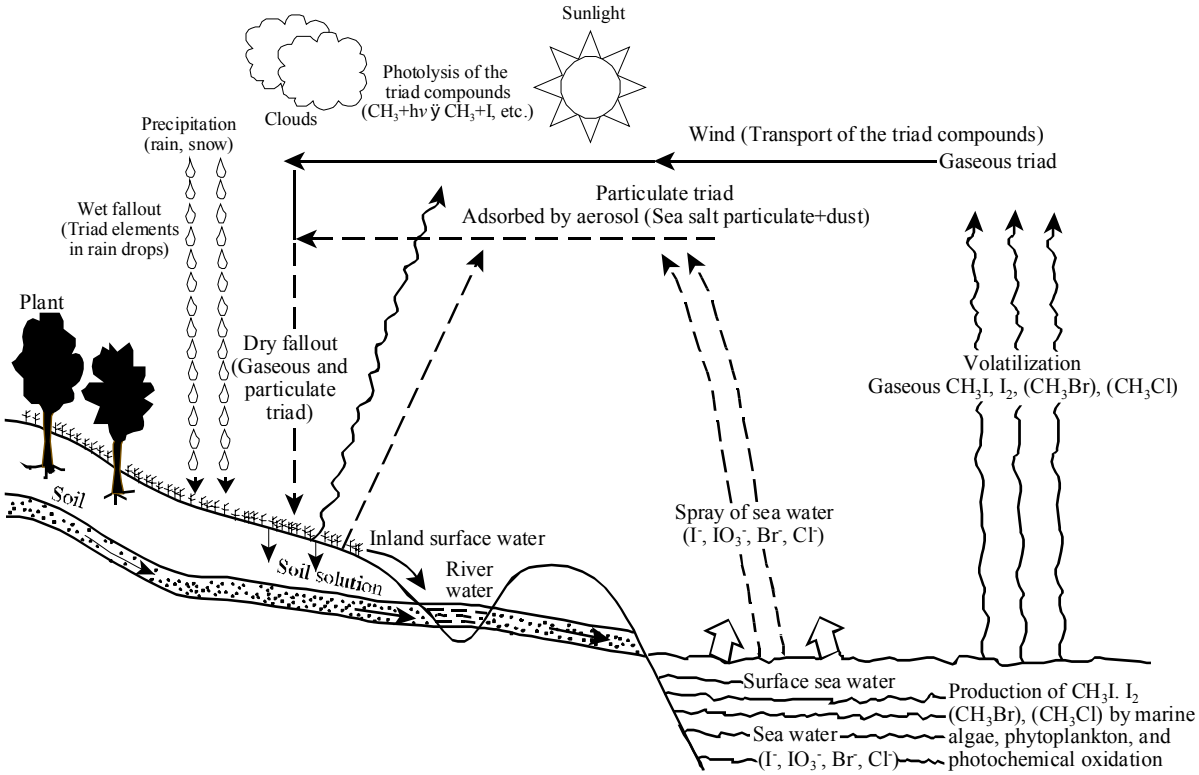
Releases of iodine and its radioisotopes into the environment occur from natural sources and from human activity (Figures 6-4 and 6-5). The emphasis of the discussion of iodine release into the atmosphere will focus on atmospheric (air), water (marine and surface waters), and soils, which are major compartments in the geochemical cycling of iodine (Figures 6-4 and 6-5). Throughout this chapter, the units used to express concentration or intake of iodine and its radioisotopes are the same units reported by the authors. In some cases, values are expressed in mass units, while in other cases, the values are expressed as activities (either in Bq or Ci). For ^{129}I, the mass/decay rate equivalencies is 1 g ^{129}I = 6.55 MBq (177 μCi) (Robkin and Shleien 1995). For ^{131}I, the specific activity of this radioisotope is 457 TBq/g or 123,429 Ci/g. For ^{125}I, the specific activity is 67.7 TBq/g or 18,277 Ci/g.

6.2.1 Air

Iodine (^{127}I), ^{129}I, and ^{131}I have been identified in 2, 1, and 5 air samples, respectively, collected from the 1,636 NPL hazardous waste sites where they were detected in some environmental media (HazDat 2004).

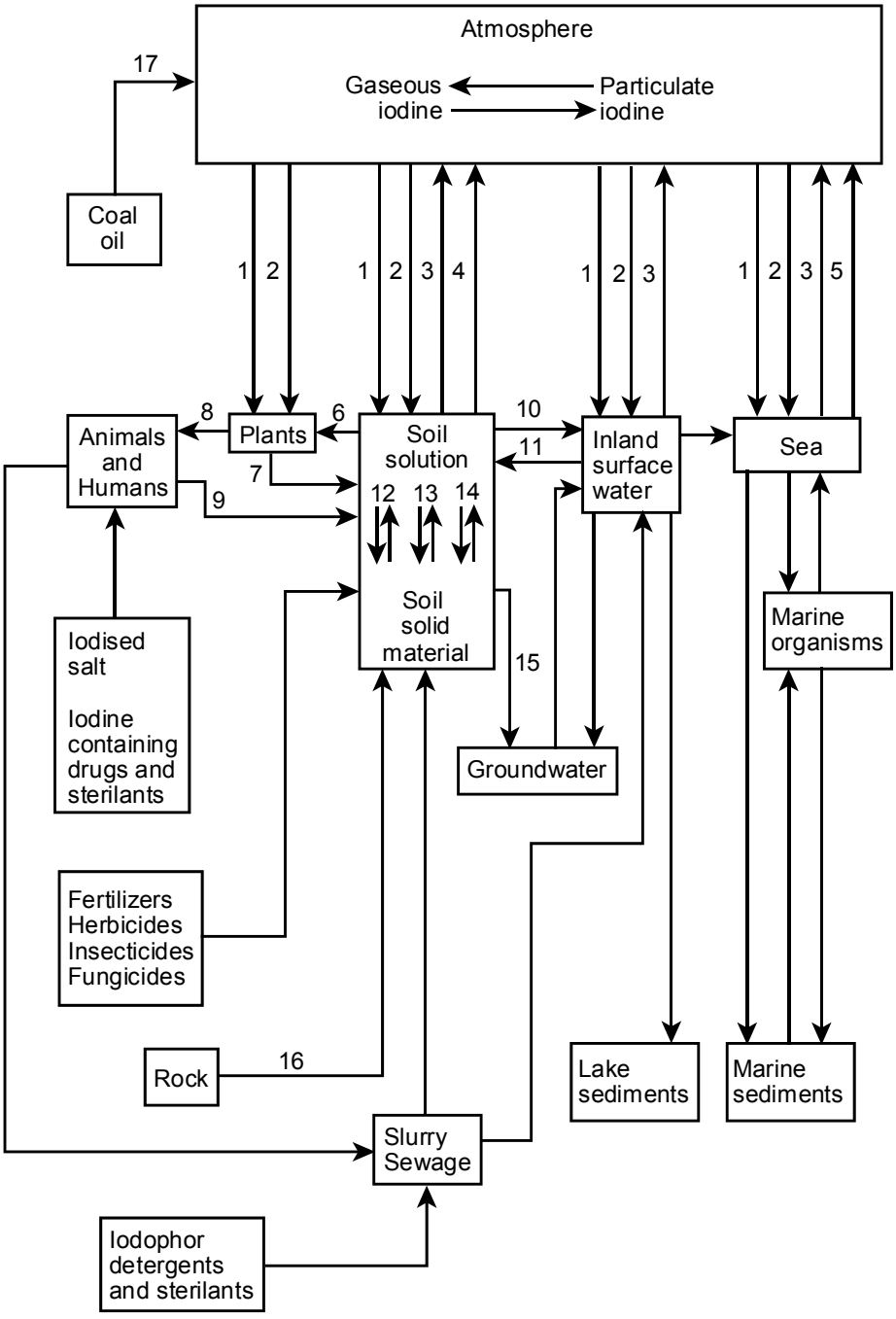
The introduction of iodine into the atmosphere is derived from both natural and human activities (Figures 6-4 and 6-5), amounting to approximately $4x10^7$ kg within the total global atmosphere at an average concentration of 10–20 ng/m^3 (Whitehead 1984). The predominant source of iodine in the atmosphere is obtained from the transfer of iodine from the ocean to the surrounding atmosphere (FDA 1974). Evaporation of sea spray is one pathway through which iodine can enter the atmosphere. However, a high ratio (ca. 1,000) of iodine to chlorine measured in the atmosphere and rainwater in comparison to that found for seawater strongly suggests that other, more important pathways are responsible for the transfer of iodine from oceans and the surrounding atmosphere. These could include the photochemical or ozone-induced oxidation of iodide to elemental iodine (NCRP 1983; Whitehead 1984). Indeed, the concentration of ozone near the ocean surface could account for upwards of 6–$12x10^7$ kg of iodine released yearly into the atmosphere from the world's oceans. Yet, the concentration of iodine at the ocean's surface is too low to support this iodide oxidation mechanism as a major

Figure 6-4. Geochemical Cycle of Triad Elements (I, Br, Cl)



Source: Yuita 1994a

Figure 6-5. An Outline of the Movement of Iodine in the Environment*



*1 = deposition in rainfall; 2 = dry deposition (including absorption by plant leaves); 3 = volatilization; 4 = suspension of dust; 5 = suspension of marine aerosols; 6 = uptake by plant roots; 7 = decomposition of plant residues; 8 = consumption of food; 9 = decomposition of animal excreta and residues; 10 = run-off; 11 = irrigation; 12 = non-specific adsorption/desorption; 14 = immobilization/mineralisation involving soil organic matter; 15 = leaching; 16 = weathering; 17 = combustion of fossil fuels

Source: Whitehead 1984

contributor to the transfer of iodine into the atmosphere. Instead, it has been suggested that the formation of methyl iodide and other alkyl iodides from the biological metabolism of iodine/iodide may, in fact, play a major role in the annual transfer of approximately 1.3–2.0x10^9 kg of iodine from the ocean into the atmosphere (Rasmussen et al. 1982; USNRC 1981; Whitehead 1984). Under this mechanism, the methyl iodide that is transferred into the atmosphere can undergo photolytic dissociation into methyl and I radicals, with the resultant formation of elemental iodine and other forms of inorganic iodine (HI, HOI, INO_2, $IONO_2$, OIO, etc.) (Chameides and Davis 1980; Cox et al. 1999; Vogt et al. 1999). Other sources of iodine introduction into the atmosphere from the ocean include the release of particulate forms of iodine (IO_3^-), iodine-bearing particulates, and/or organically-bound iodine into the marine atmosphere with an airborne concentration ranging from 2 to 4 ng/m^3 (NCRP 1983; Vogt et al. 1999; Whitehead 1984).

The transfer of iodine from land surface(s) into the atmosphere also occurs, but to a much lesser extent than what is observed for the transfer of iodine between the ocean and atmospheric compartments (Figures 6-4 and 6-5). It is estimated that 1.6x10^6 kg/year of iodine is transferred into the atmosphere from surface soils and from the terrestrial biosphere, with an average airborne concentration of iodine ranging from 3 to 49 ng/m^3 as both the gaseous and particulate forms of organic and inorganic iodine (USNRC 1981; Whitehead 1984). Iodine is transferred into the atmosphere from land sources through processes such as volatilization of iodine from soil and suspension of soil. For example, it is estimated that approximately 2x10^{10} g of iodine (as methyl iodide) volatilizes from rice fields worldwide (Muramatsu and Yoshida 1995). Like the atmosphere over the ocean compartment, iodine is found in the gaseous form ranging from 3 to 45 ng/m^3 versus 0.5–6.9 ng/m^3 bound to particulates (Whitehead 1984). The ratios of gaseous to particulate forms of iodine (2–5) and inorganic to organic forms of iodine (0.1–2) vary, depending on location (Whitehead 1984).

A natural radioisotope of iodine, ^{129}I, is also introduced into the atmosphere. Sources of ^{129}I include interaction of ^{129}Xe with high energy particles in the upper atmosphere and, to a lesser extent, spontaneous fission and the reaction of neutrons with ^{128}Te (tellurium-128) and ^{130}Te (tellurium-130) (NCRP 1983). This leads to a natural abundance of ^{129}I that varies between 10^{-12} and 10^{-15} atoms per atom of the stable isotope of iodine, ^{127}I (Soldat 1976). This amounts to approximately 80 kg of ^{129}I in the surface environment (e.g., oceans, atmosphere, land) with 5x10^{-4} kg in the atmosphere (Moran et al. 1999). Because ^{129}I has a half-life of 1.6x10^7 years, the introduction of this radioisotope into the atmosphere, and the environment as a whole, is cumulative from the standpoint of assessing human exposures.

Introduction of iodine and its radioisotopes can occur as a consequence of energy production, nuclear weapons production/use, and agricultural and medicinal/research uses. For the stable form of iodine (^{127}I), the introduction of iodine from these manufactured sources is much smaller than that observed for the introduction of iodine into the atmosphere from natural sources. However, the introduction of the radioisotopes of iodine (i.e., ^{123}I, ^{125}I, and ^{131}I) into the atmosphere, and the environment as a whole, is derived mainly from human activities.

Combustion of fossil fuels also leads to the introduction of iodine from land-based sources (Figure 6-5). The average iodine content of coal is reported to be approximately 4 mg/kg, whereas petroleum contains iodine at an average concentration of 1 mg/kg (Chameides and Davis 1980). Based on fossil fuel (e.g., coal and petroleum) consumption estimates for 1971 of approximately 2,500 million tons of oil equivalent per year (Mtoe) per year, this would amount to approximately $4x10^5$ kg of iodine introduced into the atmosphere for that year (0.1% of the total iodine transferred to and from the atmosphere) (Bertine and Goldberg 1971; Whitehead 1984). At the current rate of global coal and petroleum consumption of approximately 3,000 Mtoe/year, the introduction of iodine into the atmosphere from this source for the year 2001 would be $5x10^5$ kg per year (IEA 2000; Whitehead 1984).

The production and use of nuclear materials for the generation of electrical energy has also contributed to the release of iodine and its radioisotopes. ^{129}I is formed in nuclear fission reactions of ^{235}U and ^{239}Pu with an atomic yield of 0.12% from uranium and 0.5% from plutonium. The yields of ^{129}I from the fission of ^{235}U and ^{238}Pu are 0.9 and 1.7%, respectively (AEC 1974). This gives an approximate ratio of 4 for ^{129}I/^{127}I in the fission of ^{235}U and ^{238}Pu. Since the nuclear fuel elements are contained in a metal cladding, the release of ^{127}I and ^{129}I that is produced in the fission reactions does not occur until the fuel is reprocessed. For example, it is estimated that the DOE Savannah River fuel reprocessing plant released approximately 2.8 kg/year of ^{129}I during 1964–1965, but has now fallen below 0.7 kg/year since the 1970s. This amounts to a total of 5.7 Ci (210 GBq or 32 kg) of ^{129}I released during the 1954–1989 operating history of the plant (DOE 1998; Marter 1993). In 1999, the release into air of 7.27 mCi (0.269 GBq or 41 g) of ^{129}I and 10.1 μCi (0.374 MBq or 0.0818 ng) of ^{131}I was reported at the Savannah River site (DOE 1999). Releases of ^{129}I from the Hanford Reservation between 1944 and 1995 are estimated to be 1,900 GBq (51 Ci or 290 kg ^{129}I) (Robkin and Sheien 1995). The releases of another iodine radioisotope, ^{131}I, during the years 1966–1972 was estimated to be $3x10^5$ Bq ($8x10^{-6}$ Ci)/MW(e)y from fuel reprocessing. From the Savannah site, an estimated 2,520 Ci (93.2 TBq or 20.4 mg) of ^{131}I was released from 1954 to 1989 (DOE 1998; Marter 1993). The average releases of ^{131}I from boiling water

reactors (BWR) ranges between $2x10^{-3}$ Ci ($7x10^{7}$ Bq) and $5x10^{-3}$ Ci ($2x10^{8}$ Bq) per MW(e)y, and for pressurized water reactors (PWR), the values range from $5x10^{-5}$ Ci ($2x10^{6}$ Bq) to $50x10^{-5}$ Ci ($2x10^{7}$ Bq) per MW(e)y (NRCC 1980).

Surface testing of nuclear weapons release of ^{129}I into the environment from nuclear explosions of ^{235}U and ^{239}Pu amounted to approximately 30 and 50 μCi (1.1 and 1.9 MBq) per kiloton, respectively. Thus, it is estimated that atmospheric testing of nuclear weapons has released approximately 50 kg of ^{129}I into the atmosphere. The transport and diffusion of this radioisotope depended on initial height of the nuclear cloud and meteorological conditions; residency times were <0.5 years in the lower stratosphere and approximately 2 years at medium altitudes. Diffusion of radioisotopes from higher to lower altitudes then deposited through either precipitation or dry deposition (NCRP 1983); dry deposition could be as important as precipitation in surface deposition of iodine (Machta 1963; Straub et al. 1966). Release of ^{131}I also occurred during these surface tests of nuclear weapons; however, the ^{131}I that was released into the environment from these tests has decayed (half-life of 8.04 days) to levels that are no longer of concern in the environment.

Accidental releases of iodine and its radioisotopes are also sources of iodine introduction into the atmosphere. The 1986 Chernobyl reactor accident has released an estimated 1.3 kg of ^{129}I and 1,200–1,700 PBq (2.6–3.7 kg) of ^{131}I into the atmosphere (Balonov et al. 1999; Likhtarev et al. 1993; Moran et al. 1999; Mould 2000). Other notable accidental releases of ^{131}I include the 1957 Windscale, United Kingdom, radiochemical plant fire and the Three Mile Island accident that released approximately 700 TBq (2 kCi or 2 g) and 0.6 TBq (2 Ci or 1 mg) of ^{131}I, respectively (Likhtarev et al. 1993)

6.2.2 Water

Iodine (^{127}I), ^{129}I, and ^{131}I have been identified in 1, 2, and 1 groundwater samples, respectively, and no surface water samples collected from the 1,636 NPL hazardous waste sites, where they were detected in some environmental media (HazDat 2004).

Introduction of iodine into surface waters and groundwater occurs predominately through rainwater for noncoastal land regions and the combination of rainwater and ocean spray in coastal regions (Figures 6-4 and 6-5). It is estimated that $1.0x10^{11}$ g/year of iodine is deposited onto land surfaces, of which $8.1x10^{10}$ g/year enters surface waters and $1.5x10^{10}$ enters groundwater (USNRC 1981). The iodine in rainwater is derived from the transfer of iodine from the oceans to the atmosphere (FDA 1974).

Other natural releases of iodine into surface waters and groundwater include the leaching of iodine from the weathering of rock and volcanic activity (Figure 6-5). It is estimated that rocks contribute between $1x10^9$ and $1.6x10^{10}$ g/year depending on the iodine content of the rock (0.5–8.8 ppm) (Cohen 1985). Volcanic activity can add an estimated $1.2x10^9$ g of iodine per year to the surface environment, where the greatest contribution to the oceans is due to undersea volcanic activity (Miyake and Tsunogai 1963; USNRC 1979).

Municipal waste water treatment plants introduce iodine and ^{131}I into surface waters, predominantly derived from human waste and the use of ^{131}I in medical treatments. Iodine is poorly captured within sludge (2–25%), with the remainder released into surface waters (1.0–16 μg/L) in the waste water stream (NAS 1974; Stetar et al. 1993).

Release of radioiodine has occurred as a result of the reprocessing of nuclear fuel. Release of ^{129}I from waste water generated by the Idaho National Engineering Laboratory into Snake River Plain aquifer through deep disposal wells (before February 1984) and unlined disposal ponds (1984–1990) amounted to approximately 0.56–1.18 Ci (21–44 GBq or 3.2–6.7 kg of ^{129}I) (DOE 1994). This release in both shallow and deep groundwater horizons has been minimized through the recycling of the waste stream and storage of this stream with high-level radioactive waste. Release of ^{131}I into streams on the DOE Savannah River site between 1957 and 1978 totaled 300 Ci (11.1 TBq or 2.43 mg ^{131}I) (DOE 1998). In 1999, 0.0782 Ci (2.89 GBq or 441 g) of ^{129}I was released into surface waters at the DOE Savannah River site (DOE 1999). The Sellafield (United Kingdom) and Cape de la Hague (France) reprocessing facilities have cumulatively released 1,440 kg of ^{129}I directly into ocean waters since operations began in the 1960s; direct releases into the ocean amount to 200 kg/year since 1994 and have been increasing (Moran et al. 1999).

6.2.3 Soil

Iodine (^{127}I), ^{129}I, and ^{131}I have not been identified in soil or sediment samples collected from the 1,636 NPL hazardous waste sites (HazDat 2004).

The contribution of iodine to soils is derived from natural sources, such as the weathering of rock, decay of vegetation, iodine received from rainfall, and from human activities (Figures 6-4 and 6-5). Most soils contain, on average, approximately 5 mg/kg of iodine worldwide (Whitehead 1984). It is thought that

only a small proportion of this iodine is derived from the weathering of rock (Fuge 1987; Goldschmidt 1958; Whitehead 1984), although there is some argument to the contrary (Cohen 1985). The natural content of iodine in natural geologic materials is (in ppm): ultramafic igneous (0.06–0.3), basaltic igneous (0.5), granitic igneous (0.5), shales/clays (212–380), deep sea clays (11–50), limestones (0.4–29), sandstones (1.7), and coals/ash (1–11) (NAS 1974). It is expected that the contribution of iodine to soils in regions where the bedrock is composed primarily of igneous rock will be much less than that for regions where the underlying bedrock is composed of sedimentary rock, which has a higher iodine content (Cohen 1985; NAS 1974; Whitehead 1984).

Wet deposition of iodine from the atmosphere in rain or snowfall contains an average of 2.0 µg iodine/L. Assuming an average precipitation rate of 800 mm (32 in) per year, the wet deposition of iodine would amount to the addition of 16 g iodine/ha"year (Whitehead 1984). Dry deposition of iodine in a particulate form or bound to a particulate carrier can add an estimated 9.6 g iodine/ha"year, assuming a deposition rate of 0.2 cm/second and an average concentration of 15 ng/m^3 of particulate iodine (Whitehead 1984). However, the iodine that is derived from both the wet and dry deposition will only increase the content of the soil (to a 15 cm depth) approximately 0.7 ng/g if all of the iodine is effectively trapped in the soil (Whitehead 1984).

Agricultural activities increase iodine in soils through animal excrement and the use of fertilizers/pesticides (Figure 6-5). Animal feces can contain up to 10 mg/kg iodine, and urine can contain up to 4 mg/L iodine. The iodine in sewage sludges and fertilizers used in agriculture can vary between 0.5 and 30 mg/kg. Most inorganic fertilizers contain <0.5 µg/g iodine, except fertilizers containing Chilean nitrate, which can provide upwards of 80 µg/g iodine. Superphosphate and compound fertilizers derived from rock phosphate can contain up to 26 µg/g iodine (Whitehead 1979). The use of fertilizers, however, will not result in an appreciable increase in the iodine content of soil (Whitehead 1984). Yet, the use of iodine-containing herbicides, such as ioxynil/ioxynil octanoate (recommended application of 0.5 kg/ha) and the fungicide benodanil (recommended application of 1.1 kg/ha), can increase iodine content of soil about 0.17 and 0.21 µg/g to a depth of 15 cm, respectively (Whitehead 1979, 1984).

Combustion of coal and petroleum is another source of iodine in soils. In the combustion of coal and petroleum, the iodine is introduced to the atmosphere through the flue gases. A large proportion (~80%) of the iodine released through the flue gases is deposited onto the surrounding soils by both wet and dry deposition, adding approximately $4x10^5$ kg iodine/year to soils globally.

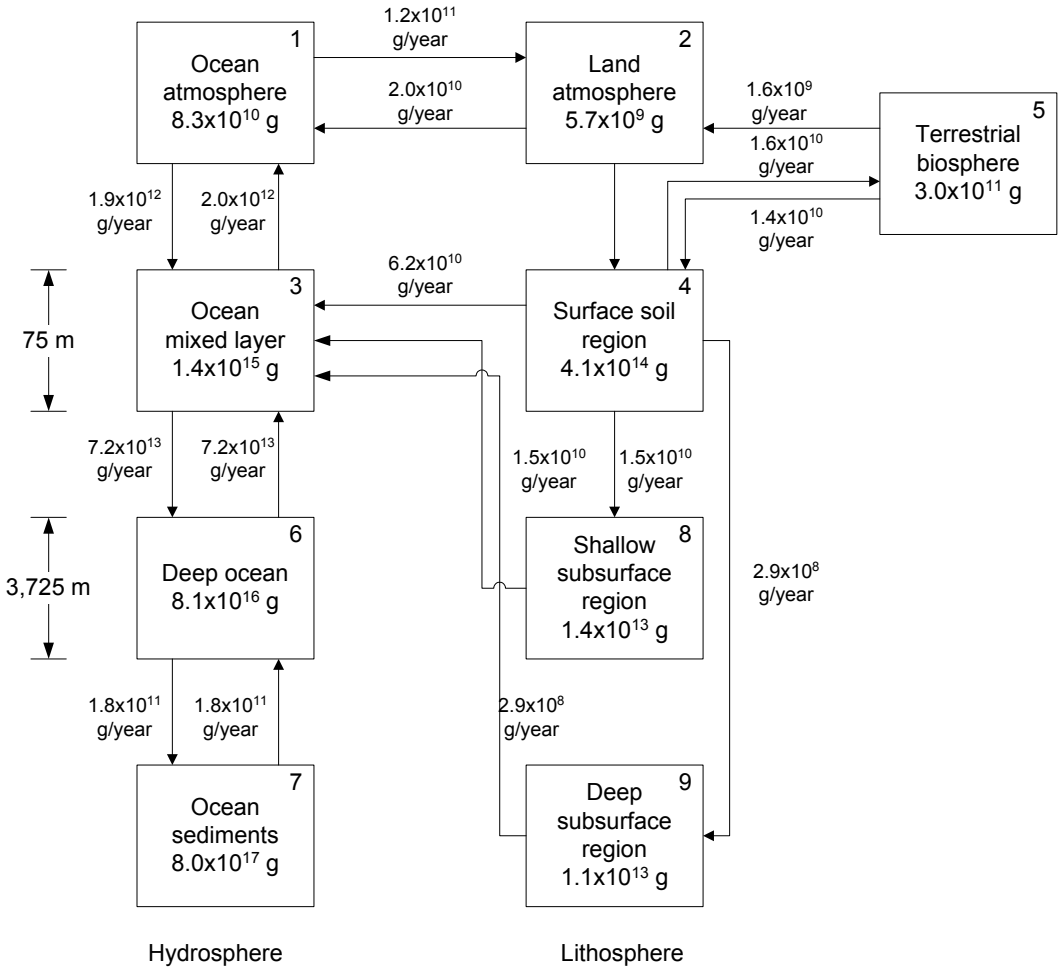
6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

It is estimated that the earth's surface contains $6.3x10^{18}$ g of iodine. The majority of this iodine is in the earth's crust ($3.4x10^{18}$ g) and in sedimentary rock ($2.9x10^{18}$ g). However, this iodine is inaccessible, except for the small portion that is liberated through weathering processes ($\approx 10^9$ g/year) and eventually enters into the oceans. The ocean, on the other hand, is the largest compartment of accessible iodine that can be transferred to other environmental compartments. The earth's oceans contain $8.1x10^{16}$ g of iodine (Figure 6-6) at an average concentration of between 45 and 60 µg/L. Other environmental compartments with steady-state levels of iodine include atmosphere ($8.8x10^{10}$ g), surface soil ($4.1x10^{14}$ g), subsurface region ($2.5x10^{13}$ g), and terrestrial biosphere ($3.0x10^{11}$ g). The iodine in the ocean is in equilibrium with the iodine in ocean sediments ($8.0x10^{17}$ g), with a net flux of $1.8x10^{11}$ g/year. A net transfer of iodine also occurs between the ocean surface and the global atmosphere at an average rate of $2.0x10^{12}$ g/year, of which $1.9x10^{12}$ g/year returns to the ocean through wet/dry deposition processes, and $1.2x10^{11}$ g/year is deposited onto land surfaces. Of the iodine that is deposited on land, $7.7x10^{10}$ g/year is returned to the ocean through groundwater and river effluents, and $1.6x10^{10}$ g/year enters into the terrestrial biosphere, of which $1.4x10^{10}$ g/year returns to the soil surface through weathering and decay of vegetation (USNRC 1979).

The transfer of iodine between the ocean compartment, atmosphere, and land surfaces is due to the volatility of iodine in its molecular (I_2) and organic (most methyl iodide) forms. The extent to which iodine partitions into these compartments, and its residency time, will depend on the chemical form of the iodine as it enters into a specific compartment, any chemical alterations that the iodine undergoes in that particular compartment, and the solubility/uptake/retention of the various chemical forms of iodine in the compartment. The formation of alkyl iodides (predominantly methyl iodide) and, to a lesser extent, molecular iodine from biological activity and photochemical reactions on the ocean's surface, provide for the transfer of these iodine species into the ocean atmosphere, where they undergo further photochemical conversions into other gaseous and particulate forms of iodine (Cox et al. 1999; Filistovic and Nedveckait 1998; Vogt et al. 1999; Whitehead 1984). The relative proportions of iodine as inorganic particulates and organic gaseous forms are on average 25% for particulates and 40–80% for organic forms as methyl iodide (Moran et al. 1999). The residence times for iodine in the atmosphere are 14 days for particulates, 10 days for inorganic gases (i.e., I_2), and 18 days for organic gases (compared to a 9-day

Figure 6-6. Diagram of the Global Iodine Cycle at Steady State Showing Environmental Compartments, Compartment Inventories in Grams (g), Transport Pathways, and Fluxes in Grams per Year (g/year)



Source: Kocher 1981

residency time for water vapor), providing for extended global transport and substantial mixing (Moran et al. 1999).

The gaseous and particulate forms of iodine in the atmosphere are deposited onto ocean or land surfaces through wet and dry deposition. Gaseous elemental iodine and particulate forms of iodine are susceptible to wet deposition, whereas methyl iodide has a low susceptibility. Accordingly, gaseous molecular iodine and particulate forms of iodine are susceptible to dry deposition; methyl iodide has a low susceptibility (Whitehead 1984).

The dry deposition rate is dependent on particle size, wind speed, and turbulence. Iodine will settle onto soil and plant surfaces. Direct deposition of iodine onto plant surfaces is limited to 7.5–14 days, where particulate iodine is removed from plant surfaces through weathering processes (AEC 1974; Heinemann and Vogt 1980; Kirchner 1994). Dry deposition onto plant surfaces is affected by the moistness of the surface; deposition is approximately 2-fold greater on moist plant surfaces versus dry surfaces (Heinemann and Vogt 1980). Also, dry deposition onto plants is affected by the surface area of the plant, as is evident from the 2-fold increase in iodine deposited on clover versus grasses (Heinemann and Vogt 1980).

The wet deposition of iodine will be predominantly deposited into soil. The relative amounts of iodine initially depositing onto the soil will greatly depend on the density and type of plant cover over the soil. Upwards of 90% of elemental iodine vapor can be intercepted by a dense cover of grassland herbage, but 40–70% can typically be expected to be intercepted by a more average density of plant cover (Whitehead 1984).

Evaporation of iodine from the land surface to the atmosphere is only about 1% of the flux of iodine from the atmosphere to the land surface (USNRC 1979) and iodine is cycled back to the ocean through groundwater and river effluent (USNRC 1979; Whitehead 1984). However, the overall content of iodine in a soil is determined by the inputs of iodine into the soil and the ability of the soil to retain iodine (versus leaching and volatilization), where the main input is from atmospheric deposition, both wet and dry, followed by degradation of plant material (mostly from adsorbed iodine) (Whitehead 1984).

The low flux of iodine from land surfaces to the atmosphere is due to the retention of iodine within surface soils, especially in soils rich in organic matter and iron/aluminum oxides (Sheppard et al. 1995). When the various chemical forms of iodine enter into the soil, these species are initially retained by their

absorbance onto soil components in equilibrium with their solubility in soil solution. Isotopic exchange studies indicate that between 5 and 30% of iodine is exchangeable (Whitehead 1984). Retention of inorganic and organic iodine will depend on both nonspecific and specific sorption onto soil components. Nonspecific ion-exchange interactions of iodide and iodate anions occur on free hydrous oxides of iron and aluminum; such exchanges involve electrostatic attractions and are dependent on pH and the concentration of other anions (Sheppard et al. 1995). Retention of molecular iodine in soil is thought to be mediated through the interaction of iodine with thiols and polyphenols present in the organic components of soils (Fawcett and Kirkwood 1953; Jirousek and Pritchard 1971; Whitehead 1984) and may also involve the oxidation/reduction of iodide and free radical reactions (Huang and Lu 1991). Methyl iodide is sorbed by soils to a lesser extent than inorganic iodide, but the factors that determine this sorption of methyl iodide to soils are unclear (Whitehead 1984).

Transport of iodine to lower soil depths is dependent on the porosity and saturation of the soil. Macropores formed from roots and earthworm channels allow for rapid transport of iodine into the soil. Mobility of iodine into the soil is greatest when the soil is saturated with water. The drier the soil, the thinner the water films within the soil, thus limiting the flow rate of water through the soil (Whitehead 1984.

In addition to the aforementioned direct deposition of particulate deposition of iodine onto plant surfaces, there is also evidence of the uptake of inorganic iodine into the plant through the roots and gaseous iodine through the leaves (Whitehead 1984). Iodide is more readily taken up into plant roots than is iodate or iodine (Burte et al. 1991; Whitehead 1984); the uptake is dependent on the concentration of iodine in the soil, the properties of the soil, and the use of fertilizers (Moiseyev et al. 1984; Shinonaga et al. 2001). Soil-to-plant transfer factors (TF), which are defined as the grams iodine per kilogram wet or dry weight of plant material divided by the grams of iodine per kilograms dry soil, typically range between 0.001 and 1.5 for plants of agricultural importance (Shinonaga et al. 2001). Molecular iodine can be absorbed through the stomata in the leaves, whereas methyl iodide and hypoiodous acid are not as readily absorbed through this route (Whitehead 1984).

Both the deposition of particulate iodine onto plant surfaces and the direct uptake of iodine into the plant factor into the transfer of iodine through the soil-plant-cow-milk pathway. The level of iodine in feed has a direct relationship with the level of iodine measured in milk (Tracy et al. 1989; Voigt et al. 1989) and is dependent on the season, nutritive quality of pastureland, and ambient temperature (Ekman et al. 1967; Lengemann and Wentworth 1979; Pennington 1990a). The transfer coefficient for iodine through the

total pathway is approximately 0.003–0.01 for cow and 0.2 for goat, expressed as the fraction of daily intake per liter milk (d/L) (AEC 1974; Kirchner 1994; Voigt et al. 1988, 1989).

Transfer of iodine in the feed-meat pathway has also been determined in various animals and tissues. Transfer factors in whole animals (expressed as the fraction of daily intake per kg [d/kg]) are 0.02 (beef), 0.09 (pork), and 0.004 (chicken). The thyroid is the organ with the greatest uptake of iodine (AEC 1974). Individual tissue measurements have transfer factors range from 10^{-4} (kidney) to 10^{-3} (liver) to 10^{-2} (muscle) (Handl and Pfau 1989; Handl et al. 1990). Transfer factors have also been determined for feed-chicken eggs (0.03) (AEC 1974).

Iodine can also bioaccumulate to varying extents in aquatic organisms. Aquatic bioaccumulation factors for iodine in fresh water are 40 (algae), 5 (invertebrates), and 15 (fish); in salt water, these factors are 4,000–10,000 (algae), 50–100 (invertebrates), and 10–20 (fish) (AEC 1974). Certain seaweeds and algae can concentrate iodine to levels as high as 0.8–4.5 g/kg of dried material; these high levels are usually associated with the relatively high levels of iodine in seawater (50 μg/kg) (FDA 1974).

6.3.2 Transformation and Degradation

Iodine consists of one stable isotope (^{127}I) and a number of radioisotopes, of which ^{123}I, ^{125}I, ^{129}I and ^{131}I are the most common in environmental and occupational exposures. The radioisotopes ^{129}I and ^{131}I decay by β-emission to form ^{129}Xe and ^{131}Xe, respectively, whereas ^{125}I decays by electron capture, emitting gamma and Te x-rays. ^{125}I and ^{131}I disappear rapidly from the environment due to their short half-lives of 60 and 8.04 days, respectively, and do not undergo long-term accumulation in the environment. However, the long physical half-life of ^{129}I (1.57×10^7 years) means that any release of this radioisotope into the environment is essentially a permanent addition to the total inventory of iodine in the environment from the standpoint of assessing human exposures (NCRP 1983).

The chemical reactions of iodine and its radioisotopes within the environment are the same, but the ratios of the isotopes in these reactions may differ, depending on the relative concentrations of the isotopes in a particular environment. ^{127}I and its radioisotopes can exist in many forms and oxidation states (iodides [-1], molecular iodine [0], iodohalides [+1], iodates [+5], and periodates [+7]) (Holland 1963); organic forms of iodine include methyl iodide, ethyl iodide, isopropyl iodide, and methylene iodide (Vogt et al. 1999). Thus, “iodine” in the discussion of the chemical reactions of iodine in the environment will be used to refer to both iodine and its radioisotopes, unless indicated otherwise.

6.3.2.1 Air

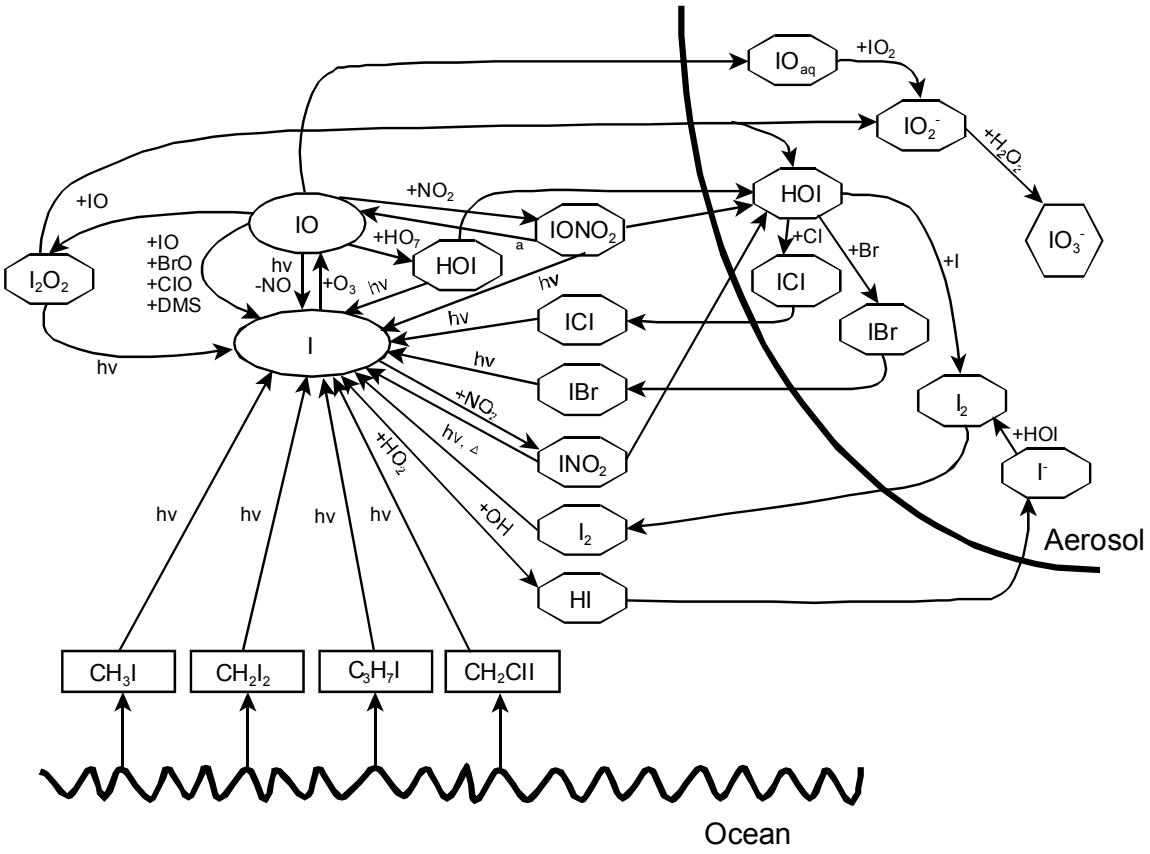
The major source of iodine in air is from the evaporation of alkyl iodides (mostly methyl iodide) and, to a lesser extent, molecular iodine from ocean surfaces (Figures 6-4 and 6-7). At ordinary pressures and temperature, methyl iodide and iodine have high vapor pressures and will exist predominately in a free gaseous form in air. Both iodine and methyl iodide undergo photochemical reactions to form iodine radicals (IC), which can then go on to form a number of other iodine species through a complex series of reaction pathways (Cox et al. 1999; Filistovic and Nedveckait 1998; Vogt et al. 1999); some of these are shown below and in Figure 6-4.

		I_2		÷	2 IC	
		CH_3I	÷	CH_3C	+	IC
IC	+	HO_2C	÷	HI	+	O_2
IC	+	NO	÷	INOC		
IC	+	NO_2	÷	INO_2C		
IC	+	O_3	÷	IOC	+	O_2
IOC	+	NO_2	÷	$IONO_2C$		
		2IOC	÷	I_2O_2		
		2IOC	÷	OIOC	+	IC

The overall photochemical dissociation of CH_3I and I_2 in the atmosphere results in the steady-state formation of inorganic iodine species consisting mostly of $IONO_2C$ (75%), IOC (15%), and HI+HOI (10%) during the daytime. Only minor changes in these percentages are observed during the night-time, $IONO_2C$ (75%), IOC (7%), and HI+HOI (18%) (Filistovic and Nedveckait 1998).

Some of these iodine species (e.g., IOC, I_2O_2) can then go on to react in aerosols or water droplets to form IO_2^- and IO_3^- (Figure 6-7). Gaseous iodine can also dissolve in water droplets to form iodide or hypoiodate ions, especially in the presence of alkaline impurities. Iodine is readily reduced to iodide by hydrogen sulfide and can be oxidized to free iodine by ozone, hydrogen peroxide, or possibly air and sunlight. If the iodine is acidified sufficiently, gaseous hydrogen iodide is liberated (Straub et al. 1966). Conversely, HI formed in air can dissolve in water droplets, forming iodide anions that can be oxidized to molecular iodine.

Figure 6-7. A Simplified Scheme of Iodine Cycling in the Marine Boundary Layer*



*Organic iodine compounds are shown in rectangular boxes; temporary iodine reservoir species in the gas and in the aerosol phase are shown in octagons

Source: Vogt et al. 1999

6.3.2.2 Water

Iodine in water exists as iodide and iodate. In rainwater, the relative proportion of iodide to iodate is 55:45. In surface waters, the proportion of iodide to iodate will vary depending on microbial activity and the release of iodine species from terrestrial sources (De Luca Rebello et al. 1990). Iodide is also converted in the surface layer of seawater to hypoiodous acid (HOI) by photochemically generated ozone (Bichsel and von Gunten 1999). Microbial action converts iodide to organic forms of iodine, primarily methyl iodide (iodomethane). The low vapor pressure and limited solubility in water promote the volatilization of methyl iodide from surface waters to the surrounding atmosphere. Likewise, microbial activity and photochemical reactions, including photolysis of biogenic iodine, can lead to the formation of iodine from iodide or iodate; iodine can evaporate into the atmosphere due to its low vapor pressure (Xie et al. 1999). In marine waters, up to 40% of iodine can be found as dissolved organic iodine (DOI), with the remainder as iodide (Wong and Cheng 1998).

Disinfection of natural waters results in the oxidation of iodide to hypoiodous acid (HOI) (Bichsel and von Gunten 1999). Ozone, chlorine, and monochloramine easily oxidize iodide to HOI. Ozone, at concentrations used in the disinfection of water, rapidly oxidizes HOI and hypoiodate (OI^-) to iodinate (IO_3^-), whereas chlorine oxidizes HOI in a slower, more complex reaction mechanism. Monochloramine was unable to oxidize HOI. As a consequence, the formation of iodoorganics (e.g., iodoform or CH_3I), which results from the reaction of HOI with organics in natural waters and often causes a problems with the taste and odor of drinking water, is much more prevalent when chlorine and chloramines are used as oxidants in the disinfection process.

6.3.2.3 Sediment and Soil

Iodine can enter sediments through accumulation of plant matter or fixation of iodide in water to humic substances in the sediments through microbial action (R@dlinger and Heumann 2000). Weaker and reversible binding of iodide to inorganic components in sediments has also been shown to occur, with affinities measured as partition coefficients [K_ds] ranging from -0.22 mL/g for chlorite minerals to 15.14 mL/g for illite minerals (Kaplan et al. 2000). Iodine can enter soil as I_2, iodide, iodate, or methyl iodide through wet or dry deposition. Molecular iodine dissolves in soil water to form iodide or is oxidized to iodate. Conversely, chemical, and to a lesser extent, microbial, reduction of iodide or iodate

forms molecular iodine that can evaporate from the soil water into the atmosphere. Iodine can react with organic components of soil, such as humic substances, undergoing iodination reactions with polyphenols and tyrosine residues (Fawcett and Kirkwood 1953; Jirousek and Pritchard 1971; Whitehead 1984), which may involve the oxidation/reduction of iodide and free radical reactions (Huang and Lu 1991).

Decreases in pH can alter the proportion of iodide to iodate in soil and water due to the protonation of iodide to form HI, which can volatilize into the atmosphere. The relative proportions of iodine species can also differ in soils under flooded and nonflooded conditions. The proportions of I_2:I^-:IO_3^-:organic iodine change from 0.045:0.065:0.89:0.016 under the oxidizing nonflooded conditions to 0.007:0.90:0.097:0 under the reducing flooded conditions (Yuita 1994a).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

The average global air iodine concentration ranges between 10 and 20 ng/m^3 with gaseous iodine usually exceeding particulate iodine by a factor of 2–6 (Whitehead 1984). Atmospheric concentrations over land range from 2 to 14 ng/m^3, while atmospheric levels over oceans average between 17 and 52 ng/m^3 (USNRC 1979). In an urban air environment, iodine content in air over San Francisco in 1970 ranged between 4.7 and 10 ng/m^3 over nine monitoring stations (John et al. 1973). In remote air environments, for example the arctic, the iodine concentrations fall dramatically. Iodine in the arctic stratosphere is 0.27 ng/m^3, and is 0.33 ng/m^3 at the marine boundary layer (Sheridan and Zoller 1989). The annual average concentration of iodine in Canadian arctic air ranges between 0.43 and 0.96 ng/m^3 (Barrie and Hoff 1985)

Iodine introduction in the form of methyl iodide emission from a municipal waste incineration plant has been measured at an average of 0.50 μg/m^3 in Karlsruhe, Germany (Stieglitz 1995).

Radioiodine releases from nuclear fuel reprocessing facilities have been well documented. Discharges of ^{129}I from the Hanford Reservation between 1983 and 1992 ranged from 0.02 to 0.6 Ci/year, with a maximum output of 0.5–0.6 between 1986 and 1988 (DOE 1993). The average airborne concentrations of ^{129}I onsite ranged from 69–2,000 to 2.2–60 attoCi/m^3 (atto=10^{-18}) along the perimeter to 0.13–2.4 attoCi/m^3 at distant monitoring sites (DOE 1993). At the Savannah River site, ^{129}I and ^{131}I releases between 1954 and 1989 totaled 5.67 and 2.52 Ci, respectively (DOE 1990). Discharges of ^{129}I into the air from the Sellafield (United Kingdom) and La Hague (France) nuclear processing facilities is thought to

contribute to the 4–40x10^8 atoms ^{129}I/L (15–150 attoCi/L or 0.086–0.86 ng/L) measured in rain and snow over Sweden between 1998 and 1999, although it is not clear how much of these releases contributed to the total concentration of ^{129}I in precipitation (Buraglio et al. 2001). Strong seasonal variations in the concentration of ^{129}I in precipitation are observed, due to such factors as seasonal changes in the volatilization of $CH_3{}^{129}I$ from soils and decaying plant matter, and seasonal changes in weather patterns that determine the source and availability of moisture in the Baltic region.

The release of radioiodine into the atmosphere from nuclear weapons testing and its deposition onto distant targets has been measured. ^{131}I that was produced in the above-ground nuclear Test Harry and deposited (wet) on select New England monitoring sites ranged from 0.2x10^9 Bq/km in Buffalo to 3.4x10^9 Bq/km in Pittsburgh to 6.1x10^9 Bq/km in Binghamton (Hoecker and Machta 1990). The emissions of radioiodine are often associated with particulates. The amount of ^{131}I associated with particulates increases with the distance from the source of release. Upwards of 60% of ^{131}I released into atmosphere is associated with particulates, based on ground-level measurements. It is assumed that 80–85% of the fallout of ^{131}I is in the reduced state, 15–20% is present as IO_3^-, and a few percent or more is present as IO_4^- (Perkins 1963; Straub et al. 1966). The cumulative release of ^{129}I (expressed as Ci) in nuclear weapons testing beginning in 1945 and ending in 1975 has been estimated and is shown in Table 6-1 (NCRP 1983).

6.4.2 Water

The average iodine content in seawater is 40–65 µg/L (USNRC 1979). The iodine content in rainwater averages between 0.1 and 15 µg/L, and in rainwater over oceans, the iodine content is 1–15 µg/L (USNRC 1979). The iodine content in river water averages between 0.1 and 18 µg/L (USNRC 1979). The concentration of iodine in river water will be locally influenced by municipal waste water streams. The average iodine content in municipal waste water effluent is 4.0 µg/L (range 1.0–16 µg/L) (NAS 1974). In groundwater, the average iodine concentration is 1 µg/L (Yuita 1994a).

The concentration of ^{129}I in ocean surface waters averages between 10^7 and 10^8 atoms ^{129}I per kg (Cooper et al. 2001). Some examples reported by Cooper et al. (2001) are 0.18–0.82x10^8 atoms ^{129}I/kg in the Bering, East, and Chukchi Seas, with several concentrations as high as 9.60x10^8 and 16.7x10^8 atoms ^{129}I/kg in the Chirikov and Chukchi benthic zones, respectively. Cooper et al. (2001) also showed that the concentration of ^{129}I in ocean waters varies as a function of depth of the water column. In the East Sea

Table 6-1. Approximate Releases of ^{129}I from Atmospheric and High Altitude Nuclear Weapons Tests

Year	Cumulative ^{129}I Released (Ci)
1945–1951	0.04
1952–1954	2
1955–1956	3
1957–1958	5
1959–1961	6
1962–1963	10
1963–1975	10

Source: NCRP 1983

(Sea of Japan), the concentration of ^{129}I decreased from approximately $0.35x10^8$ atoms ^{129}I/kg in surfaces water to $0.05x10^8$ atoms/kg at a depth of 2,000 meters, but increased again to $0.15x10^8$ atoms/kg at a depth of 2,800 meters near the sea floor (3,000 meters). It is suspected that the increase in ^{129}I concentration near the sea floor is due to a flux of iodine from sediments (^{129}I concentrations in sediments were 168–$902x10^8$ atoms/kg), although this could not be confirmed in their study.

The iodine content in drinking water typically varies between 0 and 8 µg/kg, with a more nominal range averaging between 2 and 4 µg/kg. Concentrations of iodine in drinking water approaching or exceeding 8 µg/kg are usually associated with water that is directly contaminated with sewage or effluent from sewage discharge sites or from urban run-off (FDA 1974). For example, the concentration of iodine in the Potomac River was 4.0 µg/L upstream of Alexandria, but increased to 8.0 µg/L downstream. Sewage effluent from Alexandria was believed to be the cause. Some effluent streams can have iodine concentrations as high as 1,910 µg/L (FDA 1974).

Seasonal variations in iodine have been measured in Rhode Island precipitation. The volume-weighted mean concentration in annual precipitation is 1.71 µg/L, with a concentration range of 0.04–11.3 µg/L. The seasonal variations in volume-weighted iodine concentration were 2.14 µg/L during the warm season and 1.35 µg/L during the cold season (Heaton et al. 1990).

Radioiodine is released into surface waters through the effluent of municipal sewage treatment plants. On an average working day, approximately 24 mCi (0.89 GBq) of ^{131}I is released into the Ohio River, resulting in a concentration of 0.3 pCi (11 mBq) ^{131}I/L downstream from the treatment plant (Sodd et al. 1975). The concentration of ^{131}I in water downstream from other municipal treatment plants throughout the United States has also been determined, ranging from 0 to 83 pCi (0 –3.1 Bq) ^{131}I/L (Prichard et al. 1981). The ^{131}I that has been measured in these waters is due to the introduction of ^{131}I into the sewer systems of cities from the excrement of patients undergoing treatments with this radioisotope.

The release of ^{129}I into surface waters has also been measured. It has been estimated that the above-ground total fission yield of a 207 megaton equivalent of plutonium fission devices contributed approximately 10 Ci (370 GBq) of ^{129}I to the environment (NCRP 1983). Reprocessing of spent fuel could release additional amounts of ^{129}I into the environment (at most 2 Ci or 70 GBq) depending on the amount of fuel that is reprocessed and the efficiency of gaseous effluent decontamination equipment. This has resulted in an increase in the ratio of $^{129}I/^{127}I$, which has been changing since 1945 due to the release of ^{129}I into environment from nuclear weapon explosions and nuclear facilities. These releases

range from 10^{-8}–10^{-7} in the ambient environment to 10^{-4}–10^{-3} near some nuclear facilities, as measured in thyroid tissues (NCRP 1983). The release of ^{129}I has also resulted in a steady-state inventory of $8.7x10^{26}$ atoms (31 Ci or $1.8x10^{5}$ g) of ^{129}I in the oceans (AEC 1966). Slow releases of ^{129}I from radioactive waste dump sites in the North Atlantic and Pacific Oceans, Arctic Ocean, Sea of Japan, and Sea of Okhotsk are also contributing to increased inventories of ^{129}I in ocean waters (Povinec et al. 2000). The concentrations of ^{129}I can vary significantly.

The average content of ^{127}I and ^{129}I in air over the United States varies between 0.6 and 12.1 ppb (Table 6–2). These ^{129}I concentrations did not appear to differ greatly between coastal (e.g., Galveston, Texas) and interior (e.g., Lafayette, Indiana) measurement sites (Moran et al. 1999). The measured ratios of ^{129}I to ^{127}I in air and in precipitation was found to vary, ranging between 2.03 and 27.90 ($x10^{-12}$) in air and between 755 and 12,390 ($x10^{-12}$) in precipitation (Moran et al. 1999). These variations in the ratios of ^{129}I to ^{127}I may reflect the distances of the various collection sites from the sources of these isotopes (e.g., distance from coastal regions for ^{127}I and distance from nuclear fuel reprocessing facilities for ^{129}I) (Moran et al. 1999).

The effect of ^{129}I release from nuclear fuel reprocessing facilities on surface water and groundwater has been measured. In 1990–1991, ^{129}I concentrations in the Snake River aquifer at and near the Idaho National Engineering Laboratory range between 0.6 aCi/L (22 nBq/L) and 3.82 pCi/L (0.141 Bq/L), with a mean of 0.81 pCi/L (30 mBq/L), which is a change from 1.30 pCi/L (48.1 mBq/L) measured in 1986. This change reflects a decrease in the amount of ^{129}I disposal and changes in disposal techniques (DOE 1994). Between January 1993 and June 1994, ^{129}I concentrations measured at 29 sites in and around the Savannah River site in surface waters ranged between 0.027 and 3.2 pCi/L (1.0 and 120 mBq/L) and are primarily derived from continued discharges of ^{129}I from the facility (Beals and Hayes 1995).

6.4.3 Sediment and Soil

The natural occurrence of iodine in igneous and sedimentary rock is approximately 0.2–5.8 ppm and it is 5–10 times higher in shales rich in organic matter, in soils, and in coals (NAS 1974). Some references indicate that these estimates may be low, suggesting instead an average soil content for iodine as high as 5.85 ppm (range: 1.5–13.5 ppm) (NAS 1974). Indeed, in one survey of iodine content in soils (Table 6-3), the iodine concentration in common soil types is consistent with the mean of 5.85 ppm (Whitehead 1979). This survey also shows the large variation in iodine concentrations as a function of soil type (Whitehead 1979, Table 6-3). In a study of the iodine concentration of soils in the contiguous

Table 6-2. Concentration of Iodine, Chloride, and $^{129}I/^{127}I$ Ratio in Air and Precipitation as a Function of Location and Collection Time

	Air		Rain/Snow			
Location[a]	I (ppb)	$^{129}I/^{127}I$ (10^{-12})	$^{129}I/^{127}I$ (10^{-12})	^{129}I atoms/L (10^{7})	Cl^- (ppm)	I/Cl
WL 12/95-2	1.4	12.03	5,756	3.7		
WL 12/95-3	0.9	12.45	8,327	3.7	0.2	0.0045
WL 12/95-4	0.6	13.85	12,390	3.7		
B 11/95	1.2	7.38	2,027	1.1	1.6	0.0008
CS 8/22/96	6.6	10.39	755	2.3		
CS 9/1/96–9/15/96	1.9	4.17	913	2.4	0.3	0.0061
CS 9/15/96–10/15/96	2.5					
CS 10/20/96–10/26/96	2.0				1.2	0.0017
CS 10/26/96–11/24/96	1.7	2.03	893	0.7	1.1	0.0015
CS 11/24/96–11/30/96	3.3				1.6	0.0021
CS 12/21/96–1/16/97	2.9	26.80	3,408	4.5		
CS 1/20/97–1/30/97	2.5	7.60	2,121	2.5		
CS 2/20/97–2/26/97	1.8	5.30	975	0.9		
CS 3/18/97-1	1.4					
CS 3/18/97-2	1.3					
CS 3/18/97-3	0.6					
CS 3/18/97-4	0.8					
CS 3/18/97-5	0.7					
G 1/96–10/96	1.9	9.44	1,735	1.6		
G 11/96	12.1	27.90	1,064	6.0	46.5	0.0003
G 12/6/96–1/6/97	1.7				4.9	0.0003
G 1/7/97–1/16/97	1.2	14.87	3,946	2.3		
Ohio snow 1/14/97	0.7	11.10	9,150	3.0		

[a]WL = West Lafayette, IN; B = Bryan, TX; CS = College Station, TX; G = Galveston, TX

Source: Moran et al. 1999

Table 6-3. Iodine Content in Specific Soil Types

Soil	Concentration of iodine (µg/g dry soil)	
Acid igneous rocks and associated till	10.4	(4.4–15.7)[a]
Till associated with basic igneous rocks	10.9	(3.4–16.3)
Slate, shale, and associated till	9.8	(4.4–27.6)
Sand and sandstone	3.7	(1.7–5.4)
Chalk and limestone	12.3	(7.9–21.8)
Clay	5.2	(2.1–8.9)
River and river terrace, alluvium	3.8	(0.5–7.1)
Marine and estuarine alluvium	19.6	(8.8–36.9)
Peat	46.8	(18.7–46.8)

[a]Average iodine concentration with the range of measurements given in the parentheses

Source: Whitehead 1979

United States, the average iodine concentration in soils was 1.2 μg/g. This average does not differ between soils measured in the western United States (west of 96th meridian) (1.2 μg/g) or the eastern United States (1.2 μg/g) (USGS 1984). Iodine concentration in soils has also been measured as a function of soil depth (Table 6-4), showing minimal variation in iodine concentration to depths of 12–24 inches (Fuge 1987). The data in Table 6-4 also show that soil concentrations were typically higher than the concentration of iodine in the underlying bedrock.

The iodine content in sewage sludges ranges between 1.0 and 17.1 μg/g dry weight; these values are similar to those found in soils, with the mean for iodine in sludges generally being lower. Iodine content of sludges was not related to size or degree of industrialization of a particular city or town. Measurements of iodine in sludge indicate that iodine does not partition strongly into sludges (Whitehead 1979). ^{131}I content in sludge generated from the Oak Ridge municipal waste water plant averages 0.16 nCi/L (5.9 Bq/L or 1.3 fg/L). The background concentration of ^{131}I content in sludge generated at a municipal sewage treatment in Ann Arbor, Michigan, was reported to be 1.4 pCi/L (52 mBq/L or 0.011 fg/L), but could rise as high as 15 pCi/L (0.55 Bq/L or 0.12 fg/L) (Fenner and Martin 1997). These concentrations of ^{131}I in sewage sludge are due to the introduction of ^{131}I into city sewer systems from the excrement from patients who are undergoing treatment therapies that utilize ^{131}I (Stetar et al. 1993)

The soil content of ^{129}I has been compared to ^{127}I and has been found to be generally higher near nuclear fuel reprocessing facilities than elsewhere. The ^{129}I/^{127}I ratios near facilities range between 10^{-4} and 10^{-3}, whereas more remote locations yield ratios between 10^{-9} and 10^{-8} (Robens and Aumann 1988).

6.4.4 Other Environmental Media

Iodine content of aquatic plants varies, depending on whether they are fresh or salt water. Freshwater algae contain 10^{-5}% by weight of iodine, whereas marine algae contain 10^{-3}% by weight (NCRP 1983). For example, concentrations of iodine have been measured in edible marine algae obtained from the St. Lawrence River, which vary as a function of species. *Enteromorpha* and *Porphyra* had the lowest average concentrations of iodine of 22.7 and 31.7 μg/g (dry weight) in contrast to *Ascophyllum nodosum* and *Laminaria longicruris,* which contained the highest average iodine concentrations of 482 and 763 μg/g (dry weight) (Phaneuf et al. 1999).

Epiphytes (plants that have no root systems and acquire their nutrients from the air), such as Spanish moss in the southern United States, are used to measure long-term exposures of airborne trace elements.

Table 6-4. Iodine Content in Missouri Soils as a Function of Depth and Parent Material

Bedrock	Soil depth (inches)	Iodine concentration (µg/g)
Sandstone	0–5	0.80
	5–8	0.78
	8–12	1.05
	Bedrock	<0.04
Dolomite	0–4	0.89
	4–8	0.85
	8–12	1.13
	12–18	1.08
	18–24	1.28
	Bedrock	<0.04
Alluvium-river valley	0–3	0.91
	3–6	0.65
	6–12	0.72
	12–18	0.91
Limestone (thin soil)	0–3	5.98
Shale	0–6	1.02
	6–12	1.03
	12–18	1.13
	Bedrock	0.37
Granite	0–5	2.90
	5–10	5.00
	10–15	7.21
	Bedrock	<0.04
Glacial material	0–5	0.12
	5–10	0.31
	10–15	0.68
	15–20	0.28
	20–24	0.53

Source: Fuge 1987

The concentration of ^{129}I in Spanish moss varies between 0.4 and 4.9 ppm and roughly correlates with estimated airborne concentrations of ^{129}I (Moran et al. 1999). In Norway, the iodine in moss averages 3.3 ppm (Schaug et al. 1990).

The average content of iodine in terrestrial plants has been reported to be 0.42 mg/kg worldwide (Yuita 1994a). In some specific examples, iodine content (mg/kg) has been measured at 0.60–2.6 in beet root flesh; 0.1–2.4 in cabbage head; and 0.30–1.1 in corn kernel (Sheppard et al. 1993). The iodine content in hay has been measured at 0.08 μg/g fresh weight feed (Voigt et al. 1988). The distributions of I_2 in plants, such as wheat, can vary over the various parts of the plant. In wheat, iodine concentrations (μg/mg) change between shoots (0.136), roots (0.206), and total plant (0.153). For iodide, the distribution throughout the plant differs as well. In wheat, the iodide concentrations (μg/mg) are 0.645 in shoots, 0.100 in roots, and 0.261 in plant (Voigt et al. 1988).

The ^{129}I content in deer thyroids has been assessed as a function of proximity to a nuclear fuel processing facility. The ^{129}I thyroid concentrations were highest in deer captured near the nuclear fuel reprocessing plant at the Savannah River Site, South Carolina (1–102 Bq/g or 0.03–2.8 nCi/g thyroid in 6.8% of deer) and Oak Ridge, Tennessee (0.01–1.0 Bq/g or 0.3–27 pCi/g thyroid in 38% of deer). However, no thyroids from deer in Florida or in west Tennessee, which are distant from nuclear fuel processing facilities, contained ^{129}I at concentrations above 4 mBq/g or 0.1 pCi/g thyroid (Van Middlesworth 1993).

Iodine measurements in milk and milk products have yielded the following results (expressed as μg/100 g): low fat milk (24), skim milk (21), buttermilk (24), chocolate milk (25), plain lowfat yogurt (33), strawberry lowfat yogurt (17), evaporated milk (37), half-and-half (17), cottage cheese (27), American cheese (49), cheddar cheese (47), chocolate fast-food milkshake (55), chocolate ice cream (47), vanilla ice milk (30), ice cream sandwich (51), and chocolate instant pudding (36) (Pennington 1990a).

Measurements of ^{131}I have been monitored in milk through the Environmental Radiation Ambient Monitoring System (ERAMS) using gamma spectral analysis of milk samples taken from 65 monitoring sites with at least one located in each U.S. state, Puerto Rico, and the Panama Canal Zone. The most recent measurements of ^{131}I in milk samples taken from July–September 1993 through July–September 1997 are below the detection limit at all monitoring sites (see ERD 1993 and ERD 1997 for examples).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure and uptake of iodine and its radioisotopes can be obtained through several routes including inhalation, transepidermal absorption, dietary intake, use of medications, and medical procedures. The uptake, distribution, and effect of these exposures vary depending on the iodine isotope and the population of interest. These points are discussed below.

Inhalation Exposures. Inhalation exposure of the general population to iodine through inhalation represents an intake pathway. Normal human respiratory exposure to iodine has been estimated to be 5 μg/day from an atmospheric exposure of 0.7 $\mu g/m^3$ (FDA 1974). Uptake of ^{129}I through inhalation is a minor pathway for human intake of this radioisotope. It is has been calculated that approximately $4x10^{-5}$ g/year of ^{129}I is taken up by the average individual (USNRC 1979).

Epidermal Exposures. Iodine vapor can penetrate through the skin. Iodine penetration through the epidermis was measured under controlled conditions in which volunteers were exposed to various concentrations of ^{131}I in the air ($3.1–350x10^{-10}$ Ci/L or 11–1,300 Bq/L) (Gorodinskii et al. 1979). Entry of ^{131}I through inhalation was prevented through the use of a specially designed head mask connected to a clean air supply line. Penetration of ^{131}I through the epidermis was monitored by ^{131}I uptake in the thyroid ($3.1–303x10^{-10}$ Ci or 11–1,100 Bq), as measured by a scintillation sensor. K values were calculated to compare the uptake of ^{131}I in the thyroid (A_m) versus the ^{131}I concentration in the air (C), where $K=A_m$ (Ci)/C (Ci/L). The K values varied between 0.7 and 2.9, indicating individual variations in iodine penetration through the skin and uptake of iodine into the thyroid. The results of this study also suggest that the value A_m after a 4-hour exposure to iodine vapor can be approximated using the relationship $A_m=3C$. A comparison of the penetration of iodine through the skin to the penetration of iodine through the lungs in previous work shows that entrance of iodine through the skin is 1–2% of its entrance through the lungs.

Dietary Intake of Iodine. The average daily dietary intake of iodine varies considerably, depending on the diet. Vought and London found individual daily intakes of iodine to vary from 15 to as high as 1,540 μg iodine/day, with mean intakes varying from 64 to 379 μg/day (FDA 1974). The recommended dietary allowance for iodine is 0.150 mg/day for adults and adolescents (FDA 1989b).

Several studies have attempted to describe the daily intake of iodine as a function of diet and age grouping. Hospital diets were measured to have mean iodine intakes of 0.533 mg/day (range 0.274–

0.842 mg/day), 0.677 mg/day (range 0.595–0.713 mg/day), and 0.377 mg/day (range 0.246–0.506 mg/day) (Caplan et al. 1976; Pittman et al. 1969). One nursing home diet had an intake of 1.531 mg/day (Caplan et al. 1976). The daily iodine intake in children has also been measured: 8–15 years old (0.450 mg/day) (Trowbridge et al. 1975), 6-month-old infants (0.359 mg/day, range 0.182–0.576), 2-year-old children (0.435 mg/day, range 0.231–0.728), and 15–20-year-old males (0.527 mg/day, range 0.319–0.827) (Pennington et al. 1984).

Dietary iodine intakes have been examined among age groups and were measured to be (in mg/day): 6–11 months old (0.200), 2-year-old children (0.460), 14–16-year-old girls (0.420), 14–16-year-old boys (0.710), 25–30-year-old women (0.270), 25–30-year-old men (0.520), 60–65-year-old women (0.250), and 60–65-year-old men (0.340) (Pennington et al. 1986). The average daily iodine intake partitioned by food category (expressed as μg/day) for men and women in the age group 20–34 years old has also been reported and is shown in Table 6-5 (FDA 1974)

Drinking Water/Beverages. Human exposures to iodine through drinking water are typically too low to provide for significant uptake of iodine. Surface waters rarely exceed 5.0 μg iodine/L, except where waters are polluted with municipal waste stream effluent or urban run-off. In these cases, iodine concentrations can be as high as 8.7 μg/L (FDA 1974). Some beverages, such as beer and wine, have iodine contents in the ranges of 43–46 and 8–32 μg/kg, respectively, which could provide a significant amount of iodine to the diet, depending on the level of daily consumption of these beverages (FDA 1974).

In emergency, camping, or military uses of iodine to disinfect water supplies, iodine concentrations approach 8–16 mg/L (Zemlyn et al. 1981). Use of elemental iodine in the disinfecting of water, when improperly used, can lead to acute iodine toxicity. Tetraglycine hydroperoxide is more commonly used at a concentration of 8 mg/L to provide more accurate and reliable delivery of iodine to disinfect drinking water. Prolonged (>7 days) use of iodine as a water disinfectant can lead to mild impairment of thyroid function (Georgitis et al. 1993).

Food Exposures. The human diet is the major source of exposure to iodine for the general human population. Although marine seafoods typically contain the highest amount of iodine (160–3,200 μg/kg fresh basis, mean 660±180 μg/kg), they constitute only a small part of the American diet. The largest sources of iodine in the human diet come from vegetables (320±100 μg/kg), meat products (260±70 μg/kg), eggs (260±80 μg/kg), and diary products (130±10 μg/kg) (FDA 1974). The level of iodine in vegetables depends upon the type of plant (e.g., spinach has by far the highest content among

Table 6-5. Estimated Average Iodine Intake for Adults in the United States

Food category	Average daily consumption		Average daily iodine intake	
	Male (g/day)	Female (g/day)	Male (µg/day)	Female (µg/day)
Milk and milk products	397	269	51.6	35.0
Eggs	55	31	14.3	8.1
Meat and meat products	325	192	84.5	49.9
Seafood	14	9	9.2	5.9
Legumes	40	24	No data	No data
Grain and cereal products	12	81	12.2	8.1
Yellow and green vegetables	104	88	33.3	28.2
Other vegetables and fruits	96	56	3.8	2.2
Sugar and sweets	44	35	No data	No data
Beverages (excluding milk)	749	739	3.0	3.0
Estimated salt intake	3.42	3.42	142.0	142.0
Iodine in food as additives	No data	No data	100.1	100.1
Total			454.0	382.5

Source: FDA 1974

the common vegetables) and whether iodine was present in fertilizers. The content of iodine of eggs and milk (milk products) depends on the dietary intake of chickens and lactating cows. Eggs accumulate systemic iodine; however, systemic levels are controlled by the limit that is placed on the content of iodine in feed or water (12.5 mg/kg or liter). Similarly, the content of iodine in milk is dependent upon iodine intake, in addition to the seasonal climatological variables, level of milk production, and fullness of the mammary gland. One source of iodine in the cow's diet is the addition of potassium iodide to feed. However, the iodine content of milk varied between regions and even between individual farms. These variations were found to be caused, in part, by differences in the use of iodized salt blocks, exposures of cows to iodine in disinfectants, and the presence of iodine in sanitizers and veterinary medications (FDA 1974).

Food sources of iodine that have caused adverse effects in humans include water, seaweed, ground beef containing thyroid tissue, foods to which iodine was added as a supplement (iodized water, bread, salt), and milk that contained iodine resulting from feed supplements and iodophor disinfectants (FDA 1989b). For example, iodine in seaweed-based supplements was found to be 0.045–5.0 mg/dose (Norman et al. 1988). The value of 5.0 mg/dose is approximately 30 times higher than the RDA for iodine and 5 times higher than the value of 1.0 mg/day, where acute and chronic toxicities for iodine intake begin to be seen (Pennington 1990a). Outside of these sources of high dietary iodine, the average iodine content in various food groups (expressed as μg/kg wet weight) are: seafoods (660±180), vegetables (320±100), meat products (260±70), eggs (260±80), dairy products (130±10), bread and cereals (100±20), and fruits (40±20) (FDA 1974).

The iodine contained in milk can be readily transferred to milk products, such as cheeses and ice cream. Typically, milk has been shown to contain iodine at concentrations ranging from 0.100 to 0.770 mg/L (Pennington 1988). Cheeses containing levels as high as 425 μg/kg have been reported (FDA 1974). The high concentrations of iodine in milk and in some milk products are thought to be derived from the use of iodophor disinfectants and sanitizers in the practice of dairy farming and the processing of milk. As a topical disinfectant, the concentration of iodine in iodophors is 0.5–1.0% by weight. Iodophors with an iodine concentration of 0.001–0.0025% have been used to disinfect equipment and used in teat dips and udder washings. Teat dipping can increase the iodine content in milk by an average 174 μg/L (range, 55–353 μg/L). However, there is evidence that the major contributor to iodine content in milk is feed supplementation rather than the use of iodophors (FDA 1974).

Processed foods, such as breads, have also been shown to be a source of iodine in the human diet. Potassium iodate is used as a conditioner of bread dough by some, but not all, major bakeries. When used as a dough conditioner, a concentration of 1–2 μg iodide/g bread is typically obtained. Iodine content of fast food, ranging from McDonald's french fries to a filet-of-fish sandwich, varied between 20 and 84 μg/100 g total product, respectively (FDA 1974).

Food additives can also contribute to human iodine intake; table salt contains cuprous iodide and potassium iodide, alginic acid, and alginate salts that are used as emulsifiers, and stabilizers and thickeners that contain upwards of 9 mg/kg iodine, but may only constitute an average intake of 1 μg/person/day (FDA 1974). Iodized salt in the United States provides 0.076 mg iodine/g (0.418 mg per teaspoon) (FDA 1989b).

Distribution of Iodine in Human Tissues. Iodine concentrations in nonthyroid tissues of recently deceased individuals obtained from a healthy Chinese population have been assessed using neutron activation analysis techniques (Hou et al. 1997b). Typical intake of iodine in the Chinese diet averages between 94 and 169 μg/person/day (Hou et al. 1997a). The concentrations of iodine in five tissues, plus hair, averaged over 9–11 individuals (and expressed as ng/g wet weight tissue±1 SD) were: heart (46.6±14.9), liver (170±34), spleen (26±8.6), lung (33.3±10.6), muscle (23.5±14.3), and hair (927±528) (Hou et al. 1997b).

Exposures Through Medications/Medical Uses of Iodine. Human exposures to iodine may come from medications and vitamin supplements containing iodine in varying amounts. A survey of various pharmaceuticals found that of those tested, eight contained between 0.251 and 0.375 mg iodine per dose, with one containing 1.447 mg I/dose (Vought et al. 1972). The variation of iodine content could be attributed to the use of erythrosine (2,4,5,7-tetraiodofluorescein) as a red coloration (FDA 1974). Erythrosine can be metabolized in the digestive tract to liberate iodide, although the bioavailability of iodine from erythrosine may be only 2–5% (FDA 1989b). Some medications directly contain added potassium iodide or organic iodine compounds. For example, Lugol's solution that is used to treat thyrotoxicosis is a 5% solution of iodine solubilized in 10% potassium iodide. Other iodine-containing drugs (most commonly potassium iodide solutions) have been prescribed for their purported expectorant for action in asthma, bronchitis, cystic fibrosis, and chronic pulmonary obstructive disease; also, amiodarone is prescribed for heart arrhythmias (FDA 1989b). Topical application of iodine-containing medications and dietary supplements can increase iodine in breast milk in lactating women; use of

povidone iodine vaginal gel (50 mg/day for 6 days) increased iodine concentration in breast milk by 3–4 times (FDA 1989b).

Large exposures to iodine can be experienced during certain medical procedures (e.g., through the use of iodinated compounds as contrast agents in radiological imaging procedures). Iodine in oil is used in bronchograms, lymphangiograms, and for myelograms, and is excreted slowly, thus predisposing an individual to imbalances in iodine homoeostasis.

Radioiodine -^{131}I. The greatest periods of exposure to ^{131}I (and other radioiodine isotopes derived from nuclear fission) were during active nuclear testing in the years 1951–1958 and 1961–1962, the large quantities of fission products released from nuclear accidents such as Three Mile Island and Chernobyl, and the nuclear processing and waste facilities (e.g., Hanford, Washington; Aiken, South Carolina; Idaho Falls, Idaho). Human uptake of ^{131}I from environmental sources is largely through ingestion of contaminated food, with a smaller proportion obtained through inhalation (Straub et al. 1966; Wehmann 1963). The distribution of ^{131}I in food depends upon the time the isotope is produced, its presence in the environment, and the degree of contamination. Some potential dietary sources of ^{131}I include marine animals and plants, milk, and leafy vegetables (Straub et al. 1966).

The largest source of ^{131}I in the human diet is cow's milk. Approximately 70% of the ^{131}I that is consumed by a cow is absorbed into the thyroid, with about 1% found in milk (milk-to-plasma ratio of ^{131}I is 2:3) (Bustad et al. 1964; Lengemann and Comar 1964; Straub et al. 1966). The transfer of iodine is bi-directional, and the iodine appears to freely diffuse between mammary gland and plasma (Miller and Swanson 1963; Straub et al. 1966). ^{131}I exists in both the free inorganic form, as iodide, or bound to protein in milk. It has been determined that in cow's milk, 82–91% of the ^{131}I is in the free inorganic form, with 4.7–13% bound to protein and <0.1% associated with fat (Glassock 1954; Straub et al. 1966).

The occurrence and concentration of ^{131}I in milk is highly variable, depending on the locale and daily variations within a specific locale (Pennington 1990a). Due to meteorological conditions, a large proportion of ^{131}I from fallout is deposited on the ground through dry deposition processes, with a lesser amount deposited through wet deposition processes (i.e., precipitation) (Straub et al. 1966). The highest concentrations of ^{131}I in milk were observed shortly after atmospheric tests of nuclear weapons and accidental releases from nuclear reactors or fuel reprocessing facilities (Anderson et al. 1996a; Black et al. 1976; Cohn and Gusmano 1963; Kirchner 1994; Martin and Turner 1964; Tracy et al. 1989; Tubiana 1982; Voigt et al. 1989). The source of ^{131}I in cow's milk is derived mainly from the dry and wet

deposition (to a lesser extent uptake into plants from the soil) of ^{131}I onto grasses and other plants that are then consumed by dairy cows. A concentration of 1 μCi ^{131}I/kg (37 kBq ^{131}I/kg) of ^{131}I in pasture grass yields a ^{131}I concentration of 0.07 μCi ^{131}I/L (3 kBq ^{131}I/L) of milk (Voigt et al. 1989).

In cases of exposure to ^{131}I, the absorbed dose has been estimated in various tissues and whole body for the ingestion of 1 mCi (40 MBq) of ^{131}I. The values for the absorbed doses (expressed in cGy and based on the assumption of a 25% uptake of ingested ^{131}I into the thyroid) are: 0.48 (liver), 0.14 (ovary), 0.26 (bone marrow), 1.4 (gastric mucosa), 0.088 (testis), and 1,300 (thyroid), with a mean whole body dose of 0.71 cGy (Tubiana 1982).

The levels of ^{131}I in domestic and imported foods measured between 1987 and 1992 were found to be below the detection limit of the gamma-ray spectrometry method (<2 Bq/kg or <5 pCi/kg) (Cunningham et al. 1994). Detection and quantitation of ^{129}I is difficult due to the low energy of the beta (maximum energy=0.15 MeV) and gamma rays (0.04 MeV) that are emitted from this isotope. Concentration of ^{129}I in thyroid tissues increases the ability to detect this isotope, but a further limitation results from the low specific activity of the radioisotope (0.17 mCi/g or 6.3 MBq/g) (NCRP 1983). However, due to the steady-state levels of ^{129}I in the environment, there is a continual exposure of the general human population to this radioisotope through inhalation and intake through the diet. It has been estimated (AEC 1974) that a dose of approximately 0.2–0.5 mrem/year is delivered to the thyroid of an adult from ^{129}I, depending on diet. These estimates include the dose received through the inhalation of ^{129}I. For an infant, the doses to the thyroid from ^{129}I intake can vary between 0.15 and 0.4 mrem/year, depending on diet.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.8 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths,

sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children appear to be more susceptible to the development of thyroid cancers from the irradiation of thyroid by ^{131}I. Irradiation of the thyroid from a 1–2 Gy dose in Japanese A-bomb survivors and a 3.3 Gy dose in Marshall Islanders exposed to fallout results in a high incidence (factor of 2) of thyroid cancers in children under the age of 10 compared the exposed adult population (Tubiana 1982).

Of the iodine radioisotopes, ^{129}I poses the least risk to children with respect to thyroid irradiation. Even at a high thyroid content of 1 mCi (40 MBq) ^{129}I in 1 g of stable iodine, the dose to the thyroid in a 6-month-old infant would be 0.9 nGy/year as compared to a dose of 7.2 nGy/year in an adult thyroid. In comparison, ^{131}I can deliver much higher doses to the thyroid at lower environmental concentrations than those observed for ^{129}I, due to the higher specific activity of ^{131}I ($1.24x10^5$ Ci/g or 457 TBq/g; beta particle energies of 0.334 MeV [7.3%] and 0.606 MeV [89.9%]) versus ^{129}I (177 μCi/g or 6.55 MBq/g; beta particle energy of 0.154 MeV) (Chu et al. 1999; Robkin and Shleien 1995). For example, the annual consumption of milk containing ^{131}I at a concentration of 1–20 nCi/L (37–740 Bq/L) would result in a dose to the thyroid in children of between 0.005 and 0.1 cGy/year (Tubiana 1982). In comparison, similar concentrations of ^{129}I in milk would yield a thyroid dose of between 0.014 and 0.28 pGy/year, based on the specific activities and beta energies listed above. Breast milk is also a source of ^{131}I uptake in children. For example, concentrations of ^{131}I in breast milk measured in women exposed to nuclear weapons fallout ranged between 0.050 and 0.100 nCi/L (1.9 and 3.7 Bq/L), when the mean body burden of ^{131}I in these women was 0.060 nCi (2.2 Bq) (Cohn and Gusmano 1963).

Children (both 1 and 10 year olds) appear to have a similar fractional uptake of iodine in the thyroid (i.e., approximately 31%) of that found in adults. For newborns, however, the fractional uptake is approximately 70% at 2 days after birth, but quickly declines to values accepted for an adult by day 5. After the first few weeks, uptake changes very little with age. The estimated dietary intake of iodine in 1 year olds is 151 μg/day, and for 10 year olds, it is 184 μg/day. The percent turnover rates of iodine in the thyroid does change with age (expressed as d^{-1}) are: 0–4 years old (3.4±0.5), 4–8 years old (2.1±0.5), and 8–12 years old (0.84±0.36); this corresponds to 'apparent' half-lives of 20, 33, and 83 days, respectively. Iodine concentration in thyroid increases with age (expressed as μg/g): 1 year old (95), 2 years old (130), 4 years old (180), 10 years old (260), 16 years old (320), and adult (400) (Stather and Greenhalgh 1983).

In utero exposures of a human fetus to iodine radioisotopes with high specific activity (e.g., ^{131}I) have been assessed based on both the maternal intake of iodine radioisotopes and exposure to external radiation generated by these isotopes in the immediate environment. Iodine and its radioisotopes freely diffuse across the placenta and, as such, their levels within a fetus and the amniotic fluid will depend greatly on the concentration of iodine within the mother (Bašič et al. 1988; Dyer and Brill 1972; Etling et al. 1979; von Zallinger and Tempel 1998). Before 11 weeks of gestation, the thyroid is still undeveloped and does not actively take up iodine (Dyer and Brill 1972; von Zallinger and Tempel 1998). For example, the percent of iodine that is taken up by the thyroid in comparison to that contained in the total fetal tissues is quite low at a gestation age of 9–11 weeks (0.0002%), but increases after 11 weeks where the percentage becomes 0.001% for gestation ages between 13 and 15 weeks, and increases further to 0.002% between gestation ages of 16 and 22 weeks (Dyer and Brill 1972). A difference in placental transfer of iodine between the mother and fetus is also noted as a function of gestation time. The percentage of ^{131}I activity found in the fetus compared to the total activity within the mother at 11 weeks was 0.23%, but increased to 2.96% at 22 weeks due to the fact that the concentration of iodine in the fetal thyroid typically exceeds that of the maternal thyroid by 3–10 times (von Zallinger and Tempel 1998). Increases in the concentration of iodine in the fetus and amniotic fluid (6- to 90-fold increases) were observed in women exposed to topical iodine-containing medications (e.g., vaginal therapy with iodinated polyvinyl-pyrrolidine) or increased iodine intake in their diets (Etling et al. 1979). However, the uptake of iodine (measured by ^{131}I uptake) into the fetal thyroid (1.08 pCi/g or 0.0400 Bq/g) at a gestation time of 22 weeks is not significantly different from what is observed for the maternal thyroid (0.82 pCi/g or 0.030 Bq/g) (Beierwaltes et al. 1963).

Emission of ionizing radiation from iodine radioisotopes can also pose an exposure risk to the human fetus and the mother in occupations where the mother comes in contact with these isotopes. For example, fetal doses in imaging staff performing a whole body scan and/or therapy procedures for thyroid cancer patients using ^{131}I ranged between 6.7 and 9.0 μSv (Mountford and Steele 1995). Thus, restrictions on the exposure of pregnant women are 1.3 mSv to the maternal abdominal surface (corresponding to a 1.0 mSv dose to the fetus) (Mountford and Steele 1995).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Occupational Exposures (Medical Personnel, Laboratory Personnel, Personnel at Nuclear Power/Fabrication/Storage Facilities). Occupational exposures to airborne iodine can occur when iodine is used in the regular functions of the workplace. OSHA has set a limit for airborne iodine

concentrations in the workplace of 0.1 ppm. Exposures of workers to concentrations at or in excess of the OSHA limit can often occur. For example, at a plant that processes photo-polymer plates, most workers were exposed to an average concentration of iodine of 0.005 ppm, but were exposed to concentrations of 0.122–0.146 ppm when they were in the immediate proximity of the iodine holding tank or iodine applicator (Kim et al. 1981).

The USNRC has set Annual Limits of Intake (ALIs) for inhalation exposures to radioiodine in the workplace as specified in USNRC Regulations (10 CFR) (USNRC 2002). The ALIs are based on the annual intake of a particular radioisotope that would result in an effective dose equivalent of 5 mrems to an organ or tissue; in the case of radioiodine, the thyroid. For inhalation exposures, the ALI is derived from Derived Air Concentrations (DACs) that represent the concentration of radioiodine at which a "reference man" working 2,000 hours per year under light working conditions (inhalation rate of 1.2 m^3/hour) results in the intake of one ALI. The current ALIs for inhalation exposure based on the thyroid as the target organ are: ^{123}I, 6,000 μCi (DAC=$3x10^{-6}$ μCi/mL); ^{125}I, 60 μCi (DAC=$3x10^{-8}$ μCi/mL); and ^{131}I, 50 μCi (DAC=$3x10^{-8}$ μCi/mL).

Workers in the nuclear industry, especially in nuclear fuel reprocessing facilities, have the potential for chronic thyroid burdens of ^{131}I in addition to acute exposures from accidental releases. For example, in Indian workers, the doses from chronic ^{131}I exposures were found to be as high as 47.4–68.1 rem for thyroid and 0.024–0.047 rem for whole body (Raghavendran et al. 1978). In an acute exposure to ^{131}I in a steam leak at a nuclear power plant, the mean thyroid burden of ^{131}I in the exposed workers was 1.32 μCi (48.8 kBq) on the third day after the exposure; the ^{131}I burden decreased exponentially, falling below 0.027 μCi (1.0 kBq) on the 38th day (Bhat et al. 1973).

Internal contamination of medical personnel by ^{131}I can be a problem, especially under conditions where the release of iodine as a vapor can occur (Eadie et al. 1980; Luckett and Stotler 1980). Thyroid burdens of ^{131}I in medical personnel can typically average around 2,400 pCi (ranges of 35–18,131 pCi or 1.3–671.52 Bq) (Blum and Liuzzi 1967). Personnel working with ^{131}I could potentially receive up to 5 nCi (200 Bq) per mCi (40 Bq) handled. This means that persons handling therapeutic doses of ^{131}I could have activities of 0.1–1.0 μCi (~4,000–40,000 Bq) in their thyroids (Tubiana 1982). For the application of ^{131}I in nuclear medicine, it has been shown that the radiochemists and their support staff have yearly thyroid ^{131}I burdens of between 0.5–200 nCi (20–7,000 Bq) and 0.03–1.5 nCi (1–56 Bq), respectively (Jönsson and Mattsson 1998).

External exposures of medical personnel to radiation emitted from radioiodine have been assessed for both diagnostic and therapeutic applications of ^{131}I and ^{125}I. The dose rate per unit activity (μSv/h ▯ MBq) of ^{131}I has been determined for thyrotoxicosis, thyroid ablation, and thyroid cancer therapies as a function of distance from the patient. The dose rate as a function of distance is approximately the same for all three therapy regimens; 1.43 μSv/h ▯ MBq at 0.1 meter, 0.18 μSv/h ▯ MBq at 0.5 meter, and 0.07 μSv/h ▯ MBq at 1.0 meter (Mountford and O'Doherty 1999). Surgical implants of ^{125}I seeds in prostate brachytherapy have the potential for radiation exposures to the radiotherapist. However, in most instances when the implant procedure is performed properly, the dose rate is <1 μGy/mCi-hour (Liu and Edwards 1979).

Laboratory workers using ^{125}I are at risk for exposures to gamma- and x-rays to the hand. In a typical situation where 20 MBq (5 mCi) of ^{125}I from an unshielded source is used weekly (2 hours/week) throughout a year, a worker would receive a dose of approximately 225 mSv (22.5 rem), 3/10 of the recommended dose equivalent limit to the hands (de Groot 1979). Uptake of ^{125}I into the thyroid has also been shown to occur due to airborne radioiodine released from solutions or spills (Bogdanove and Strash 1975; Dunn and Dunscombe 1981; Krzesniak et al. 1979; Kwok and Hilditch 1982). Activity levels of 0.013–0.024 μCi (480–890 Bq) and 0.056–0.56 μCi (2,100–21,000 Bq) have been measured in the thyroid of a laboratory worker working with 1 and 5 mCi (40 and 200 MBq) of ^{125}I in the day's activities, respectively (Kivinitty et al. 1984). In a more general survey, it was found that 8% of laboratory technicians working with ^{125}I labeled materials had thyroid burdens of ^{125}I within 9–90 nCi (300–3,000 Bq). However, 33% of those individuals involved in the direct iodination of biomaterials and compounds with ^{125}I had thyroid burdens of 9–90 nCi (300–3,000 Bq) (Pomroy 1979).

Patients Undergoing Medical Treatment Involving Use of Iodinated Compounds. Patients undergoing treatment for hyperthyroidism and thyroid carcinoma typically receive between 10 and 150 mCi (370 and 5,500 MBq) of ^{131}I (Beierwaltes 1979). In addition to the radiation dose received by the thyroid from these loadings of ^{131}I, other tissue sites in the patient also receive a radiation dose, albeit a smaller dose. This is especially important when considering the impact that the radiation emitted from ^{131}I can have on bone marrow in a patient undergoing ^{131}I therapy to treat thyroid carcinomas. During these ^{131}I therapies, the bone marrow can receive a dose of 1–5 Gy (Tubiana 1982). This has been shown to lead to a 1% incidence of leukemia in these patients (Tubiana 1982).

There is also an exposure risk of a patient's immediate family to both the radiation and elemental ^{131}I that is emitted from the patient (Barrington et al. 1999). Patients are allowed to return home after the activity

of ^{131}I within them falls below 30 mCi (1.1 GBq). Due to differences in the excretion rate of radioiodine from patients, it is recommended that both biological clearance and physical decay be used in calculating the confinement time of a patient (Kaurin et al. 2000; North et al. 2001). However, the level of ^{131}I activity of 30 mCi (1.1 GBq) in a patient can produce an exposure rate to ionizing radiation (emitted in the decay of ^{131}I) of approximately 10 μGy/hour at a distance of 1 meter. Thus, family members are also at risk to exposures to ^{131}I that is emitted from the patients. The dose that a typical family member receives from a patient at home ranges between 0.17 and 126 μGy/day, as compared to the natural radiation background of 0.35 μGy/day (Jacobson et al. 1978). This can result in some family members exceeding the maximum allowable dose of mSv (1 mrem) per year. In another study, it was found that as many as 11% of children exposed to patients undergoing ^{131}I therapy exceeded the 1 mSv limit (Barrington et al. 1999). Activities of ^{131}I within the thyroids of family members of patients undergoing ^{131}I therapy were found to range from the detection limit of the measurement of 92–110,000 pCi, resulting in a dose of 4–1,330 mrem to the thyroid. Of special concern is the fact that the ^{131}I activity was highest in children (Jacobson et al. 1978).

A growing number of patients who are undergoing treatment for cancer are using alternative medicines and nutritional supplements (Cassileth 1999). It is believed that these alternative medicines and supplements will help to prevent the onset of a tumor, alleviate specific symptoms that are experienced as a consequence of their disease or treatment, or aid in the eradication of the tumor. The self administration of some of these alternative medicines and nutritional supplements can result in the intentional (e.g., elevated iodine intake to prevent breast cancer) or unintentional (e.g., when iodine is a natural component of a specific alternative medicine) elevation of the daily intake of iodine, especially when patients consume alternative medicines that contain salt water plants, such as kelp, or those individuals who take megavitamins or participate in orthomolecular therapy (Cassileth 1999). The amount of iodine intake will vary depending on the specific content of iodine in the supplement and the dosage, which could result in iodine intakes that approach toxic levels (e.g., >6 g/day). For most cancers, it is unclear what benefit increased iodine will have for the prognosis of the disease or how it can alter the incidence of a particular cancer (Cann et al. 2000; Cassileth 1999; Eskin 1970). However, there is evidence to suggest that elevated iodine intake, especially for populations where ambient iodine concentrations are low, can help to decrease the incidence of breast cancer and, in some cases, help to interfere with breast tumorogenesis (Cann et al. 2000; Eskin 1970).

Diseases/Predisposition to Iodine Toxicities. An increase in the availability of dietary iodine for a population may also cause difficulty in controlling Graves' disease with antithyroid drugs, decrease the

remission rates for those on antithyroid medication, and increase the dose of radioiodine required to induce euthyroidism (FDA 1989b). In the general population, between 0.2 and 33.3% of individuals develop goiter in response to excess iodine consumption, whereas an increase in the incidence of sensitivity or acute reactions was observed in <30% of individuals in the general population (FDA 1989b).

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of iodine and its radioisotopes is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of iodine and its radioisotopes.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Adequate pertinent data on the physical and chemical properties of iodine and its radioisotopes and compounds are available in the literature.

Production, Import/Export, Use, Release, and Disposal. Since iodine is not covered under Superfund Amendments and Reauthorization Acts (SARA), Title III, manufacturers and users are not required to report releases to the EPA. There is a lack of data on the release and disposal of iodine. There is a relatively good database on the release of radioiodine (Beals and Hayes 1995; DOE 1990, 1994; NCRP 1983; Patton and Cooper 1993), but only limited information is available on disposal and inventories of radioiodine in the disposal sites (DOE 1994).

Environmental Fate. The major source of iodine on terrestrial surfaces originates from the volatilization of iodine from the ocean surface. Adequate information is available pertaining to the chemical species and reactions that take place at and above the ocean surface that are responsible for the production of volatile forms of iodine (Cox et al. 1999; Filistovic and Nedveckait 1998; Vogt et al. 1999; Whitehead 1984). Further work is needed to examine the organisms and microbial metabolic processes that are responsible to the formation of alkyl iodides, as well as the exact contribution of alkyl iodides, molecular iodine, and spray to the introduction of iodine into the atmosphere. There is a good body of literature on the photochemical reactions of iodine, both in the gaseous phase and in/on particulates or water droplets (Cox et al. 1999; Filistovic and Nedveckait 1998; Moran et al. 1999; Vogt et al. 1999; Whitehead 1984). The factors that are responsible for the retention of iodine in soil have also been examined extensively (Fawcett and Kirkwood 1953; Jirousek and Pritchard 1971; Sheppard et al. 1995; Whitehead 1984). However, more work is needed to characterize the interactions of iodine with organic components, especially with respect to the mechanisms of the binding and release of iodine from these organic components. The environmental fate of ^{129}I and ^{131}I has been examined extensively (AEC 1974; DOE 1978a, 1986; USNRC 1979, 1981).

Bioavailability from Environmental Media. Adequate pertinent data for intake of iodine and radioiodine from inhalation, drinking water, and food intake are available (DOE 1993; NCRP 1983; USNRC 1979; Whitehead 1984).

Food Chain Bioaccumulation. Concentrations of iodine in freshwater and marine fish have been determined (Poston 1986). Concentrations of iodine in aquatic plants have also been ascertained (NCRP 1983). Although aquatic plants and fish concentrate iodine in their tissues, there is little evidence for bioaccumulation of iodine in the food chain. Iodine and radioiodine concentrations have been measured in foods, especially in the context of milk and the transfer of radioiodine through the soil-plant-cow-milk pathway (AEC 1974; Kirchner 1994; Tracy et al. 1989; Voigt et al. 1988, 1989). Although some information is available, more information is needed on the uptake of iodine from the soil into plants (Burte et al. 1991; Moiseyev et al. 1984; Whitehead 1984).

Exposure Levels in Environmental Media. Adequate pertinent data are available for current exposure of iodine in air, rainwater, surface water, groundwater, and soil (FDA 1974; Moran et al. 1999; USNRC 1979; Whitehead 1984; Yuita 1994a).

Exposure Levels in Humans. A good database exists for exposure levels of the general population to iodine and its radioisotopes in various food types and drinking water (Allegrini et al. 1983; Bruhn et al. 1983; Dellavalle and Barbano 1984; Kidd et al. 1974; Pennington et al. 1986), including exposure levels in milk (Pennington 1988). Information for the average daily intakes of iodine based on diet and age groupings is available (Caplan et al. 1976; Pennington et al. 1984, 1986). Information on occupational exposures is available, especially for exposure of medical personnel to ^{131}I and laboratory workers to ^{125}I (Blum and Liuzzi 1967; Bogdanove and Strash 1975; de Groot 1979; Dunn and Dunscombe 1981; Krzesniak et al. 1979; Kwok and Hilditch 1982; Mountford and O'Doherty 1999; Pomroy 1979; Tubiana 1982). However, exposure data are currently not available for individuals who come in contact with, work in, or live in the vicinity of, clandestine methamphetamine production laboratories. This information is especially needed due to the potential for acute and chronic exposures to iodine. Data exist for the distribution of iodine in human and fetal tissues, but more information is needed (Dyer and Brill 1972; Hou et al. 1997b; von Zallinger and Tempel 1998).

Exposures of Children. A good database exists for exposure levels of children to iodine and its radioisotopes in various environmental exposure pathways, including food types, drinking water, and especially milk and milk products (Cohn and Gusmano 1963; FDA 1974, 1989; Soldat 1976; Stather and Greenhalgh 1983; Tubiana 1982). Information for the average daily intakes of iodine for children based on age groupings is available (Pennington et al. 1984, 1986; Trowbridge et al. 1975). Information on *in utero* exposures to iodine and its radioisotopes is available (Bašič et al. 1988; Beierwaltes et al. 1963; Dyer and Brill 1972; Etling et al. 1979; Mountford and Steele 1995; von Zallinger and Tempel 1998). There is also some information on the exposure of children to ^{131}I, and the radiation that it emits, that occurs when children are in contact with, or in the vicinity of, individuals undergoing ^{131}I treatment (Barrington et al. 1999; Jacobson et al. 1978). However, more information is needed to adequately assess the risk of children to this exposure. Also, there will be a need to develop biomarkers to assess the low level exposures of children to ^{129}I. Improvements in analytical methods have provided an ability to detect the low concentrations of ^{129}I in tissues and, thus, given us an opportunity to reliably assess low level exposures of ^{129}I in children and adults. Yet, the development of biomarkers, such as the identification of DNA mutations that would be specifically formed as a consequence of ^{129}I exposure in a cell to monitor the possible biological effects of these low level exposures, have been lacking.

Child health data needs relating to susceptibility are discussed in Section 3.13.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for iodine were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. Iodine will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

Two studies are currently underway (FEDRIP 2000) to study the interaction of iodine with differing soil components and the effect of iodine intake on the underlying mechanisms contributing to autoimmune thyroiditis. In the first study, Dr. R.L. Jones, at the Department of Natural Resources and Environmental Sciences, University of Illinois, Urbana, Illinois, is conducting a study of iodine in Illinois soils. The objective of this work is to determine the concentrations of iodine in a group of selected surface soils so that estimates of iodine concentrations can be made for major soil areas in Illinois. Analysis of soils as a function of depth and soil type will identify proportions of iodine in organic matter, and iron and aluminum fractions with the objective of identify whether differences occur between soils because of differences in soil development and genesis.

In another study, conducted by Dr. Carol L. Burek at Johns Hopkins University, Baltimore, Maryland, work is underway to determine whether increased intake of iodine contributes to an increase in the incidence of autoimmune thyroiditis (AT). The researchers intend to show that increases in iodine intake lead to an increased level of a highly iodinated form of thyroglobulin protein. It is thought that this highly iodinated form of thyroglobulin can act as an auto-immunogen and may be responsible for the T-cell mediated auto-immune response that is targeted against the thyroid gland. Using the NOD mouse model, the researchers will examine whether increased doses of iodine lead to an increase in the incidence of AT in these mice. Once this is established, the researchers will examine whether this increased incidence in AT is accompanied by an increase in the levels of highly iodinated thyroglobulin protein and increased activity of T-cells against this potential auto-immunogen.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring iodine and its radioisotopes, their metabolites, and other biomarkers of exposure and effect to iodine and its radioisotopes. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

Entry of iodine and its radioisotopes into the human body can be gained through ingestion, inhalation, or penetration through skin (IAEA 1988; NCRP 1985). The quantities of iodine within the body can be assessed through the use of bioassays that are comprised of *in vivo* measurements and/or *in vitro* measurements. *In vivo* measurements can be obtained through techniques that directly quantify internally-deposited iodine using, for example, thyroid or whole body counters. These *in vivo* measurement techniques are commonly used to measure body burdens of iodine radioisotopes, but cannot be used to assess the stable isotope of iodine. Instead, *in vitro* measurements provide an estimate of internally deposited iodine (both the stable and radioactive isotopes), utilizing techniques that measure iodine in body fluids, feces, or other human samples (Gautier 1983). Examples of these analytical techniques are given in NCRP Report No. 87 (1987) and are also listed in Table 7-1.

7.1 BIOLOGICAL MATERIALS

7.1.1 Internal Iodine Measurements

In vivo measurement techniques are the most direct and widely used approach for assessing the burden of iodine radioisotopes within the body. The *in vivo* measurement of these radioisotopes within the body is performed with various radiation detectors and associated electronic devices that are collectively known as *in vivo* thyroid monitors or whole body counters, depending on the body site of interest. These

Table 7-1. Analytical Methods for Determining Iodine in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Sample purified on Dowex 1x8 resin column; dried resin fused with $NaOH/KNO_3$, dissolved in water; dry 0.5 mL aliquot on polythene sheet; irradiated, dissolved in water with iodine carrier; extracted with trioctylamine/xylene; back extracted with 1 N ammonia, precipitate as AgI_2	INAA (γ-ray spectrometry)	0.01 µg/L	94%	Ohno 1971
Urine	Sample digested in chloric acid; arsenious acid added and then submitted for automated analysis	As-Ce catalytic spectro-photometry	Between 0.01 and 0.06 µg per sample (0.02–0.50 mL sample volume)	96–97%	Benotti and Benotti 1963; Benotti et al. 1965
Thyroid	Powdered or fresh tissue digested with H_2SO_4; iodide converted to Al_2I_6, neutron irradiated; iodine precipitated with Pd	Neutron activation plus mass spectrometry	0.11–2.17 mg/g (range of measured values)	No data	Ballad et al. 1976, Boulos et al. 1973, Oliver et al. 1982b
Adipose tissue	Sample placed into polyethylene vials and neutron irradiated	INAA (γ-ray spectrometry)	1.4–8.6 µg/g	No data	EPA 1986
Non-thyroid tissues	Tissue samples lyophilized, sealed in polyethylene film, and irradiated with epithermal neutrons using a boron nitride shield	INAA (γ-ray spectrometry)	9.4–2,880 ng/g (range of measured values)	No data	Hou et al. 1997b

Table 7-1. Analytical Methods for Determining Iodine in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Tissues	Aqueous NaOH and $Na_2S_2O_5$ added to tissue homogenates; ashed; residue dissolved in water and then injected into an HPLC for the separation of components on a two-column system followed by quantitation of iodine by UV	HPLC with UV detection	0.07–1,060 µg/g (range of measured values)	87–97%	Andersson and Forsman 1997
Plasma (protein bound)	Protein precipitated by Somogyi's zinc sulfate reagent, digested in CrO_3, purified by distillation	As-Ce catalytic spectro-photometry	0.01 µg/mL	75–100% (0.01–0.05 µg/mL)	Barker 1948
Feces	Dried; pulverized; digested in HNO_3/HF; treated with HCl/HNO_3	ICP-AES	0.1 µg/mL	88–90%	Que Hee and Boyle 1988
Feces	Dried; pulverized; digested in chloric acid; arsenious acid added and then submitted for automated analysis	As-Ce catalytic spectro-photometry	Between 0.01 and 0.06 µg per sample (20–30 mg sample size)	97–101%	Benotti and Benotti 1963, Benotti et al. 1965
Milk, serum	Sample is mixed with acteonitrile (1:2), centrifuged; supernatant dried; dissolved in acetonitrile/water and a 1 mL aliquot derivatized with 2-iodosobenzoate in phosphate buffer containing 2,6-di-methylphenol	HPLC with UV detection	0.5 µg/L	97.6–102.4%	Verma et al. 1992
Milk, yogurt, cream	Sample incubated in two parts (v:v) methanol; filtered; 4 mL filtrated passed through Sep-Pak C_{18} cartridge; final 2 mL of eluate filtered; 100 µL aliquot analyzed by HPLC	HPLC with amperometric detection	25 µg/L	92–114%	Chadha and Lawrence 1990

Table 7-1. Analytical Methods for Determining Iodine in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Bread	Bread is dried; ground; treated with 2N Na_2CO_3 plus 1% $KClO_3$; dried; incinerated; dissolved; analyzed by the ceric arsenite reaction	As-Ce catalytic spectro-photometry	0.05 µg/g	No data	Sachs et al. 1972

As-Ce catalytic spectrophotometry = arsenious-ceric ion catalytic spectrophotometry; HPLC = high performance liquid chromatography; ICP-AES = inductively coupled plasma-atomic emission spectrometry; INAA = instrument neutron activated analysis; UV = ultraviolet/visible

radiation detectors commonly utilize sodium iodide (NaI), hyperpure germanium, and organic liquid scintillation detectors to measure the gamma rays and x-rays emitted from ^{125}I and ^{131}I.

The gamma-ray and x-ray photopeaks that are commonly used in the detection and quantification of these iodine radioisotopes are the 28 keV (0.0665 photons/transition) gamma-ray and/or the $K_{\alpha 1}$ (27.5 keV, 0.739 photons/transition), $K_{\alpha 2}$ (27.2 keV, 0.397 photons/transition), $K_{\beta 1}$ (31.0 keV, 0.140 photons/transition), and $K_{\beta 2}$ (31.7 keV, 0.043 photons/transition) x-rays for ^{125}I, and the 364 keV gamma-ray for ^{131}I (Jönsson and Mattsson 1998; Landon et al. 1980; Palmer et al. 1976). The third iodine radioisotope that is commonly encountered in the environment, ^{129}I, is difficult to quantify using *in vivo* monitoring and scanning techniques, due to its low specific activity (0.17 mCi/g), low abundance in the environment, and low energy β^- (150 keV) and gamma (40 keV) radiation (NCRP 1983).

Because approximately 20–30% of the iodine that enters the body is taken up by the thyroid gland, *in vivo* thyroid monitoring is preferably and reliably used for assessing ^{125}I and ^{131}I burdens in exposed individuals (Bartolini et al. 1988; Bhat et al. 1973; Blum and Liuzzi 1967; Jacobson et al. 1978; Jönsson and Mattsson 1998; Landon et al. 1980; Mandó and Poggi 1988; Nishiyama et al. 1980; Palmer et al. 1976; Plato et al. 1976; Pomroy 1979). As such, *in vivo* thyroid scanning techniques are routinely used to assess thyroid burdens of ^{125}I and ^{131}I in individuals with occupational exposures to these radioisotopes; for example, medical personnel, laboratory technicians, nuclear medicine staff, radiochemists, and personnel involved with nuclear fuel processing. The relatively low attenuation of the gamma rays emitted from ^{131}I by most tissues allows for whole body and thyroid scanning techniques to be used in quantifying this iodine radioisotope within an individual (Berg et al. 1987; Nishiyama et al. 1980). Attenuation of lower energy gamma-ray and x-ray emissions for ^{125}I through tissues is greater than what is observed for the higher energy ^{131}I gamma-ray. However, the position and close proximity of the thyroid at the base and surface of the neck helps to minimize the effect that attenuation can have on the detection and quantification of ^{125}I in the thyroid, as compared to deeper tissues.

Many configurations of the thyroid and whole body counter and scanning methods have been used for monitoring and quantifying thyroid iodine radioisotope burdens, ranging from unshielded, single-crystal field detectors to shielded, multi-detector scanning detectors (IAEA 1962, 1970, 1972, 1976, 1985; NCRP 1987; Palmer et al. 1976; Plato et al. 1976). The minimum detectable activity of these devices is typically around 30–300 pCi (1–10 Bq) for thyroid monitoring and approximately 2 nCi (70 Bq) for whole body scanners (Nishiyama et al. 1980; Palmer et al. 1976; Plato et al. 1976). Where appropriate, shielding of the room that houses the thyroid or whole body counter can be used to increase the detection sensitivity of

the equipment by minimizing background radiation. To further insure that internalized iodine radioisotopes are accurately measured, removal of external contamination with radioactive iodine or other gamma-emitting radioisotopes on the clothing or skin of the individual to be scanned is recommended (Palmer et al. 1976). Also, *in vitro* measurements of iodine (see Section 7.1.2) can be used in conjunction with *in vivo* thyroid monitoring when assessing individuals working with iodine radioisotopes, especially in the assessment of individuals who have experienced accidental or routine exposures to iodine radioisotopes (Bhat et al. 1973; Nishiyama et al. 1980).

Calibration of thyroid and whole body counting is achieved through the use of tissue-equivalent phantoms. These phantoms are constructed to mimic the shape and density of the anatomical structure using tissue equivalent materials such as water-filled canisters or masonite (Bhat et al. 1973; Jönsson and Mattsson 1998; Landon et al. 1980; Nishiyama et al. 1980; Palmer et al. 1976; Plato et al. 1976). An example of a neck phantom is a polyethylene or Lucite cylindrical container filled with water to approximate the dimensions and density of the neck (Jönsson and Mattsson 1998; Landon et al. 1980; Palmer et al. 1976; Plato et al. 1976). Radioiodine standards are measured either as point sources along the phantom or, more typically, dissolved within two water-filled polyethylene or glass tubes (1–2.5 cm in diameter by 5–7 cm in length) that are set at an appropriate distance apart to approximate the positioning of the two lobes of the thyroid glands in the base of the neck. The dimensions of the Lucite and polyethylene neck phantoms are varied to more accurately mimic the actual ranges of adult and children's neck sizes (Palmer et al. 1976; Plato et al. 1976; Pomroy 1979). Other types of modified thyroid-neck phantom models and whole body phantoms have been used to calibrate radioiodine measurements as well (Nishiyama et al. 1980). Comparisons of the actual counting rates obtained from the phantom and the known activity of the radioiodine standards are used to determine the efficiency of the counting technique and, thus, provide the basis for calibration.

Assessment of short- and long-term retention of iodine radioisotopes must take into account the turnover rate for radioiodine within the human body. For ^{125}I, the mean effective half-life within the body is 37–39 days (Bartolini et al. 1988; Landon et al. 1980); for ^{131}I, the mean effective half-life is 5–7.6 days (Bhat et al. 1973). These values are much less than the actual biological half-life of iodine (^{127}I) in the body of 96–138 days (Bartolini et al. 1988; Landon et al. 1980), due to the relatively short physical half-lives of these radioisotopes. For acute and chronic exposures to radioiodine, the estimates of radioiodine retention are best calculated from results of multiple thyroid or whole-body measurements. This is because of individual variability in thyroid uptake rates, excretion rates, and uncertainties in determining uptake of radioiodine through inhalation, ingestion, and the skin (Landon et al. 1980; Mandó and Poggi

1988). However, direct comparisons between laboratory studies of body burdens and clearance rates for specific radioisotopes can be complicated by the differing whole body measurement techniques, calibration methods, and methods used to account for normal background radiation counts used within the different laboratories.

7.1.2 External Measurements

In vitro analyses of iodine are routinely performed in situations where *in vivo* analyses cannot be obtained or in support of an *in vivo* monitoring program. Urine is the preferred sample for *in vitro* analyses of iodine, although other sample types, such as feces, tissue, blood, serum, and hair, can also be used on a more limited basis with good detection sensitivities that are typically on the order of <1 μg per sample (NAS 1974). Urine provides for an analysis of soluble iodine, fecal analysis can be used to assess the fraction of ingested iodine not absorbed by the gut, and tissue is used to assess whole or regional body burdens of iodine (NCRP 1987).

The *in vitro* analysis of the stable isotope of iodine, ^{127}I, in commonly acquired human samples (e.g., urine, tissue, feces) is performed by a number of methods that have the selectivity and/or sensitivity to measure iodine in biological matrices (Table 7-1). These methods include arsenious-ceric ion catalytic spectrophotometry, instrumental neutron activation analysis (INAA), inductively coupled plasma atomic emission spectrometry (ICP-AES), and high performance liquid chromatography/ultra-violet-visible detection techniques (Andersson and Forsman 1997; Barker 1948; Benotti and Benotti 1963; Benotti et al. 1965; Cornelis et al. 1975; EPA 1986; Hou et al. 1997b; Ohno 1971; Que Hee and Boyle 1988). The INAA and ICP-AES methods offer the greatest sensitivity for the detection of iodine in human samples (Table 7-1). An example of an application of INAA to the measurement of iodine in urine involves a prepurification of the urine sample to remove interfering ions, such as bromide, upon activation by neutrons (photopeaks are 0.45 MeV for ^{128}I and 0.55 MeV for ^{82}Br). The urine sample is first passed over Dowex 1X8 anion exchange resin, and then followed by the fusion of the washed and dried resin with $NaOH/HNO_3$. The fusion residue is dissolved in water with a 0.5 mL aliquot transferred to a polyethylene sheet and dried. The sample is then irradiated with neutrons, dissolved in a solution containing an iodide carrier, extracted with trioctylamine/xylene, back extracted first with 1 M sodium nitrate to remove bromine, and then back extracted into 1 N ammonia. From here, the iodine is precipitated as silver iodide, filtered, and analyzed by gamma-ray spectrometry (Ohno 1971).

For the *in vitro* analysis of the iodine radioisotopes, ^{125}I and ^{131}I, in human samples, there are a number of the analytical methods that can measure these radioisotopes directly in the samples without the requirement for an extensive sample preparation procedure (Table 7-2), as has been demonstrated for other radioisotopes (Gautier 1983). In the radiochemical analysis of radioiodine in urine, a 24-hour urine collection (approximately 2 L) is obtained followed by the transfer of a 1 L aliquot to a Marinelli beaker for counting in a gamma-ray spectrometer. This simple procedure offers high recoveries of 98% and the minimum detection sensitivity 100 pCi/L (3.70 Bq/L) that is required to evaluate individuals for exposures to ^{125}I and ^{131}I. Similar methods can also used for the analysis of these iodine radioisotopes in tissues, feces, blood, milk, and food (AOAC 1984; Baratta and Easterly 1989; Ekman et al. 1967; Gautier 1983).

For the quantification of ^{129}I, more sensitive methods are required than those described above for ^{125}I and ^{131}I (Table 7-2). One approach utilizes the transmutation of the ^{129}I isotope to another isotope that can be quantified using mass spectrometric techniques. For example, neutron activation of iodine extracted from thyroid tissues, followed by noble gas mass spectrometry analysis of the resulting xenon isotopes, has been used to measure ^{129}I and the $^{129}I/^{127}I$ ratio in these tissues (Boulos et al. 1973). This procedure uses the measurement of ^{126}Xe, ^{128}Xe, and ^{130}Xe isotopes that are formed in the decay of the iodine isotopes, ^{126}I, ^{128}I, and ^{130}I, to determine the amount ^{129}I and ^{127}I in tissue extracts (see below).

$$^{127}I(n,\gamma)^{128}I \rightarrow {}^{128}Xe \quad (\beta^-, \text{half-life} = 25 \text{ minutes})$$

$$^{127}I(n,2n)^{126}I \rightarrow {}^{126}Xe \quad (\beta^-, \text{half-life} = 13 \text{ days})$$

$$^{129}I(n,\gamma)^{130}I \rightarrow {}^{130}Xe \quad (\beta^-, \text{half-life} = 12.4 \text{ hours})$$

$$^{127}I(n,\gamma)^{128}I(n,\gamma)^{129}I(n,\gamma)^{130}I \rightarrow {}^{130}Xe \quad (\beta^-, \text{half-life} = 12.4 \text{ hours})$$

Both the ratio of $^{130}Xe/^{128}Xe$ and $^{130}Xe/^{126}Xe$ will be proportional to the ratio of $^{129}I/^{127}I$ in the extract. The method is able to provide a detection sensitivity that is sufficient to measure ^{129}I as low as 45 pg/g tissue and/or a ratio of $^{129}I/^{127}I$ of 10^{-10}. In those cases where INAA methods cannot be applied due to a large sample set size, availability of an appropriate reactor, the short half-life of the isotope of interest (e.g., ^{130}I), or the cost of activation, there are other techniques available to enhance the detection sensitivity for the ^{129}I isotope (Gabay et al. 1974). For example, preconcentration of ^{129}I using anion exchange methods in addition to purifying the sample of interfering materials has been used successfully to analyze samples containing low amounts of ^{129}I (Gabay et al. 1974, Table 7-2). Also, inductively coupled plasma-mass spectrometry (ICP-MS) methods have been used to quantify iodine in biological samples using differing sample preparation methods, including Schöniger combustion and extraction

Table 7-2. Analytical Methods for Determining Radioiodine in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Sample transferred to Marinelli beaker and counted	γ-Spectrometry with NaI detector	100 pCi/L (^{131}I)	98%	Gautier 1983
Thyroid	^{129}I counted directly in thyroid tissue	X-Ray spectrometry with HP Ge detector	0.04 pCi/g (^{129}I)	No data	Van Middlesworth 1993
Thyroid	Powdered or fresh tissue digested with H_2SO_4; iodide converted to Al_2I_6; neutron irradiated, and iodine precipitated with Pd	Neutron activation and mass spectrometry	45 pg/g (^{129}I)	No data	Boulos et al. 1973; Oliver et al. 1982b
Thyroid and other tissues	Tissue sample were lyophiized and ground; pyrolyzed in O_2/N_2 stream; iodine absorbed onto charcoal; iodine liberated from charcoal by heating; isolated by distillation on cooled glass and then neutron irradiated	INAA with Ge(Li) γ-spectrometry	18–74 fCi/g (^{129}I)	85% (thyroid) 50–60% (other tissues)	Handl et al. 1990
Saliva	Saliva samples obtained and directly counted	Scintillation counter	1.26–36.5 nCi/mL (range of measured values) (^{125}I)	No data	Nishizawa et al. 1985
Feces	Sample directly counted in detector	γ-Spectrometry with NaI detector	0.14 nCi/L (^{131}I)	No data	Lipsztein et al 1991
Cow's milk	Sample (50–100 mL) directly counted in iron shielded gamma spectrometer	γ-Spectrometry with NaI detector	4–100 pCi/L (range of measured values) (^{131}I)	No data	Ekman et al. 1967
Cow's milk	Conversion of iodine to iodide; concentrated on anion exchange resin; extracted through CCl_4, water, then toluene	Liquid scintillation counter	0.3 pCi/L (^{129}I)	58% raw milk, 80% pasteurized milk; with 30 mg iodine carrier	Gabay et al. 1974
Food	Food samples directly counted in gamma-ray spectrometer	γ-Spectrometry with NaI or Ge(Li) detector	0.05 pCi/g (^{131}I)	No data	Cunningham et al. 1989, 1994

HP = high purity; INAA = instrument neutron activation analysis

methods, providing limits of detection (50 and 0.3 ng/g, respectively) that are appropriate for performing trace analysis of iodine in a large number of environmental and biological samples (Gélinas et al. 1998).

Accuracy of *in vivo* and *in vitro* measurements of iodine and its radioisotopes is determined through the use of standard, certified solutions or radioactive sources with known concentrations or activities of iodine. National Institute of Standards and Technology (NIST) traceable standards for ^{125}I and ^{127}I can be obtained through a number of commercial sources. The primary source of certified iodine radioisotope standards is the NIST. Standard reference materials (SRM) for ^{129}I (SRM 4401LZ, 30MBq [0.8 mCi]) and ^{131}I (SRM 4949C, 17 kBq [0.45 μCi]) are available from NIST. SRMs are also available for ^{127}I measurements, including SRM 909 (serum), SRM 1486 (bone meal), SRM 1548 (mixed diet), SRM 1549 (nonfat milk powder), SRM 1846 (infant formula), and SRM 2383 (baby food).

7.2 ENVIRONMENTAL SAMPLES

There are two common approaches for measuring iodine radioisotopes in the environment. Iodine radioisotopes can either be measured directly in the field (*in situ*) using portable survey instruments or samples can be procured from the field and returned to the laboratory for quantification of iodine. However, quantification of the stable iodine isotope in environmental samples is generally conducted in the laboratory.

7.2.1 Field Measurements of Iodine

In situ measurement techniques are extremely useful for the rapid characterization of radionuclide contamination in the environment, such as soils, sediments, and vegetation, or when monitoring personnel for exposure to radionuclides. The measurement of gamma-ray-emitting radionuclides in the environment is conducted with portable survey instruments such as Gieger-Mueller detectors, sodium iodide scintillation detectors, and gamma-ray spectrometers. However, the use of gamma-spectrometers in field survey equipment is preferred for measuring ^{131}I in the field because of their selectivity and sensitivity (EML 1997). The energy and penetrance of the gamma-rays that are emitted during the decay of ^{131}I provides an advantage for assessing the level of iodine both on and below the surface using portable field survey instruments such as the gamma-ray spectrometer (EML 1997). These gamma-ray spectrometers are equipped with a high purity germanium detector that is able to resolve the 364 keV gamma-ray emitted from ^{131}I from the gamma-rays emitted from other radionuclides; for example, ^{40}K

(USNRC 1997). The concentration and distribution of ^{131}I that have been detected in the field will need to be determined by laboratory-based analyses of soil samples procured from the survey area.

7.2.2 Laboratory Analysis of Environmental Samples

Analytical methods for quantifying iodine and iodine radioisotopes in environmental samples (e.g., air, water, soil, biota, and food) are summarized in Tables 7-3 (^{127}I) and 7-4 (^{125}I, ^{129}I, and ^{131}I). The methods that are commonly used in the analysis of ^{127}I are based on instrument-based analytical techniques, such as spectrophotometry, electrochemistry, INAA, mass spectrometry (MS), and some colorimetric techniques. The analysis of ^{125}I, ^{129}I, and ^{131}I can be determined either as total mass or total activity, depending on the analytical technique that is used. Typically, radiochemical methods of analysis employing gamma-ray spectrometry and β-γ coincidence scintillation techniques are used to quantify ^{125}I and ^{131}I in environmental samples. However, more sensitive analytical techniques, such as INAA and MS, are typically required to analyze ^{129}I in environmental samples (Lindstrom et al. 1991; Stephenson and Motycka 1994). Neutron activation and mass spectrometric methods are especially useful, since the amount of ^{129}I in a sample is often expressed in proportion to amount of ^{127}I in the same sample (Muramatsu et al. 1985). For example, the mass spectrometry techniques that are utilized to measure iodine in samples, such as neutron activation-noble gas mass spectrometry or accelerator mass spectrometry, provide the ability to resolve the ^{127}I and ^{129}I isotopes in the quantitation step and also have the required sensitivity range to measure ratios of 10^{-10}–10^{-7} for $^{129}I/^{127}I$ in most environmental and biological samples (Gramlich and Murphy 1989; Schmidt et al. 1998).

The analysis of ^{127}I in air is based on the quantification of this isotope of iodine in its gaseous form (I_2) or within aerosols or particulates, either separately or combined (Dams et al. 1970; Gäbler and Heumann 1993; Kim et al. 1981; Sheridan and Zoller 1989; Tsukada et al. 1991). The concentration of gaseous iodine in air can be determined by passing a known volume of air through a tube containing activated charcoal, followed by extraction of the iodine from the charcoal and analysis by a number of techniques, including ion chromatography (Kim et al. 1981). Both the gaseous and particulate forms of iodine can be simultaneously assessed by passing a specified volume of air through a filtering device containing a series of filters with differing pore sizes and coatings (Gäbler and Heumann 1993; Tsukada et al. 1991). Both gaseous and particulate forms of iodine are trapped on the various filter stages, depending on the type of coating and pore size of the filter stage after a calibrated amount of air is pulled through the filters. For the analysis of ^{127}I on the filters, the filter is solvent extracted and the extracted iodine is analyzed by INAA (Sheridan and Zoller 1989; Tsukada et al. 1991), nondestructive neutron activation analysis (Dams

Table 7-3. Analytical Methods for Determining Iodine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Aerosol (ambient)	Aerosols collected using an Anderson cascade impactor; iodine separated from filters by ignition and adsorbed onto charcoal; extracted from charcoal using NaOH solution; acidified; extracted into CCl_4 as iodine; back extracted into dilute H_2SO_4 and precipitated as PdI_2, then neutron irradiated	INAA with Ge γ-ray detector	1.68–4.23 ng/m^3 (range of measured values)	No data	Tsukada et al. 1991
Air (ambient)	A known volume of air is passed through a multistage filter assembly; filters extracted in a heated $NaOH/Na_2SO_3$ solution containing $^{129}I^-$ as an internal standard; filtered; acidified; iodide precipitated as AgI; filtered; precipitate dissolved in aqueous NH_3 and analyzed	IDMS	0.02–0.024 ng/m^3 (for an average air volume of 70 m^3)	97–99%	Gäbler and Heumann 1993
Air (occupational)	A known volume of air is drawn into a glass tube containing 150 mg of charcoal; iodine extracted into 0.01 M Na_2CO_3 using an ultrasonic bath; filtered; injected into ion chromatograph	Ion chromato-graphy	0.45 µg/mL	101%	Kim et al. 1981
Water and waste water (EPA Method 345.1)	CaO added to sample; filtered; sodium acetate/acetic acid then bromine water added; excess bromine with sodium formate removed; KI and H_2SO_4, titrate added with phenylarsine oxide or sodium thiosulfate using starch indicator	Colorimetric	2–20 mg/L (range of measured values)	80–97% (at 4.1–21.6 mg/L)	EPA 1983
Water	Sample acidified with HCl; oxidized with H_2O_2 or $KMnO_4$; treated with $NaSO_3$ to remove excess oxidant; titrated with KIO_3	Spectrophoto-metry	25 µg/L–6.35 mg/L	-100% (at 0.13–6.35 mg/L)	Pesavento and Profumo 1985

Table 7-3. Analytical Methods for Determining Iodine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water (iodide)	Sample reacted with acidified $NaNO_2$; evolved iodine extracted into xylene; back extracted into 0.5 % aqueous ascorbic acid and analyzed at the emission intensity for iodine of 178.28 nm	ICP-AES	1.6 µg/L	97–102%	Miyazaki and Bansho 1987
Water (iodine species)	Samples divided and spiked with $^{129}I^-$ or $^{129}IO_3^-$; oxidized with UV or HNO_3/H_2O_2 (total I), or concentrated/ purified on an anion exchange column (I^-, IO_3^-; anionic organoiodine); samples are then reduced with Na_2SO_3 and precipitated as AgI	IDMS	0.5 µg/L (I^-) 0.1 µg/L (IO_3^-) 0.2 µg/L (anionic organoiodine) 0.05 µg/L (total iodine)	No data	Reifenhäuser and Heumann 1990
Drinking water	Sample separated on a Dionex AS12 analytical HPLC column; the eluted iodate reacted with acidified bromide in post-column reaction to form tribromide that is detected at 267 nm	HPLC with UV detection	0.05 µg/L	110–111% (at 0.5–2.0 µg/L)	Weinberg and Yamada 1997
Tap water	Sample acidified to 0.1 mN nitric acid + Hg^{+2} (as $Hg(NO_3)_2$) added to 300 µg/L; 20 µL aliquot injected into atomizer	Electrothermal atomic absorption spectrometry	3.0 µg/L	94.8–104.4% (at 5–20 µg/L)	Bermejo-Barrera et al. 1994
Fresh water (total iodine)	Iodine-iodide is directly measured in water sample	As-Ce catalytic spectrophoto-metry	0.1 µg/L	100%	Jones et al. 1982b
Fresh water (iodate)	Iodine-iodide is removed from sample through extraction into chloroform as ion-pair with tetraphenylarsonium cation	As-Ce catalytic spectrophoto-metry	0.1 µg/L	-100% (at 2 µg/L iodate)	Jones et al. 1982b
Fresh water	One liter sample is acidified with nitric acid; 5 mL sample is irradiated, filtered, and counted	INAA using Ge(Li) γ-spectrometry	0.20 µg/L	No data	Salbu et al. 1975
Drinking water (total iodine)	K_2CO_3 added to sample; centrifuged to remove precipitated alkaline earth metals; iodine measured by addition of nitric acid, NaCl, $NH_4Fe(SO_4)_2$ and KSCN	Spectrophoto-metry	0.2 µg/L	90–108%	Moxon 1984

Table 7-3. Analytical Methods for Determining Iodine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water (free iodide)	K_2CO_3 added to sample; centrifuged to remove precipitated alkaline earth metals; iodide measured by addition of reduced amounts of nitric acid, NaCl, $NH_4Fe(SO_4)_2$, and KSCN	Spectrophotometry	0.4 µg/L	89–109%	Moxon 1984
Fresh and sea waters	Samples directly injected onto a weakly anionic ion-exchange column for iodide analysis; iodate measured through reduction to iodide by ascorbic acid	HPLC with ion-selective electrode detector	2 µg/L	No data	Butler and Gershey 1984
Sea water and river water	Sample (neat or diluted) were treated with $HClO_4$, acetone, and $KMnO_4$; $KMnO_4$ reduced with oxalic acid, then treated with NaS_2O_3/chromic acid followed by extraction into benzene containing p-dichlorobenzene as an internal standard	GC-ECD	0.1 µg/L	No data	Maros et al. 1989
Sea water	Sample acidified with acetic acid; bromine vapor dissolved into sample; excess removed through volume reduction; titrated with iodate	Amperometric method	5 µg/L	98–112%	Barkley and Thompson 1960
Sea water (iodine)	Iodide in sample precipitated with $AgNO_3$; precipitate dissolved in acetic acid saturated with Br_2; filtered; filtrate reduced in volume; then reacted with starch solution and CdI_2	Spectrophotometry	0.025 µg/L	99% (at 10 µg/L iodine)	Tsunogai 1971
Sea water (iodate)	Iodide in sample precipitated with $AgNO_3$; iodate in fitrate is reduced to iodide with $NaSO_3/H_2SO_4$, acetic acid saturated with Br_2 added; filtered; filtrate reduced in volume; reacted with starch solution and CdI_2	Spectrophotometry	0.025 µg/L	No data	Tsunogai 1971

Table 7-3. Analytical Methods for Determining Iodine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sea water	Sample filtered and concentrated/purified on an AG1X4 anion exchange column; I^-, IO_3^-, and organic iodine were isolated preferentially isolated; neutron irradiated; iodide carrier added; treated with $NaNO_2$ in HNO_3; extracted into CCl_4; back extracted into a $KHSO_3$ solution and counted	INAA using Ge(Li) γ-spectrometry	0.2 µg/L	99.5% (post-irradiation recovery)	Hou et al. 1999
Sea water and brackish water	Sample treated with CaO; iodide oxidized with Br_2 in acetate buffer; excess Br_2 removed with sodium formate; iodate converted to iodine and titrated with NaS_2O_3 using starch indicator	Spectrophoto-metry	0.2–2,000 mg/L (range of measured values)	93.6–96.7% (at 12.1–1,375 mg/L)	ASTM 1995
Sea water and brackish water	Sample is acidified with HCl; iodide converted to iodine with KNO_2 and extracted into CCl_4; absorbance of iodine-CCl_4 measured at 517 nm	Spectrophoto-metry	0.2–2,000 mg/L (range of measured values)	100–108% (at 12.1–1,375 mg/L)	ASTM 1995
Sea water and brackish water	500 µL of sample diluted to 50 ml with water plus $NaNO_2$ solution; measured potential; quantitated using standard additions	Iodide selective electrode	1–2,000 mg/L (range of measured values)	102–109% (at 12.1–1,375 mg/L)	ASTM 1995
Brine and thermal waters	Sample treated with 14 N H_2SO_4 plus 3 M H_2O_2; extracted with CCl_4; back into 0.1 mM NaS_2O_3; then iodine/methylene blue ion pair extracted into 1,2-dichloro-ethane	Spectrophoto-metry	10 µg/L	68% (at 0.4 mM iodine)	Koh et al. 1988
Groundwater	Metals chelated with EDTA and iodate is directly measured; iodide can be indirectly measured through conversion to iodate by treatment with chlorine water	Single-sweep polarography	0.005 µg/L	No data	Whitnack 1975
Soil	Sample dried; sieved (7 mm diameter), ground; sieved (2 mm diameter); extracted with 2 N NaOH; arsenious acid added then submitted for automated analysis	As-Ce catalytic spectrophoto-metry	0.5 µg/g	No data	Whitehead 1979

Table 7-3. Analytical Methods for Determining Iodine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil, sediments, rock	Sample dried and pulverized; mixed with V_2O_5 and pyrohydrolyzed; evolved iodine dissolved in NaOH solution digested with acid	As-Ce catalytic spectrophoto-metry	0.05 µg/g (0.5 g sample size)	75–90%	Rae and Malik 1996
Coal and fly ash	<250 mg samples dried; irradiated with neutrons and then counted	INAA using Ge(Li) γ-spectrometry	0.6–1.8 µg/g (range of measured values)	No data	Germani et al. 1980
Vegetation	Sample prepared by microwave digestion using HNO_3/H_2O_2; treated with $Na_2S_2O_3$ or ascorbic acid solution to convert iodate to iodide	ICP-MS	100 pg/g	96–104%	Kerl et al. 1996

As-Ce catalytic spectrophotometry = arsenious-ceric ion catalytic spectrophotometry; GC-ECD = gas chromatography-electron capture detection; HPLC = high performance liquid chromatography; ICP-AES = inductively coupled plasma-atomic emission spectrometry; ICP-MS = inductively coupled plasma-mass spectrometry; IDMS = isotope dilution mass spectrometry; INAA = instrumental neutron activation analysis; UV detection = ultraviolet/visible detection

Table 7-4. Analytical Methods for Determining Radioiodine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (occupational)	Air samples drawn into a regulated, constant-flow air sampler for personnel monitoring at a flow rate off 2 L/minute for several periods of 2–7 minutes; air-borne iodine was trapped in a charcoal sampling tube, then counted	Scintillation counter with NaI detector	2 fCi/mL (^{131}I)	No data	Luckett and Stotler 1980
Aerosols (occupational)	Air drawn through a 25 mm cellulose nitrate/acetate filter at a constant flow rate of 2 L/minute; filter counted	Scintillation counter with NaI detector	5 fCi/mL (^{125}I) 0.3 fCi/mL (^{131}I)	No data	Eadie et al. 1980
Aerosols (ambient)	Aerosols were collected using an Anderson cascade impactor; filters removed from impactor and then neutron irradiated	INAA with Ge γ-ray detector	0.24–0.26 aCi/m^3 (range of measured values) (^{129}I)	No data	Tsukada et al. 1991
Water	Add iodide carrier and NaOCl to 4 L sample; stir; add $NH_2OH·HCl$ and $NaHSO_3$; stir; filter; extract through anion exchange resin; elute iodide with NaOCl; treat with HNO_3; extract with toluene and aqueous $NH_2OH·HCl$, back extract with aqueous $NaHSO_3$; precipitate iodide as CuI	γ-Spectrometry with Ge detector	<1 pCi/L (^{131}I)	No data	ASTM 1995
Drinking water	Iodate carrier added to sample and iodate reduced to iodide with $NaSO_3$; iodide precipitated with $AgNO_3$; AgI dissolved and purified with Zn powder and sulfuric acid; iodide reprecipitated as PdI_2	β-γ Coincidence scintillation system	0.1 pCi/L (^{131}I)	No data	EPA 1976, 1980

Table 7-4. Analytical Methods for Determining Radioiodine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water	Iodate carrier and tartaric acid are added to sample, HNO_3 added and sample distilled into NaOH solution; distillate acidified with H_2SO_4 and oxidized with $NaNO_2$; extracted into CCl_4; back extracted into $NaHSO_3$; and iodide reprecipitated as PdI_2	B-γ Coincidence scintillation system	0.1 pCi/L (^{131}I)	No data	EPA 1976
Fresh water	Conversion of iodine to iodide; concentrated on anion exchange resin; extracted with CCl_4, water, then toluene	Liquid scintillation counter	0.3 pCi/L (^{129}I)	74% with 30 mg iodine carrier	Gabay et al. 1974
Fresh water	Iodide carrier added to sample; treated with HCl and sodium metabisulfite; iodide concentrated on a strong anion exchange resin with iodine carrier; ^{125}I directly detected on resin	γ-Spectrometry with Ge(Li) detector and x-ray fluorescence for yield correction	30 pCi/L (^{125}I)	No data	Howe and Bowlt 1991
River water	Sample directly analyzed or concentrated on an anion exchange resin; eluted with nitric acid; analyzed, using indium as an internal standard	ICP-MS	0.5 pCi/L (^{129}I)	No data	Beals and Hayes 1995; Beals et al. 1992
Aqueous sample	Sample concentrated on a Dowex 1x8 anion exchange resin; resin pyrolyzed; iodine adsorbed onto activated charcoal; iodine removed by heating charcoal; neutron irradiated; iodine carrier added; iodine extracted into xylene; iodide precipitated with silver	INAA with Ge(Li) detector	3.8 fCi/L (^{129}I)	50%	Anderson 1978

Table 7-4. Analytical Methods for Determining Radioiodine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Iodide carrier was added to samples; treated with sodium hypochlorite, purified; reduced to isolate iodine and iodine precipitated as AgI; AgI was mixed with either a niobium or ultrapure silver metal binder and dried onto stainless-steel sample holders for analysis	AMS	<0.3 pg/g (^{129}I)	No data	DOE 1994; Elmore and Phillips 1987; Elmore et al. 1980
Water and waste water	Direct count of sample	γ-Spectrometry with Ge/Li detector	<2 pCi/L (^{131}I)	92–100% at 2–94 pCi/L	ASTM 1998
Treated sewage effluent	Sample directly counted in 3.5 L aluminum beaker	γ-Spectrometry with NaI(Tl) detector	No data (^{131}I)	No data	Sodd et al. 1975
Treated sewage (influent/effluent)	Sample counted directly or first concentrated on anion exchange column after reduction of iodine to iodide in sample; eluted with acid then counted	γ-Spectrometry with NaI(Tl) detector	180 pCi/L (direct count), 0.35 pCi/L (concentrated) (^{131}I)	No data	Prichard et al. 1981
Soil, sediments, vegetation	Sample dried; iodine extracted through combustion of soil in oxygen; iodine trapped onto charcoal after passage over hydrated manganese dioxide (HMD); neutron irradiated; Br removed through passage over HMD	INAA with Ge(Li) detector	5 aCi/g (^{129}I)	No data	Lindstrom et al. 1991; Lutz et al. 1984
Vegetables	Sample lyophilized; Na_2CO_3, NaCl, and ^{131}I (internal standard) added; dried and ashed; treated with MnO_2 and evolved iodine trapped in 0.1% $NaHSO_3$ containing iodide carrier	ICP-MS	1.4 pg/g (0.24 fCi/g) (^{129}I)	88%	Cox et al. 1992

Table 7-4. Analytical Methods for Determining Radioiodine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plants	Plant samples were lyophiized and ground; ^{125}I added as internal standard; sample was pyrolyzed in O_2/N_2 stream; iodine absorbed onto charcoal; iodine liberated from charcoal by heating; isolated by distillation on cooled glass and then neutron irradiated	INAA with Ge(Li) γ-spectrometry	18–74 fCi/g (^{129}I)	50–60%	Handl et al. 1990

AMS = accelerator mass spectrometry; ICP-MS = inductively coupled plasma-mass spectrometry; INAA = instrumental neutron activation analysis

et al. 1970), and isotope dilution mass spectrometry (Gäbler and Heumann 1993). Analysis of airborne ^{125}I, ^{129}I, and ^{131}I can also be performed using the filtering techniques described above, followed by a direct measurement by beta- or gamma-ray counting of these radioisotopes on the filter or within activated charcoal (Eadie et al. 1980; Luckett and Stotler 1980) or quantified with more sensitive techniques (^{129}I) such as INAA (Tsukada et al. 1991).

For the analysis of iodine in water, there is a broad array of sample preparation and detection methodologies that are available (see Tables 7-3 and 7-4). A number of methods can directly quantify iodine or its radioactive isotopes within a water sample using spectrophotometric, ion-selective electrodes, INAA, ICP-MS, polarography, or radiochemical techniques with minimal sample preparation and good detection sensitivities (0.1–2.0 µg/L for ^{127}I, <2 pCi/L [0.07 Bq/L] for ^{131}I) (ASTM 1995, 1998, Beals and Hayes 1995; Beals et al. 1992; Butler and Gershey 1984; Jones et al. 1982b; Prichard et al. 1981; Salbu et al. 1975; Sodd et al. 1975; Stephenson and Motycka 1994; Whitnack 1975). Some analytical methods provide for the analysis of total iodine in the sample as well as the various iodine species in water (e.g., I^-, I_2, IO_3^-, and organic iodine) (Reifenhäuser and Heumann 1990; Wong and Cheng 1998). However, poor or inconsistent recovery of some iodine species (e.g., I^- and IO_3^-) during the ion exchange stage of the sample preparation, which is due to both irreversible binding of these iodine species to some ion exchange resins and interference from dissolved organic carbon, often can limit the accuracy of these methods for determining iodine species in aqueous samples (Stephenson and Motycka 1994).

One of the more commonly used assays for analyzing iodine at µg/L concentrations in water can be done directly using the catalytic spectrophotometric method. In the assay, iodine acts as a catalyst in the reduction of the ceric ions [Ce(IV)] by arsenous ions [As(III)]:

$$2Ce(IV) + As(III) \xrightarrow{I^-} 2Ce(III) + As(V)$$

In the absence of iodine, the reaction is very slow (~35 hours), but is on the order of minutes in the presence of iodine. The changes in the reaction rate, as followed by the decay in the Ce(IV) absorbance at either 420 or 366 nm, are inversely proportional to the iodine concentration in the sample (Jones et al. 1982b; Lauber 1975; Truesdale and Smith 1975). This assay has been developed into an automated process offering the advantage of large sample batch analyses (Truesdale and Smith 1975).

However, like many of the methods that are used to quantify iodine, a number of interferences can affect the measurement of iodine by the catalytic spectrophotometric method, including background coloration,

turbidity, and compounds, such as Fe(II), that are capable of reducing Ce(IV) (Jones et al. 1982b; Truesdale and Smith 1975). Thus, methods have been developed that purify iodine by first extracting iodine into an organic solvent and then back extracting the iodine into an appropriate aqueous solution for As–Ce catalytic spectrophotometric analysis (Jones et al. 1982b; Whitehead 1979). Likewise, for most methods, there is often a need to preconcentrate, redox convert the various iodine species (e.g., I^-, I_2, IO_3^-), and/or isolate iodine or its radioisotopes from the sample in order to improve sensitivity or remove interfering species, as is illustrated in Tables 7-3 and 7-4. Newer techniques have been developed to improve the separate quantification of iodine species. An example is the use of ICP-MS to quantify iodide directly in the samples after filtering, whereas iodine is quantified as a vapor that is evolved from the sample following treatment of the sample with potassium nitrite in sulfuric acid. This approach provides a detection limit of 0.04 μg/mL and recoveries of 86.5–118.6% (Anderson et al. 1996b)

The quantity of iodine and its radioisotopes in soil, sediments, minerals, vegetation, and biota is determined using detection methods similar to those described above (Tables 7-3 and 7-4). Analysis of iodine in samples by spectrophotometry, electrochemistry, and MS requires some form of sample digestion, either treatment in acid or pyrolysis. For most methods, sample concentration or purification is required to remove interfering species and/or improve detection sensitivity.

In the quantification of ^{129}I in soil, mineral, and biological samples by the INAA method, improvements to the INAA method for determining ^{129}I have been developed to minimize the possible interferences that can occur from $^{133}Cs(n,\alpha)^{130}I$, $^{127}I(3n,\gamma)^{130}I$, $^{235}U(n,f)^{129}I$ as well as neutron capture by ^{128}Te and ^{130}Te. The presence of bromine within a particular sample also can interfere with the quantification of ^{129}I due to the higher activity of ^{82}Br, the small difference in the photopeak maxima for ^{129}I (0.45 MeV) and ^{82}Br (0.55 MeV) and chemical similarities for I and Br (Ohno 1971; Rook et al. 1975). Most of these interferences have been eliminated through the use of pre-irradiation separation step that involves the combustion of iodine from biological materials followed by the collection of iodine on activated charcoal (Rook et al. 1975). A post-irradiation step also has been developed using a electromagnetic mass separator with a hot cathode arc ion chamber source to separate and collect sample components within a specific mass range onto a aluminum foil for subsequent quantification by a β-γ coincidence analysis system (Rook et al. 1975).

The detection limits, accuracy, and precision of any analytical methodology are important parameters in determining the appropriateness of a method to quantify a specific analyte at the desired level of sensitivity within a particular matrix. The Lower Limit of Detection (LLD) has been adopted to refer to

the intrinsic detection capability of a measurement procedure (sampling through data reduction and reporting) to aid in determining which method is best suited for the required sample quantification (EML 1997; USNRC 1984). Several factors influence the LLD, including background counting-rates, size or concentration of sample, detector sensitivity, recovery of desired analyte during sample isolation and purification, level of interfering contaminants, and, particularly, counting time. Because of these variables, the LLDs between laboratories, utilizing the same or similar measurement procedures, will vary.

The accuracy of a measurement technique in determining the quantity of a particular analyte in environmental samples is greatly dependent on the reliability of the calibrating technique. Thus, the availability of standard, certified radiation sources with known concentrations of iodine and its radioisotopes are required in order to insure the reliability of the calibration methods and accuracy of iodine measurements in environmental samples. NIST traceable standards for ^{127}I can be obtained through a number of commercial sources. The primary source of certified iodine radioisotope standards is the NIST. Standard reference materials for ^{129}I (SRM 4401LZ, 30 MBq [0.8 mCi]) and ^{131}I (SRM 4949C, 17 kBq [0.45 μCi]) are available from NIST. SRMs are also available for ^{127}I measurements, including SRM 1515 (apple leaves), SRM 1547 (peach leaves), SRM 1566 (oyster tissue), SRM 1572 (citrus leaves), SRM 1573 (tomato leaves), SRM 1575 (pine needles), SRM 1577 (bovine liver), SRM 1632 (coal), SRM 1633 (fly ash), SRM 1643 (water), SRM 2704 (sediment), and SRM 2709 (soil).

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of iodine and its radioisotopes is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of iodine and its radioisotopes.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Analytical methods with satisfactory sensitivity and precision are available to determine the levels of iodine and its radioisotopes in human tissues and body fluids.

Exposure. Analytical methods with satisfactory sensitivity and precision are available to determine the exposure levels of iodine and its radioisotopes in human tissues and body fluids.

Effect. Analytical methods with satisfactory sensitivity and precision are available to determine the levels of effect for iodine and its radioisotopes in human tissues and body fluids.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods with the required sensitivity and accuracy are available for quantifying iodine, both total and isotopic, in environmental matrices (Tables 7-3 and 7-4). Knowledge of the levels of iodine in various environmental media, along with appropriate modeling (see Chapters 3 and 6), can be used to evaluate potential human exposures through inhalation and ingestion pathways.

Whether in the environment or in the human body, iodine radioisotopes will undergo radioactive decay to form a series of compounds that are also radioactive (see Chapter 3). Current analytical methods, such as mass spectrometry, have the necessary resolution and sensitivity to detect and quantify these decay products.

7.3.2 Ongoing Studies

Current research studies, as provided by a search of the Federal Research in Progress (FEDRIP) database, are looking at improvements in the resolution and sensitivity of gamma-ray scintillation spectrometers through the development of innovative scintillating materials. In the work proposed in the research grant entitled “Ultra-Compact Cesium Iodide - Mercuric Iodide Gamma-Ray Scintillation Spectrometer” (B.E. Patti, Principal Investigator), the investigators are working with CsI/HgI scintillation pairs to develop a room temperature gamma-spectrometer after having some preliminary success with the detection of the 660 keV gamma-ray from ^{137}Cs (4.58% FWHM) (FEDRIP 2000). In another study entitled “Bismuth

Iodide Crystal Growth" (L.A. Boatner, Principal Investigator), the investigators are working on developing techniques for growing bismuth iodide crystals for room temperature radiation detectors and testing these crystals for their efficiency and energy resolution characteristics (FEDRIP 2000).

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding stable iodine in air, water, and other media are summarized in Table 8-1. The regulations regarding radioactive iodine are summarized in Tables 8-2 and 8-3.

No MRLs were derived for inhalation exposure to stable or radioactive iodine. Oral MRLs of 0.01 mg/kg/day were derived for both acute- and chronic-duration exposures. No oral MRL was derived for intermediate-duration exposure.

The EPA has not classified iodine for human carcinogenicity, nor has the EPA derived reference concentrations (RfCs) or reference doses (RfDs) for stable or radioactive iodine (IRIS 2000).

Table 8-1. Regulations and Guidelines Applicable to Stable Iodine

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	STEL (ceiling)	0.1 ppm	ACGIH 2000
NIOSH	REL (ceiling) IDLH	0.1 ppm 2.0 ppm	NIOSH 2001
OSHA	PEL (ceiling)—general industry	0.1 ppm	OSHA 2001b 29CFR1910.1000
	PEL (ceiling)—construction industry	0.1 ppm	OSHA 2001a 29CFR1926.55
	PEL (ceiling)—shipyard industry	0.1 ppm	OSHA 2001c 29CFR1915.1000
b. Water			
EPA	Effluent limitation guidelines; inorganic chemicals manufacturing point source category for iodine production	Effluent reduction attainable by the application of BPT; no discharge of process wastewater pollutants to navigable waters	EPA 2001b 40CFR415.432
c. Food			
FDA	Drug products containing certain active ingredients offered over-the-counter for certain uses	Digestive aid and weight control drug product	FDA 2000a 21CFR310.545
	Drugs; recommended warning and caution statements—iodine and iodides (oral)	If a skin rash appears, discontinue use and consult physician	FDA 2000b 21CFR369.20
	Food additives permitted for direct addition to food for human consumption (as potassium iodide) Total amount for foods labeled without reference to age or physiological state	 225 μg	FDA 2000c 21CFR172.375
	Food additives permitted for direct addition to food for human consumption (as potassium iodide) Infants Children under 4 years of age Adults and children 4 or more years of age Pregnant or lactating women	 45 μg 105 μg 225 μg 300 μg	FDA 2000c 21CFR172.375
	Food labeling—RDI	150 μg	FDA 2001b 21CFR101.9

Table 8-1. Regulations and Guidelines Applicable to Stable Iodine

Agency	Description	Information	References
NATIONAL *(cont.)*			
FDA	Indirect food additives; sanitizing solutions	Aqueous solution used on food and dairy processing equipment and utensils	FDA 2000d 21CFR178.1010 (b)(40)
	Nutrients—minimum amount per 100 kilocalories	5.0 μg	FDA 2001a
	Nutrition labeling of dietary supplements		FDA 2000e 21CFR101.36
	Nutritional quality guidelines RDI[a] Amount per 100 calories[b]	 150 μg 7.5 μg	FDA 2000f 21CFR104.20 (d)(3)
	Trace minerals added to animal feeds—calcium iodate, calcium iodobehenate, cuprous iodide, 3,5-diiodosalicylic acid, ethylenediamine dihydroiodide, potassium iodate, potassium iodide, sodium iodate, sodium iodide, and thymol iodide	Recognized as safe when added at levels consistent with good feeding practice	FDA 2000i 21CFR582.80
d. Other			
ATF	List of denaturants authorized for denatured spirits		ATF 2001a 27CFR21.151
	List of products and processes using specially denatured alcohol and rum, and authorized formula		ATF 2001b 27CFR21.141
USC	List II chemical—regulated by the Attorney General as a chemical used in manufacturing a controlled substance		USC 2001 21USC802
STATE Regulations and Guidelines:			
a. Air			
Alaska	PEL (ceiling)	0.1 ppm	BNA 2001h
California	Airborne contaminant		BNA 2001h
	HAP		BNA 2001h
Hawaii	Air contaminant		BNA 2001h
Idaho	Toxic air pollutants OEL EL AAC (24-hour average)	 0.1 mg/m^3 $6.7x10^{-3}$ pounds/hour $5x10^{-3}$ mg/m^3	BNA 2001h
Michigan	Occupational air contaminant; maximum allowable concentrations	0.1 ppm	BNA 2001h
	Limits for air contaminants PEL (ceiling)	 0.1 ppm	BNA 2001h

Table 8-1. Regulations and Guidelines Applicable to Stable Iodine

Agency	Description	Information	References
STATE *(cont.)*			
Montana	Occupational air contaminant		BNA 2001h
	TLV	0.1 ppm	
New Hampshire	Regulated toxic air pollutant		BNA 2001h
	OEL	1 mg/m^3	
New Mexico	Toxic air pollutant and emissions		BNA 2001h
	OEL	0.1 ppm	
	Emissions	$6.67x10^{-2}$ pounds/hour	
New York	Exposure limits		BNA 2001h
	PEL (ceiling)	0.1 ppm	
Oregon	Air contaminant		BNA 2001h
	PEL (8-hour TWA)	0.1 ppm	
Texas	Airborne contaminant		BNA 2001h
Vermont	Hazardous air contaminant		BNA 2001h
	Hazardous air contaminants that cause short-term irritant effects		BNA 2001h
	Annual average	100 $\mu g/m^3$	
	Averaging time	8 hours	
	Action level	4.2 pounds/8 hours	
Washington	Toxic air pollutant and acceptable source impact levels	3.3 $\mu g/m^3$ per 24-hour average	BNA 2001h
b. Water			
Maine	Drinking water guideline—iodide ion	340 $\mu g/L$	HSDB 2001
Rhode Island	Water resources—toxic pollutant		BNA 2001h
c. Food		No data	
d. Other			
California	Hazardous substance list		BNA 2001h
Florida	Toxic substance in the workplace		BNA 2001h
Massachusetts	Oil and hazardous material list		BNA 2001h
Pennsylvania	Worker and Community Right-to-Know Act—hazardous substance list		BNA 2001h

[a]RDI for adults and children 4 or more years of age
[b]100 calories, based on 2,000 calorie intake as a daily standard

AAC = acceptable ambient concentrations; ACGIH = American Conference of Governmental Industrial Hygienists; ATF = Alcohol, Tobacco, and Firearms; BPT = best practicable control technology; BNA = Bureau of National Affairs; CFR = Code of Federal Regulations; EL = emissions level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HAP = hazardous air pollutant; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; NIOSH = National Institute of Occupational Safety and Health; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RDI = recommended daily intake; REL = relative exposure limit; STEL = short term exposure limit; TLV = threshold limit value; TWA = time weighted average; USC = United States Code

Table 8-2. Regulations and Guidelines Applicable to Radioactive Iodine

Agency	Description	Information		References
INTERNATIONAL Guidelines:				
IARC	Carcinogenicity classification	No data		
ICRP	Occupational recommended dose limits[a]; effective dose	20 mSv per year, averaged over defined period of 5 years[b]		ICRP 1991
	Annual equivalent dose			
	Lens of the eye	150 mSv		
	Skin[c]	500 mSv		
	Hands and feet	500 mSv		
	General population recommended dose limits[a]			ICRP 1991
	Effective dose	1.0 mSv per year[d]		
	Annual equivalent dose			
	Lens of the eye	15 mSv		
	Skin[c]	50 mSv		
	Hands and feet	No data		
NATIONAL Regulations and Guidelines:				
a. Air				
ACGIH	Effective dose			ACGIH 2000
	Any single year	50 mSv		
	Averaged over 5 years	20 mSv		
	Annual equivalent dose to			
	Lens of the eye	150 mSv		
	Skin	500 mSv		
	Hands and feet	500 mSv		
	Embryo-fetus exposures once the pregnancy is known			
	Monthly equivalent dose	0.5 mSv		
	Dose to the surface of women's abdomen (lower trunk)	2 mSv for the remainder of the pregnancy		
	Intake of radionuclide	1/20 ALI		
NIOSH	REL	No data		
USNRC	Occupational values—inhalation	ALI (μCi)	DAC[e] (μCi/mL)	USNRC 2001a 10CFR20, Appendix B
	^{120}I	$1x10^{4}$	$4x10^{-6}$	
	^{120m}I	$2x10^{4}$	$9x10^{-6}$	
	^{121}I	$5x10^{4}$	$8x10^{-6}$	
	^{123}I	$6x10^{3}$	$3x10^{-6}$	
	^{124}I	$3x10^{2}$	$3x10^{-8}$	
	^{125}I	$2x10^{2}$	$3x10^{-8}$	
	^{126}I	$1x10^{2}$	$1x10^{-8}$	
	^{128}I	$1x10^{5}$	$5x10^{-5}$	

Table 8-2. Regulations and Guidelines Applicable to Radioactive Iodine

Agency	Description	Information		References
NATIONAL *(cont.)*				
USNRC *(cont.)*	Occupational values—inhalation	ALI (μCi)	DAC[e] (μCi/mL)	USNRC 2001a
	^{129}I	$3x10^{1}$	$4x10^{-9}$	10CFR20,
	^{130}I	$2x10^{3}$	$3x10^{-7}$	Appendix B
	^{131}I	$2x10^{2}$	$2x10^{-8}$	
	^{132}I	$1x10^{4}$	$3x10^{-6}$	
	^{132m}I	$2x10^{4}$	$4x10^{-6}$	
	^{133}I	$9x10^{2}$	$1x10^{-7}$	
	^{134}I	$5x10^{4}$	$2x10^{-5}$	
	^{135}I	$4x10^{3}$	$7x10^{-7}$	
	Effluent concentrations (μCi/mL)			USNRC 2001a
	^{120}I	$2x10^{-8}$		10CFR20,
	^{120m}I	$3x10^{-8}$		Appendix B
	^{121}I	$7x10^{-8}$		
	^{124}I	$4x10^{-10}$		
	^{125}I	$3x10^{-10}$		
	^{126}I	$2x10^{-10}$		
	^{128}I	$2x10^{-7}$		
	^{129}I	$4x10^{-11}$		
	^{130}I	$3x10^{-9}$		
	^{131}I	$2x10^{-10}$		
	^{132}I	$2x10^{-8}$		
	^{132m}I	$3x10^{-8}$		
	^{133}I	$1x10^{-9}$		
	^{134}I	$6x10^{-8}$		
	^{135}I	$6x10^{-9}$		
OSHA	PEL (8-hour TWA)	No data		
b. Water				
USNRC	Effluent concentrations (μCi/mL)			USNRC 2001a
	^{120}I	$1x10^{-4}$		10CFR20,
	^{120m}I	$2x10^{-4}$		Appendix B
	^{121}I	$4x10^{-4}$		
	^{124}I	$2x10^{-6}$		
	^{125}I	$2x10^{-6}$		
	^{126}I	$1x10^{-6}$		
	^{128}I	$8x10^{-4}$		
	^{129}I	$2x10^{-7}$		
	^{130}I	$2x10^{-5}$		
	^{131}I	$1x10^{-6}$		
	^{132}I	$1x10^{-4}$		
	^{132m}I	$1x10^{-4}$		
	^{133}I	$7x10^{-6}$		
	^{134}I	$4x10^{-4}$		
	^{135}I	$3x10^{-5}$		
	Releases to sewers; monthly average concentration (μCi/mL)			USNRC 2001a 10CFR20,
	^{120}I	$1x10^{-3}$		Appendix B
	^{120m}I	$2x10^{-3}$		
	^{121}I	$4x10^{-3}$		
	^{124}I	$2x10^{-5}$		

Table 8-2. Regulations and Guidelines Applicable to Radioactive Iodine

Agency	Description	Information	References
NATIONAL *(cont.)*			
USNRC *(cont.)*	Releases to sewers; monthly average concentration (μCi/mL)		USNRC 2001a 10CFR20, Appendix B
	^{125}I	$2x10^{-5}$	
	^{126}I	$1x10^{-5}$	
	^{128}I	$8x10^{-3}$	
	^{129}I	$2x10^{-6}$	
	^{130}I	$2x10^{-4}$	
	^{131}I	$1x10^{-5}$	
	^{132}I	$1x10^{-3}$	
	^{132m}I	$1x10^{-3}$	
	^{133}I	$7x10^{-5}$	
	^{134}I	$4x10^{-3}$	
	^{135}I	$3x10^{-4}$	
c. Food			
FDA	Derived intervention level[f] (DIL; Bq/kg food) for ^{131}I in accidentally-contaminated human food	167	FDA 1998
	Sources of radiation used for food inspection; sealed units producing radiation (^{125}I)	Not more than 2.2 million electron volts	FDA 2000h 21CFR179.21
	Requirements regarding certain radioactive drugs (^{131}I)	Diagnosis of thyroid functions; thyroid scans; treatment of hyper-thyroidism and/or cardiac dysfunction; treatment of thyroid carcinoma	FDA 2000g 21CFR310.503
d. Other			
DOE	Radiation standards; DAC[g] for controlling radiation exposure to workers at DOE facilities[h](μCi/mL)		DOE 2001b 10CFR835, Appendix A
	^{120m}I	$9x10^{-6}$	
	^{120}I	$4x10^{-6}$	
	^{121}I	$7x10^{-6}$	
	^{123}I	$3x10^{-6}$	
	^{124}I	$3x10^{-8}$	
	^{125}I	$3x10^{-8}$	
	^{126}I	$1x10^{-8}$	
	^{128}I	$5x10^{-5}$	
	^{129}I	$4x10^{-9}$	
	^{130}I	$3x10^{-7}$	
	^{131}I	$2x10^{-8}$	
	^{132m}I	$4x10^{-6}$	
	^{132}I	$3x10^{-6}$	
	^{133}I	$1x10^{-7}$	
	^{134}I	$2x10^{-5}$	
	^{135}I	$7x10^{-7}$	

Table 8-2. Regulations and Guidelines Applicable to Radioactive Iodine

Agency	Description	Information		References
NATIONAL *(cont.)*				
DOE	Radiation standards; DAC[g] for workers from external exposure during immersion in contaminated atmospheric cloud (Ci/mL)			DOE 2001a 10CFR835, Appendix C
	^{122}I	$5x10^{-6}$		
	^{128}I	$5x10^{-5}$		
	^{132}I	$2x10^{-6}$		
	^{134}I	$1x10^{-6}$		
	^{135}I	$7x10^{-7}$		
	^{136}I	$1x10^{-6}$		
	Values for establishing sealed radioactive source accountability and radioactive material posting and labeling requirements			DOE 2001c 10CFR835, Appendix E
	^{125}I	$3.5x10^{2}$		
	^{129}I	$1.8x10^{2}$		
DOT	General requirements for shipments and packagings; A1 and A2 values for radionuclides	A1 (Ci)	A2 (Ci)	DOT 2001a 49CFR173.435
	^{123}I	6	162	
	^{124}I	0.9	24.3	
	^{125}I	2	54.1	
	^{126}I	0.9	24.3	
	^{129}I	Unlimited	Unlimited	
	^{131}I	0.5	13.5	
	^{132}I	0.4	10.8	
	^{133}I	0.5	13.5	
	^{134}I	0.3	8.11	
	^{135}I	0.3	13.5	
	Hazardous substance and reportable quantity (Ci)			DOT 2001b 49CFR171.101, Appendix A
	^{120}I	10		
	^{120m}I	100		
	^{121}I	100		
	^{123}I	10		
	^{124}I	0.1		
	^{125}I	0.01		
	^{126}I	0.01		
	^{128}I	1,000		
	^{129}I	0.001		
	^{130}I	1.0		
	^{131}I	0.01		
	^{132}I	10		
	^{132m}I	10		
	^{133}I	0.1		
	^{134}I	100		
	^{135}I	10		

Table 8-2. Regulations and Guidelines Applicable to Radioactive Iodine

Agency	Description	Information			References
NATIONAL *(cont.)*					
EPA	Annual possession quantities for environmental compliance (Ci/year)	Gas	Liquid/ Solid	Powder	EPA 2001a 40CFR61, Appendix E
	^{123}I	4.9×10^{-1}	4.9×10^{5}	4.9×10^{2}	
	^{124}I	9.3×10^{-3}	9.3×10^{3}	9.3×10^{0}	
	^{125}I	6.2×10^{-3}	6.2×10^{3}	6.2×10^{0}	
	^{126}I	3.7×10^{-3}	3.7×10^{3}	3.7×10^{0}	
	^{128}I	9.3×10^{0}	9.3×10^{6}	9.3×10^{3}	
	^{129}I	2.6×10^{-4}	2.6×10^{2}	2.6×10^{-1}	
	^{130}I	4.6×10^{-2}	4.6×10^{4}	4.6×10^{1}	
	^{131}I	6.7×10^{-3}	6.7×10^{3}	6.7×10^{0}	
	^{132}I	2.0×10^{-1}	2.0×10^{5}	2.0×10^{2}	
	^{133}I	6.7×10^{-2}	6.7×10^{4}	6.7×10^{1}	
	^{134}I	3.2×10^{-1}	3.2×10^{5}	3.2×10^{2}	
	^{135}I	1.2×10^{-1}	1.2×10^{5}	1.2×10^{2}	
	Release limits for containment[i]				BNA 2001e 40CFR191, Appendix A
	^{129}I	100 Ci			
	Reportable quantity (Ci)				BNA 2001f 40CFR302.4, Appendix B
	^{120m}I	100			
	^{120}I	10			
	^{121}I	100			
	^{123}I	10			
	^{124}I	0.1			
	^{125}I	0.01			
	^{126}I	0.01			
	^{128}I	1,000			
	^{129}I	0.001			
	^{130}I	1.0			
	^{131}I	0.01			
	^{132m}I	10			
	^{132}I	10			
	^{133}I	0.1			
	^{134}I	100			
	^{135}I	10			
	Carcinogenicity slope factors[j]				EPA 2002b
	Ingestion—lifetime excess total cancer risk/pCi				
	Water				
	^{122}I	No data			
	^{123}I	6.96×10^{-13}			
	^{125}I	2.54×10^{-11}			
	^{126}I	8.73×10^{-11}			
	^{129}I	1.48×10^{-10}			
	^{130}I	6.36×10^{-12}			
	^{131}I	4.55×10^{-11}			
	^{132}I	8.44×10^{-13}			
	^{133}I	1.44×10^{-11}			
	^{134}I	2.50×10^{-13}			
	^{135}I	3.05×10^{-12}			

Table 8-2. Regulations and Guidelines Applicable to Radioactive Iodine

Agency	Description	Information	References
NATIONAL *(cont.)*			
EPA *(cont.)*	Ingestion—lifetime excess total cancer risk/pCi		EPA 2002b
	Food		
	^{122}I	No data	
	^{123}I	2.05×10^{-12}	
	^{125}I	6.29×10^{-11}	
	^{126}I	2.48×10^{-10}	
	^{129}I	3.22×10^{-10}	
	^{130}I	1.88×10^{-11}	
	^{131}I	1.34×10^{-10}	
	^{132}I	2.34×10^{-12}	
	^{133}I	4.40×10^{-11}	
	^{134}I	6.44×10^{-13}	
	^{135}I	8.99×10^{-12}	
	Ingestion—lifetime excess total cancer risk/pCi		
	Soil		
	^{122}I	No data	
	^{123}I	1.96×10^{-12}	
	^{125}I	5.55×10^{-11}	
	^{126}I	2.31×10^{-10}	
	^{129}I	2.71×10^{-10}	
	^{130}I	1.80×10^{-11}	
	^{131}I	1.26×10^{-10}	
	^{132}I	2.22×10^{-12}	
	^{133}I	4.26×10^{-11}	
	^{134}I	5.96×10^{-13}	
	^{135}I	8.62×10^{-12}	
	Inhalation[k]—lifetime excess total cancer risk/pCi		
	^{122}I	No data	
	^{123}I	3.03×10^{-13}	
	^{125}I	1.06×10^{-11}	
	^{126}I	3.70×10^{-11}	
	^{129}I	6.07×10^{-11}	
	^{130}I	2.76×10^{-12}	
	^{131}I	1.95×10^{-11}	
	^{132}I	3.74×10^{-13}	
	^{133}I	6.25×10^{-12}	
	^{134}I	1.02×10^{-13}	
	^{135}I	1.34×10^{-12}	
	External exposure[l]—risk/year per pCi/g in soil		
	^{122}I	4.17×10^{-6}	
	^{123}I	5.10×10^{-7}	
	^{125}I	7.24×10^{-9}	
	^{126}I	1.96×10^{-6}	
	^{129}I	6.10×10^{-9}	
	^{130}I	9.67×10^{-6}	

Table 8-2. Regulations and Guidelines Applicable to Radioactive Iodine

Agency	Description	Information		References
NATIONAL *(cont.)*				
EPA *(cont.)*	External exposure[l]—risk/year per pCi/g in soil			EPA 2002b
	^{131}I	1.59×10^{-6}		
	^{132}I	1.06×10^{-5}		
	^{133}I	2.72×10^{-6}		
	^{134}I	1.24×10^{-5}		
	^{135}I	7.83×10^{-6}		
NCRP	Occupational exposures[m]			NCRP 1993
	Effective dose limits			
	Annual	50 mSv		
	Cumulative	10 mSv x age		
	Equivalent dose annual limits for tissues and organs			
	Lens of eye	150 mSv		
	Skin, hands, and feet	500 mSv		
	Public exposures (annual)			
	Effective dose limit, continuous or frequent exposure[m]	1.0 mSv		
	Effective dose limit, infrequent exposure[m]	5 mSv		
	Equivalent dose limits for tissues and organs[m]			
	Lens of eye	15 mSv		
	Skin, hands, and feet	50 mSv		
USNRC	ALI (μCi)—oral ingestion			USNRC 2001a
	^{120}I	8×10^{3}		10CFR20,
	^{120m}I	1×10^{4}		Appendix B
	^{121}I	3×10^{4}		
	^{123}I	3×10^{3}		
	^{124}I	2×10^{2}		
	^{125}I	1×10^{2}		
	^{126}I	7×10^{1}		
	^{128}I	6×10^{4}		
	^{129}I	2×10^{1}		
	^{130}I	1×10^{3}		
	^{131}I	9×10^{1}		
	^{132}I	9×10^{3}		
	^{132m}I	1×10^{4}		
	^{133}I	5×10^{2}		
	^{134}I	3×10^{4}		
	^{135}I	3×10^{3}		
	Byproduct material listing (Ci)	Column I[n]	Column II[o]	USNRC 2001b
	^{125}I	0.1	0.00	10CFR33.100,
	^{126}I	0.1	0.001	Schedule A
	^{129}I	0.1	0.01	
	^{131}I	0.1	0.001	
	^{132}I	10	0.1	
	^{133}I	1.0	0.01	
	^{134}I	10	0.1	
	^{135}I	1.0	0.01	

Table 8-2. Regulations and Guidelines Applicable to Radioactive Iodine

Agency	Description	Information			References
NATIONAL *(cont.)*					
USNRC	Individual monitoring ^{131}I	1.0 Ci			BNA 2001a 10CFR20.2206
	Laboratory testing and use ^{125}I and ^{131}I	≤10 μCi			BNA 2001b 10CFR32.71
	Packaging and transportation of radioactive material; determination of A1 and A2	A1 (Ci)	A2 (Ci)	Specific Activity	USNRC 2001c 10CFR71, Appendix A
	^{123}I	6.0	162	$1.9x10^6$	
	^{124}I	0.9	24.3	$2.5x10^5$	
	^{125}I	2.0	54.1	$1.7x10^4$	
	^{126}I	0.9	24.3	$8.0x10^4$	
	^{129}I	Unlimited	Unlimited	$1.8x10^4$	
	^{131}I	0.5	13.5	$1.2x10^5$	
	^{132}I	0.4	10.8	$1.0x10^7$	
	^{133}I	0.5	13.5	$1.1x10^6$	
	^{134}I	0.3	8.11	$2.7x10^7$	
	^{135}I	0.5	13.5	$3.5x10^6$	
	Quantities requiring consideration of the need for an emergency plan; ^{125}I and ^{131}I				BNA 2001c 10CFR30.72, Schedule C
	Release fraction	0.5%			
	Quantity	10 Ci			
	Standards for protection against radiation; quantities of licensed material requiring labeling (μCi)				BNA 2001d 10CFR20, Appendix C
	^{120m}I	1,000			
	^{120}I	100			
	^{121}I	1,000			
	^{123}I	100			
	^{124}I	10			
	^{125}I	1.0			
	^{126}I	1.0			
	^{128}I	1,000			
	^{129}I	1.0			
	^{130}I	10			
	^{131}I	1.0			
	^{132m}I	100			
	^{132}I	100			
	^{133}I	10			
	^{134}I	1,000			
	^{135}I	100			
	Waste classification Concentration of ^{129}I	0.08 Ci/m^3			USNRC 2001d 10CFR61.55
STATE Regulations and Guidelines:					
a. Air		No data			
b. Water					
Kentucky	Maximum groundwater contaminant level ^{131}I	3 pCi/L			BNA 2001h
c. Food		No data			

Table 8-2. Regulations and Guidelines Applicable to Radioactive Iodine

Agency	Description	Information		References
d. Other				
Arkansas	Licensing of radioactive materials; exempt concentrations (Ci/mL, solids are Ci/g)	Column 1[n]	Column 2[o]	BNA 2001h
	^{126}I	3×10^{-9}	6×10^{-4}	
	^{131}I	2×10^{-5}	1×10^{-8}	
	^{132}I	3×10^{-9}	7×10^{-5}	
	^{133}I	2×10^{-5}	2×10^{-7}	
	^{134}I	8×10^{-8}	1×10^{-3}	
California	Licensing of radioactive materials; Schedule C (μCi/mL)	Column 1[n]	Column 2[o]	BNA 2001h
	^{126}I	3×10^{-9}	2×10^{-5}	
	^{131}I	3×10^{-9}	2×10^{-3}	
	^{132}I	8×10^{-8}	6×10^{-4}	
	^{133}I	1×10^{-8}	7×10^{-3}	
	^{134}I	2×10^{-7}	1×10^{-3}	
Florida	Quantities requiring consideration of the need for an emergency plan; ^{125}I and ^{131}I			BNA 2001h
	Release fraction	0.5%		
	Quantity	10 Ci		
Indiana	Licensing of radioactive materials; Schedule A; exempt concentrations (μCi/mL)	Column 1[n]	Column 2[o]	BNA 2001h
	^{126}I	3×10^{-9}	2×10^{-5}	
	^{131}I	3×10^{-9}	2×10^{-3}	
	^{132}I	8×10^{-8}	6×10^{-4}	
	^{133}I	1×10^{-8}	7×10^{-3}	
	^{134}I	2×10^{-7}	1×10^{-3}	
Kansas	Licensing of sources of radiation; Schedule B; exempt quantities of radioactive material (μCi)			BNA 2001h
	^{123}I	100		
	^{125}I	1.0		
	^{126}I	1.0		
	^{129}I	0.1		
	^{131}I	1.0		
	^{132}I	10		
	^{133}I	1.0		
	^{134}I	10		
	^{135}I	10		
Louisiana	Standards for protection against radiation			BNA 2001h
	^{120m}I	100		
	^{120}I	10		
	^{121}I	100		

Table 8-2. Regulations and Guidelines Applicable to Radioactive Iodine

Agency	Description	Information	References
STATE *(cont.)*			
Louisiana *(cont.)*	Standards for protection against radiation		BNA 2001h
	^{123}I	10	
	^{124}I	0.1	
	^{125}I	0.01	
	^{126}I	0.01	
	^{128}I	1,000	
	^{129}I	0.001	
	^{130}I	1.0	
	^{131}I	0.01	
	^{132m}I	10	
	^{132}I	10	

[a]The limits apply to the sum of the relevant doses from external exposure in the specified period and the 50-year committed dose (to age 70 years for children) from intakes in the same period.
[b]With the further provision that the effective dose should not exceed 50 mSv in any single year. Additional restrictions apply to the occupational exposure of pregnant women.
[c]The limitation on the effective dose provides sufficient protection for the skin against stochastic effects. An additional limit is needed for localized exposures in order to prevent deterministic effects.
[d]In special circumstances, a higher value of effective dose could be allowed in a single year, provided that the average over 5 years does not exceed 1.0 mSv per year.
[e]DAC is the concentration of radioactive material in air and the time of exposure to that radionuclide, in hours. An NRC licensee may take 2,000 hours to represent one ALI, equivalent to a committed effective dose equivalent of 5 rems (0.05 sievert).
[f]The FDA-recommended Derived Intervention Level (DIL) for radionuclides of ^{131}I, is defined as the DIL for the most sensitive age group (1 year) that was calculated from the most limiting Protective Action Goal (PAG; 50 mSv committed dose equivalent to the thyroid).
[g]DAC for the radionuclides listed in Appendix A of 10CFR835, the airborne concentration that equals ALI divided by the volume of air breathed by an average worker for a working year of 2,000 hours (assuming a breathing volume of 2,400 m^3). For the radionuclides listed in Appendix C of 10CFR835, the air immersion DACs were calculated for a continuous, non-shielded exposure via immersion in a semi-infinite atmospheric cloud.
[h]Class D: approximate length of retention in the pulmonary region is less than 10 days.
[i]Release limit per 1,000 metric tons of heavy metal or other unit of waste.
[j]Radioactive slope factors calculated by EPA's Office of Radiation and Indoor Air (ORIA). Slope factors are central estimates in a linear model of the age-averaged, lifetime attributable radiation cancer incidence (fatal and nonfatal cancer) risk per unit of activity ingested, expressed as risk per picocurie (pCi).
[k]Inhalation slope factors are central estimates in a linear model of the age-average, lifetime attributable radiation cancer incidence (fatal and nonfatal cancer) risk per unit of activity inhaled, expressed as risk per picocurie (pCi).
[l]External slope factors are central estimates of the lifetime attributable radiation cancer incidence risk for each year of exposure to external radiation from photon-emitting radionuclides distributed uniformly in a thick layer of soil, expressed as risk/year per pCi per gram of soil.
[m]Sum of external and internal exposures but excluding doses from natural sources.
[n]Column 1: gas concentration
[o]Column 2: liquid and solid concentration

ACGIH = American Conference of Governmental Industrial Hygienists; ALI = annual limits on intake; BNA = Bureau of National Affairs; CFR = Code of Federal Regulations; DAC = derived air concentrations; DOE = Department of Energy; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; ICRP = International Commission on Radiological Protection; mSv = millisievert; NIOSH = National Institute of Occupational Safety and Health; NCRP = National Council on Radiation Protection; USNRC = U.S. Nuclear Regulatory Commission; OSHA = Occupational Safety and Health Administration; PAG = protective action guide; PEL = permissible exposure limit; REL = relative exposure limit; TLV = threshold limit value; TWA = time-weighted average

Table 8-3. Dose Coefficients[a] (e(50)) for Intakes of Iodine Radionuclides

Radionuclide	Half-life	f1[c]	Inhalation, 1μm AMAD[b] e(50)	Inhalation, 5μm AMAD e(50)	Ingestion e(50)
^{120}I	1.35/hour	1.0	1.0×10^{-10}	1.9×10^{-10}	3.4×10^{-10}
^{120m}I	0.883/hour	1.0	8.7×10^{-11}	1.4×10^{-10}	2.1×10^{-10}
^{121}I	2.12/hour	1.0	2.8×10^{-11}	3.9×10^{-11}	8.2×10^{-11}
^{123}I	13.2/hour	1.0	7.6×10^{-11}	1.1×10^{-10}	2.1×10^{-10}
^{124}I	4.18/day	1.0	4.5×10^{-9}	6.3×10^{-9}	1.3×10^{-8}
^{125}I	60.1/day	1.0	5.3×10^{-9}	7.3×10^{-9}	1.5×10^{-8}
^{126}I	13.0/day	1.0	1.0×10^{-8}	1.4×10^{-8}	2.9×10^{-8}
^{128}I	0.416/hour	1.0	1.4×10^{-11}	2.2×10^{-11}	4.6×10^{-11}
^{129}I	1.57×10^{7}/year	1.0	3.7×10^{-8}	5.1×10^{-8}	1.1×10^{-7}
^{130}I	12.4/hour	1.0	6.9×10^{-10}	9.6×10^{-10}	2.0×10^{-9}
^{131}I	8.04/day	1.0	7.6×10^{-9}	1.1×10^{-8}	2.2×10^{-8}
^{132}I	2.30/hour	1.0	9.6×10^{-11}	2.0×10^{-10}	2.9×10^{-10}
^{132m}I	1.39/hour	1.0	8.1×10^{-11}	1.1×10^{-10}	2.2×10^{-10}
^{133}I	20.8/hour	1.0	1.5×10^{-9}	2.1×10^{-9}	4.3×10^{-9}
^{134}I	0.876/hour	1.0	4.8×10^{-11}	7.9×10^{-11}	1.1×10^{-10}
^{135}I	6.61/hour	1.0	3.3×10^{-10}	4.6×10^{-10}	9.3×10^{-10}

[a]ICRP (1994a)
[b]ICRP (1994a) calculated inhalation dose coefficients for particles with AMAD of 1 or 5 μm.
[c]Fractional absorption factor used by ICRP (1994, Annexes E and F) to calculate effective dose coefficients.

ALI = annual limits on intake; AMAD = activity median average diameters; Ci = curies

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10. GLOSSARY

Some terms in this glossary are generic and may not be used in this profile.

Absorbed Dose, Chemical—The amount of a substance that is either absorbed into the body or placed in contact with the skin. For oral or inhalation routes, this is normally the product of the intake quantity and the uptake fraction divided by the body weight and, if appropriate, the time, expressed as mg/kg for a single intake or mg/kg/day for multiple intakes. For dermal exposure, this is the amount of material applied to the skin, and is normally divided by the body mass and expressed as mg/kg.

Absorbed Dose, Radiation—The mean energy imparted to the irradiated medium, per unit mass, by ionizing radiation. Units: rad (rad), gray (Gy).

Absorbed Fraction—A term used in internal dosimetry. It is that fraction of the photon energy (emitted within a specified volume of material) which is absorbed by the volume. The absorbed fraction depends on the source distribution, the photon energy, and the size, shape and composition of the volume.

Absorption—The process by which a chemical penetrates the exchange boundaries of an organism after contact, or the process by which radiation imparts some or all of its energy to any material through which it passes.

Absorption Coefficient—Fractional absorption of the energy of an unscattered beam of x- or gamma-radiation per unit thickness (linear absorption coefficient), per unit mass (mass absorption coefficient), or per atom (atomic absorption coefficient) of absorber, due to transfer of energy to the absorber. The total absorption coefficient is the sum of individual energy absorption processes (see Compton Effect, Photoelectric Effect, and Pair Production).

Absorption Coefficient, Linear—A factor expressing the fraction of a beam of x- or gamma radiation absorbed in a unit thickness of material. In the expression $I=I_o e^{-\mu x}$, I_o is the initial intensity, I the intensity of the beam after passage through a thickness of the material x, and μ is the linear absorption coefficient.

Absorption Coefficient, Mass—The linear absorption coefficient per cm divided by the density of the absorber in grams per cubic centimeter. It is frequently expressed as μ/ρ, where μ is the linear absorption coefficient and ρ the absorber density.

Absorption Ratio, Differential—Ratio of concentration of a nuclide in a given organ or tissue to the concentration that would be obtained if the same administered quantity of this nuclide were uniformly distributed throughout the body.

Activation—The process of making a material radioactive by bombardment with neutrons or protons.

Activity—The number of radioactive nuclear transformations occurring in a material per unit time (see Curie, Becquerel). The term for activity per unit mass of a radioactive element is specific activity.

Activity Median Aerodynamic Diameter (AMAD)—The diameter of a unit-density sphere with the same terminal settling velocity in air as that of the aerosol particle whose activity is the median for the entire size distribution of the aerosol.

Acute Exposure, Chemical—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Acute Exposure, Radiation—The absorption of a relatively large amount of radiation (or intake of a radioactive material) over a short period of time.

Acute Radiation Syndrome—The symptoms which taken together characterize a person suffering from the effects of intense radiation. The effects occur within hours or days.

***Ad libitum*—**Available in excess and freely accessible.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit surface area or per unit weight of organic carbon of a specific particle size in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)—See Distribution Coefficient

Alpha Particle—A positively charged particle ejected spontaneously from the nuclei of some radioactive elements. It is identical to a helium nucleus, i.e., 2 neutrons and two protons, with a mass number of 4 and an electrostatic charge of +2.

Alpha Track—The track of ionized atoms (pattern of ionization) left in a medium by an alpha particle that has traveled through the medium.

Annihilation (Positron-Electron)—An interaction between a positive and a negative electron in which they both disappear; their rest mass, being converted into electromagnetic radiation (called annihilation radiation) with two 0.51 MeV gamma photons emitted at an angle of 180E to each other.

Annual Limit on Intake (ALI)—The derived limit for the amount of radioactive material taken into the body of an adult worker by inhalation or ingestion in a year. It is the smaller value of intake of a given radionuclide in a year by the reference man that would result in a committed effective dose equivalent of 5 rem or a committed dose equivalent of 50 rem to any organ or tissue.

Atom—The smallest particle of an element that cannot be divided or broken up by chemical means. It consists of a central core called the *nucleus*, which contains *protons* and *neutrons* and an outer shell of *electrons*.

Atomic Mass (u)—The mass of a neutral atom of a nuclide, usually expressed in terms of "atomic mass units." The "atomic mass unit" is one-twelfth the mass of one neutral atom of carbon-12; equivalent to 1.6604×10^{-24} g.

Atomic Mass Number—See Mass Number.

Atomic Number—The number of protons in the nucleus of an atom. The "effective atomic number" is calculated from the composition and atomic numbers of a compound or mixture. An element of this atomic number would interact with photons in the same way as the compound or mixture. (Symbol: Z).

Atomic Weight—The weighted mean of the masses of the neutral isotopes of an element expressed in atomic mass units.

Attenuation—A process by which a beam from a source of radiation is reduced in intensity by absorption and scattering when passing through some material.

Attenuation Coefficient—The fractional reduction in the intensity of a beam of radiation as it passes through an absorbing medium. It may be expressed as reduction per unit distance, per unit mass thickness, or per atom, and is called the linear, mass, or atomic attenuation coefficient, respectively.

Auger Effect—The emission of an electron from the extranuclear portion of an excited atom when the atom undergoes a transition to a less excited state.

Background Radiation—The amount of radiation to which a member of the general population is exposed from natural sources, such as terrestrial radiation from naturally occurring radionuclides in the soil, cosmic radiation originating from outer space, and naturally occurring radionuclides deposited in the human body.

Becquerel (Bq)—International System of Units unit of activity and equals that quantity of radioactive material in which one transformation (disintegration) occurs per second (see Units).

Terabecquerel (TBq)—One trillion becquerel.
Gigabecquerel (GBq)—One billion becquerel.
Megabecquerel (MBq)—One million becquerel.
Kilobecquerel (kBq))—One thousand becquerel.
Millibecquerel (mBq)—One-thousandth of a becquerel.
Microbecquerel (µBq)—One-millionth of a becquerel.

Beta Particle—An electron that is emitted from the nucleus of an atom during one type of radioactive transformation. A beta particle has a mass and charge equal in magnitude to that of the electron. The charge may be either +1 or -1. Beta particles with +1 charges are called positrons (symbolized β^+), and beta particles with -1 charges are called negatrons (symbolized β^-).

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biologic Effectiveness of Radiation—See Relative Biological Effectiveness.

Biological Half-time—The time required for a biological system, such as that of a human, to eliminate by natural process half of the amount of a substance (such as a chemical substance, either stable or radioactive) that has entered it.

Biomagnification—The progressive increase in the concentration of a bioaccumulated chemical in organisms as that chemical is passed from the bottom to the top of the food web.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Body Burden, Chemical—The total amount of a chemical found in an animal or human body.

Body Burden, Radioactivity—The amount of radioactive material found in an animal or human body.

Bone Seeker—Any compound or ion which migrates in the body and preferentially deposits into bone.

Branching—The occurrence of two or more modes by which a radionuclide can undergo radioactive decay. For example, ^{214}Bi can undergo alpha or beta minus decay, ^{64}Cu can undergo beta minus, beta plus, or electron capture decay. An individual atom of a nuclide exhibiting branching disintegrates by one mode only. The fraction disintegrating by a particular mode is the "branching fraction" for that mode. The "branching ratio" is the ratio of two specified branching fractions (also called multiple disintegration).

Bremsstrahlung—X rays that are produced when a charged particle accelerates (speeds up, slows down, or changes direction) in the strong field of a nucleus.

Buildup Factor—The ratio of the radiation intensity, including both primary and scattered radiation, to the intensity of the primary (unscattered) radiation.

Cancer Effect Level (CEL)—The lowest dose of chemical or radiation in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Capture, Electron—A mode of radioactive decay involving the capture of an orbital electron by its nucleus. Capture from a particular electron shell, e.g., K or L shells, is designated as "K-electron capture" or "L-electron capture."

Capture, K-Electron—Electron capture from the K shell by the nucleus of the atom. Also loosely used to designate any orbital electron capture process.

Carcinogen—A chemical or radiation that is capable of inducing cancer.

Carcinoma—Malignant neoplasm composed of epithelial cells, regardless of their derivation.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Cataract—A clouding of the crystalline lens of the eye which obstructs the passage of light.

Ceiling Value—A concentration of a substance that should not be exceeded, even temporarily.

Charged Particle—A nuclear particle, atom, or molecule carrying a positive or negative charge.

Chronic Exposure—A long-term, continuous exposure to a chemical or radioactive material. For example, exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Collective Dose—The sum of the individual doses received in a given period of time by a specified population from exposure to a specified source of radiation. Collective dose is expressed in units such as man-rem and person-sievert.

Compton Effect—An attenuation process observed for x- or gamma radiation in which an incident photon interacts with an orbital electron of an atom to produce a recoil electron and a scattered photon whose energy is less than the incident photon.

Containment—The confinement of a chemical or radioactive substance in such a way that it is prevented from being dispersed from its container or into the environment, or is released only at a specified rate.

Contamination—Deposition of a stable or radioactive substance in any place where it is not desired.

Cosmic Rays—High-energy particulate and electromagnetic radiations that originate outside the earth's atmosphere and interact with the atmosphere to produce a shower of secondary cosmic rays.

Count (Radiation Measurements)—The external indication of a radiation-measuring device designed to enumerate ionizing events. It refers to a single detected event. The term “count rate” refers to the total number registered in a given period of time. The term is sometimes erroneously used to designate a disintegration, ionizing event, or voltage pulse.

Counter, Gas-flow Proportional (GPC)—An instrument for detecting beta particle radiation. Beta particles are detected by ionization of the counter gas which results in an electrical impulse at an anode wire.

Counter, Geiger-Mueller (GM counter)—Highly sensitive, gas-filled radiation-measuring device that detects (counts) individual photons or particulate radiation.

Counter, Scintillation—The combination of a crystal or phosphor, photomultiplier tube, and associated circuits for counting light emissions produced in the phosphors by ionizing radiation. Scintillation counters generally are more sensitive than GM counters for gamma radiation.

Counting, Cerenkov—Relatively energetic β-particles pass through a transparent medium of high refractive index and a highly-directional, bluish-white light ("Cerenkov" light) is emitted. This light is detected using liquid scintillation counting equipment.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Curie (Ci)—A unit of radioactivity. One curie equals that quantity of radioactive material in which there are 3.7×10^{10} nuclear transformations per second. The activity of 1 gram of radium is approximately 1 Ci.

Attocurie (aCi)—One-thousandth of a femtocurie (3.7×10^{-8} disintegrations per second).
Femtocurie (fCi)—One-billionth of a microcurie (3.7×10^{-5} disintegrations per second).
Megacurie (MCi)—One million curies (3.7×10^{16} disintegrations per sec).
Microcurie (μCi)—One-millionth of a curie (3.7×10^{4} disintegrations per sec).
Millicurie (mCi)—One-thousandth of a curie (3.7×10^{7} disintegrations per sec).
Nanocurie (nCi)—One-billionth of a curie (3.7×10^{1} disintegrations per sec).
Picocurie (pCi)—One-millionth of a microcurie (3.7×10^{-2} disintegrations per second).

Daughter Products—See Progeny and Decay Product

Decay Chain or Decay Series—A sequence of radioactive decays (transformations) beginning with one nucleus. The initial nucleus, the parent, decays into a daughter or progeny nucleus that differs from the first by whatever particles were emitted during the decay. If further decays take place, the subsequent nuclei are also usually called daughters or progeny. Sometimes, to distinguish the sequence, the daughter of the first daughter is called the granddaughter, etc.

Decay Constant (λ)—The fraction of the number of atoms of a radioactive nuclide which decay in unit time (see Disintegration Constant).

Decay Product, Daughter Product, Progeny—A new nuclide formed as a result of radioactive decay. A nuclide resulting from the radioactive transformation of a radionuclide, formed either directly or as the result of successive transformations in a radioactive series. A decay product (daughter product or progeny) may be either radioactive or stable.

Decay, Radioactive—Transformation of the nucleus of an unstable nuclide by spontaneous emission of radiation, such as charged particles and/or photons (see Disintegration).

Delta Ray—An electron removed from an atom of a medium that is irradiated, or through which radiation passes, during the process of ionization (also called secondary electron). Delta rays cause a track of ionizations along their path.

Derived Air Concentration (DAC)—The concentration of radioactive material in air that, if breathed by the reference man for a working year of 2000 hours under conditions of light work (at a rate of 1.2 liters of air per hour), would result in an intake of one ALI (see Annual Limit on Intake).

Deterministic Effect—A health effect, the severity of which varies with the dose and for which a threshold is believed to exist (also called a non-stochastic effect).

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical or radiation prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Disintegration Constant—Synonymous with decay constant. The fraction of the number of atoms of a radioactive material that decays per unit time (see Decay Constant.)

Disintegration, Nuclear—A spontaneous nuclear transformation (radioactivity) characterized by the emission of energy and mass from the nucleus. When large numbers of nuclei are involved, the process is characterized by a definite half-life (see Transformation, Nuclear).

Distribution Coefficient (K_d)—Describes the distribution of a chemical between the solid and aqueous phase at thermodynamic equilibrium, is given as follows:

$$K_d = \frac{[C]_s}{[C]_w}, \text{ Units = (L solution)/(kg solid),}$$

where $[C]_s$ is the concentration of the chemical associated with the solid phase in units of (mg)/(kg solid), and $[C]_w$ is the concentration of the chemical in the aqueous phase in units of (mg)/(L solution). As the magnitude of K_d decreases, the potential mobility of the chemical to groundwater systems increases and vice versa.

Dose—A general term denoting the quantity of a substance, radiation, or energy absorbed. For special purposes it must be appropriately qualified. If unqualified, it refers to radiation absorbed dose.

Absorbed Dose—The energy imparted to matter by ionizing radiation per unit mass of irradiated material at the place of interest. The unit of absorbed dose is the rad. One rad equals 100 ergs per gram. In SI units, the absorbed dose is the gray which is 1 J/kg (see Rad).

Cumulative Dose (Radiation)—The total dose resulting from repeated or continuous exposures to radiation.

Dose Assessment—An estimate of the radiation dose to an individual or a population group usually by means of predictive modeling techniques, sometimes supplemented by the results of measurement.

Dose Equivalent (DE)—A quantity used in radiation safety practice to account for the relative biological effectiveness of the several types of radiation. It expresses all radiations on a common scale for calculating the effective absorbed dose. The NRC defines it as the product of the absorbed dose, the quality factor, and all other modifying factors at the location of interest. ICRP has changed its definition to be the product of the absorbed dose and the radiation weighting factor. (The unit of dose equivalent is the rem. In SI units, the dose equivalent is the sievert, which equals 100 rem.)

Dose, Fractionation—A method of administering therapeutic radiation in which relatively small doses are given daily or at longer intervals.

Dose, Protraction—A method of administering therapeutic radiation by delivering it continuously over a relatively long period at a low dose rate.

Dose, Radiation—The amount of energy imparted to matter by ionizing radiation per unit mass of the matter, usually expressed as the unit rad, or in SI units, the gray. 100 rad ' 1 gray (Gy) (see Absorbed Dose).

Committed Dose Equivalent ($H_{T,50}$)—The dose equivalent to organs or tissues of reference (T) that will be received from an intake of radioactive material by an individual during the 50 years following the intake.

Committed Effective Dose Equivalent ($H_{E,50}$)—The sum of the products of the weighting factors applicable to each of the body organs or tissues that are irradiated and the committed dose equivalent to those organs or tissues.

Effective Dose—A dose value that attempts to normalize the detriment to the body (for cancer mortality and morbidity, hereditary effects, and years of life lost) from a non-uniform exposure to that of a uniform whole body exposure. Effective dose is calculated as the sum of products of the equivalent dose and the tissue weighting factor (w_T) for each tissue exposed. ($E = \sum D_{T,R}\ w_R\ w_{T)}$).

Effective Dose Equivalent (H_E)—This dose type is limited to internal exposures and is the sum of the products of the dose equivalent to the organ or tissue (H_T) and the weighting factors (w_T) applicable to each of the body organs or tissues that are irradiated. ($H_E = \sum w_T\ H_T$).

Equivalent Dose—A dose quantity that places the biological effect of all radiation types on a common scale for calculating tissue damage. Alpha particles, for example, are considered to cause 20 times more damage than gamma rays. Equivalent dose is calculated as the sum of products of the average absorbed dose (in gray) in an organ or tissue ($_{DT,R}$) from each type of radiation and the radiation weighting factor (w_R) for that radiation ($\sum D_{T,R}\ w_R$).

External Dose—That portion of the dose equivalent received from radiation sources outside the body.

Internal Dose—That portion of the dose equivalent received from radioactive material taken into the body.

Limit—A permissible upper bound on the radiation dose.

Maximum Permissible Dose (MPD)—The greatest dose equivalent that a person or specified part thereof shall be allowed to receive in a given period of time.

Median Lethal Dose (MLD)—Dose of radiation required to kill, within a specified period (usually 30 days), 50% of the individuals in a large group of animals or organisms. Also called the LD_{50}, or $LD_{50/30}$ if for 30 days..

Threshold Dose—The minimum absorbed dose that will produce a detectable degree of any given effect.

Tissue Dose—Absorbed dose received by tissue in the region of interest, expressed in rad (see Dose, Gray, and Rad).

Dose Rate—The amount of radiation dose delivered per unit time. Generically, the rate at which radiation dose is delivered to any material or tissue.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Dosimetry—Quantification of radiation doses to cells, tissues, organs, individuals or populations resulting from radiation exposures.

Early Effects (of radiation exposure)—Effects that appear within 60 days of an acute exposure.

Electron—A stable elementary particle having an electric charge equal to $\pm 1.60210 \times 10^{-19}$ C (Coulombs) and a rest mass equal to 9.1091×10^{-31} kg. A positron is a positively charged "electron" (see Positron).

Electron Volt—A unit of energy equivalent to the energy gained by an electron in passing through a potential difference of one volt. Larger multiple units of the electron volt are frequently used: keV for thousand or kilo electron volts; MeV for million or mega electron volts (eV). $1\ eV = 1.6 \times 10^{-12}$ erg.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Energy—Capacity for doing work. Gravitationally, "potential energy" is the energy inherent in a mass because of its spatial relation to other masses. Chemically or radiologically, “potential energy” is the energy released when a chemical reaction or radiological transformation goes to completion. "Kinetic energy" is the energy possessed by a mass because of its motion (SI unit: joules):

> **Binding Energy (Electron)—**The amount of energy that must be expended to remove an electron from an atom.
>
> **Binding Energy (Nuclear)—**The energy represented by the difference in mass between the sum of the component parts and the actual mass of the nucleus. It represents the amount of energy that must be expended to break a nucleus into its component neutrons and protons.
>
> **Excitation Energy—**The energy required to change a system from its ground state to an excited state. Each different excited state has a different excitation energy.
>
> **Ionizing Energy—**The energy required to knock an electron out of an atom. The average energy lost by electrons or beta particles in producing an ion pair in air or in soft tissue is about 34 eV.
>
> **Radiant Energy—**The energy of electromagnetic radiation, such as radio waves, visible light, x and gamma rays.

Enrichment, Isotopic—An isotopic separation process by which the relative abundances of the isotopes of a given element are altered, thus producing a form of the element that has been enriched in one or more isotopes and depleted in others. In uranium enrichment, the percentage of uranium-235 in natural uranium can be increased from 0.7% to >90% in a gaseous diffusion process based on the different thermal velocities of the constituents of natural uranium (^{234}U, ^{235}U, ^{238}U) in the molecular form UF_6.

EPA Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Equilibrium, Radioactive—In a radioactive series, the state which prevails when the ratios between the activities of two or more successive members of the series remains constant.

> **Secular Equilibrium—**If a parent element has a very much longer half-life than the daughters (so there is not appreciable change in its amount in the time interval required for later products to attain equilibrium) then, after equilibrium is reached, equal numbers of atoms of all members of the series disintegrate in unit time. This condition is never exactly attained, but is essentially established in such a case as ^{226}Ra and its transformation series to stable ^{206}Pb. The half-life of ^{226}Ra is about 1,600 years; of ^{222}Rn, approximately 3.82 days, and of each of the subsequent members, a few minutes. After about a month, essentially the equilibrium amount of radon is present; then (and for a long time) all members of the series disintegrate the same number of atoms per unit time. At this time, the activity of the daughter is equal to the activity of the parent.

Transient Equilibrium—If the half-life of the parent is short enough so the quantity present decreases appreciably during the period under consideration, but is still longer than that of successive members of the series, a stage of equilibrium will be reached after which all members of the series decrease in activity exponentially with the period of the parent. At this time, the ratio of the parent activity to the daughter activity is constant.

Equilibrium, Electron—The condition in a radiation field where the energy of the electrons entering a volume equals the energy of the electrons leaving that volume.

Excitation—The addition of energy to a system, thereby transferring it from its ground state to an excited state. Excitation of a nucleus, an atom, or a molecule can result from absorption of photons or from inelastic collisions with other particles. The excited state of an atom is an unstable or metastable state and will return to ground state by radiation of the excess energy.

Exposure (Chemical)—Contact of an organism with a chemical or physical agent. Exposure is quantified as the amount of the agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut) and available for absorption.

Exposure (Radiation)—Subjection to ionizing radiation or to a radioactive material. For example, exposure in air is a measure of the ionization produced in air by x or gamma radiation; the sum of the electric charges on all ions of one sign produced in air when all electrons liberated by photons in a volume of air are completely stopped in air (dQ), divided by the mass of the air in the volume (dm). The unit of exposure in air is the roentgen, or coulomb per kilogram (SI units). One roentgen is equal to 2.58×10^{-4} coulomb per kilogram (C/kg).

Fission, Nuclear—A nuclear transformation characterized by the splitting of a nucleus into at least two other nuclei with emission of several neutrons, accompanied by the release of a relatively large amount of energy.

Gamma Ray, Penetrating—Short wavelength electromagnetic radiation of nuclear origin.

Genetic Effect of Radiation—Inheritable change, chiefly mutations, produced by the absorption of ionizing radiation by germ cells. Genetic effects have not been observed in any human population exposed at any dose level.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Gray (Gy)—SI unit of absorbed dose, 1 J/kg. One gray equals 100 rad (see Units).

Half-life, Effective—See Half-Time, Effective.

Half-life, Radioactive—Time required for a radioactive substance to lose 50% of its activity by decay. Each radio-nuclide has a unique physical half-life. Known also as physical half-time and symbolized as T_r or T_{rad}.

Half-time, Biological—Time required for an organ, tissue, or the whole body to eliminate one-half of any absorbed substance by regular processes of elimination. This is the same for both stable and radioactive isotopes of a particular element, and is sometimes referred to as half-time, symbolized as t_{biol} or T_b.

Half-time, Effective—Time required for a radioactive element in an organ, tissue, or the whole body to be diminished 50% as a result of the combined action of radioactive decay and biological elimination, symbolized as T_e or T_{eff}.

$$\text{Effective half-time} = \frac{\text{Biological half-time} \times \text{Radioactive half-life}}{\text{Biological half-time} + \text{Radioactive half-life}}$$

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube. Literally, "in glass."

***In Vivo*—**Occurring within the living organism. Literally, "in life."

Intensity—Amount of energy per unit time passing through a unit area perpendicular to the line of propagation at the point in question.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Internal Conversion—Process in which a gamma ray knocks an electron out of the same atom from which the gamma ray was emitted. The ratio of the number of internal conversion electrons to the number of gamma quanta emitted in the de-excitation of the nucleus is called the "conversion ratio."

Ion—Atomic particle, atom or chemical radical bearing a net electrical charge, either negative or positive.

Ion Pair—Two particles of opposite charge, usually referring to the electron and positive atomic or molecular residue resulting after the interaction of ionizing radiation with the orbital electrons of atoms.

Ionization—The process by which a neutral atom or molecule acquires a positive or negative charge.

> **Primary Ionization—**(1) In collision theory: the ionization produced by the primary particles as contrasted to the "total ionization" which includes the "secondary ionization" produced by delta rays. (2) In counter tubes: the total ionization produced by incident radiation without gas amplification.
>
> **Specific Ionization—**Number of ion pairs per unit length of path of ionizing radiation in a medium; e.g., per centimeter of air or per micrometer of tissue.
>
> **Total Ionization—**The total electric charge of one sign on the ions produced by radiation in the process of losing its kinetic energy. For a given gas, the total ionization is closely proportional to the initial ionization and is nearly independent of the nature of the ionizing radiation. It is frequently used as a measure of absorption of radiation energy.

Ionization Density—Number of ion pairs per unit volume.

Ionization Path (Track)—The trail of ion pairs produced by an ionizing particle in its passage through matter.

Ionizing Radiation—Any radiation capable of knocking electrons out of atoms and producing ions. Examples: alpha, beta, gamma and x rays, and neutrons.

Isobars—Nuclides having the same mass number but different atomic numbers.

Isomers—Nuclides having the same number of neutrons and protons but capable of existing, for a measurable time, in different quantum states with different energies and radioactive properties. Commonly the isomer of higher energy decays to one with lower energy by the process of isomeric transition.

Isotopes—Nuclides having the same number of protons in their nuclei, and hence the same atomic number, but differing in the number of neutrons, and therefore in the mass number. Identical chemical properties exist in isotopes of a particular element. The term should not be used as a synonym for nuclide because isotopes refer specifically to different nuclei of the same element.

Stable Isotope—A nonradioactive isotope of an element.

Joule—The S.I. unit for work and energy. It is equal to the work done by raising a mass of one newton through a distance of one meter (J = Nm), which corresponds to about 0.7 ft-pound.

Kerma (k)—A measure of the kinetic energy transferred from gamma rays or neutrons to a unit mass of absorbing medium in the initial collision between the radiation and the absorber atoms. The SI unit is J/kg. The special name of this unit is the rad (traditional system of units) or Gray (SI).

Labeled Compound—A compound containing one or more radioactive atoms intentionally added to its structure. By observations of radioactivity or isotopic composition, this compound or its fragments may be followed through physical, chemical, or biological processes.

Late Effects (of radiation exposure)—Effects which appear 60 days or more following an acute exposure.

$LD_{50/30}$—The dose of a chemical or radiation expected to cause 50% mortality in those exposed within 30 days. For radiation, this is about 350 rad (3.5 gray) received by humans over a short period of time.

Lethal Concentration$_{(Lo)}$ (LC_{Lo})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population within a specified time, usually 30 days.

Lethal Dose$_{(Lo)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals within a specified time, usually 30 days.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT$_{50}$)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Linear Energy Transfer (LET)—A measure of the energy that a charged particle transfers to a material per unit path length.

> **Average LET—**The energy of a charged particle divided by the length of the path over which it deposits all its energy in a material. This is averaged over a number of particles.
>
> **High-LET—**Energy transfer characteristic of heavy charged particles such as protons and alpha particles where the distance between ionizing events is small on the scale of a cellular nucleus.
>
> **Low-LET—**Energy transfer characteristic of light charged particles such as electrons produced by x and gamma rays where the distance between ionizing events is large on the scale of a cellular nucleus.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lung Clearance Class (fast, F; medium, M; slow, S)—A classification scheme for inhaled material according to its rate of clearance from the pulmonary region of the lungs to the blood and the gastrointestinal tract.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Mass Numbers (A)—The number of nucleons (protons and neutrons) in the nucleus of an atom.

Minimal Risk Level—An estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mutagen—A substance that causes changes (mutations) in the genetic material in a cell. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a substance.

Neutrino (ν)—A neutral particle of infinitesimally small rest mass emitted during beta plus or beta minus decay. This particle accounts for conservation of energy in beta plus and beta minus decays. It plays no role in damage from radiation.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a substance at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Nuclear Reactor—A power plant that heats the medium (typically water) by using the energy released from the nuclear fission of uranium or plutonium isotopes instead of burning coal, oil, or natural gas. All of these sources of energy simply heat water and use the steam which is produced to turn turbines that make electricity or propel a ship.

Nucleon—Common name for a constituent particle of the nucleus. Applied to a proton or neutron.

Nuclide—A species of atom characterized by the constitution of its nucleus. The nuclear constitution is specified by the number of protons (Z), number of neutrons (N), and energy content; or, alternatively, by the atomic number (Z), mass number A(N+Z), and atomic mass. To be regarded as a distinct nuclide, the atom must be capable of existing for a measurable time. Thus, nuclear isomers are separate nuclides, whereas promptly decaying excited nuclear states and unstable intermediates in nuclear reactions are not so considered.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Pair Production—An absorption process for x- and gamma radiation in which the incident photon is absorbed in the vicinity of the nucleus of the absorbing atom, with subsequent production of an electron and positron pair (see annihilation). This reaction can only occur for incident photon energies exceeding 1.02 MeV.

Parent—Any radionuclide nuclide which, upon disintegration, yields a new nuclide (termed the progeny or daughter), either directly or as a later member of a radioactive series.

Permissible Exposure Limit (PEL)—A maximum allowable atmospheric level of a substance in workplace air averaged over an 8-hour shift.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereas the physiologically-based model compartments represent real anatomic regions of the body.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A model comprising a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Photoelectric Effect—An attenuation process observed for x and gamma radiation in which an incident photon interacts with a tightly bound inner orbital electron of an atom delivering all of its energy to knock the electron out of the atom. The incident photon disappears in the process.

Photon—A quantum of electromagnetic energy (E) whose value is the product of its frequency (ν) in hertz and Planck's constant (h). The equation is: $E = h\nu$.

Population dose—See Collective dose.

Positron—A positively charged electron.

Potential, Ionization—The energy expressed as electron volts (eV) necessary to separate one electron from an atom, resulting in the formation of an ion pair.

Power, Stopping—A measure of the ability of a material to absorb energy from an ionizing particle passing through it; the greater the stopping power, the greater the energy absorbing ability (see Linear Energy Transfer).

Progeny—The decay product or daughter products resulting after a radioactive decay or a series of radioactive decays. The progeny can also be radioactive, and the chain continues until a stable nuclide is formed.

Proton—Elementary nuclear particle with a positive electric charge equal numerically to the charge of the electron and a rest mass of 1.007 mass units.

Quality—A term describing the distribution of the energy deposited by a particle along its track; radiations that produce different densities of ionization per unit intensity are said to have different "qualities."

Quality Factor (Q)—The linear-energy-transfer-dependent factor by which absorbed doses are multiplied to obtain (for radiation protection purposes) a quantity that expresses - on a common scale for all ionizing radiation - the approximate biological effectiveness of the absorbed dose.

Type of radiation	Quality Factor
X, gamma, or beta	1
Alpha particles	20
Neutrons of unknown energy	10
High energy protons	10

Rad—The traditional unit of absorbed dose equal to 100 ergs per gram, or 0.01 joule per kilogram (0.01 Gy) in any medium (see Absorbed Dose).

Radiation—The emission and propagation of energy through space or through a material medium in the form of waves (e.g., the emission and propagation of electromagnetic waves, or of sound and elastic waves) or particles. The term radiation or radiant energy, when unqualified, usually refers to electromagnetic radiation. Such radiation commonly is classified according to frequency, as microwaves, infrared, visible (light), ultraviolet, and x and gamma rays (see Photon.). However, radiation also occurs as corpuscular emission, such as alpha and beta radiation, neutrons, or rays of mixed or unknown type, such as cosmic radiation.

Radiation, Annihilation—Photons produced when an electron and a positron unite and cease to exist. The annihilation of a positron-electron pair results in the production of two photons, each of 0.51 MeV energy.

Radiation, Background—See Background Radiation.

Radiation, Characteristic (Discrete)—Radiation originating from an excited atom after removal of an electron from an atom. The wavelength of the emitted radiation is specific, depending only on the element and particular energy levels involved.

Radiation, External—Radiation from a source outside the body.

Radiation, Internal—Radiation from a source within the body (as a result of deposition of radionuclides in body tissues).

Radiation, Ionizing—Any electromagnetic or particulate radiation capable of producing ions, directly or indirectly, in its passage through matter (see Radiation).

Radiation, Monoenergetic—Radiation of a given type in which all particles or photons originate with and have the same energy.

Radiation, Scattered—Radiation which during its passage through a substance, has been deviated in direction. It may also have been modified by a decrease in energy.

Radiation, Secondary—A particle or ray that is produced when the primary radiation interacts with a material, and which has sufficient energy to produce its own ionization, such as bremsstrahlung or electrons knocked from atomic orbitals with enough energy to then produce ionization (see Delta Rays).

Radiation Weighting Factor (also called Quality Factor)—In radiation protection, a factor (1 for x-rays, gamma rays, beta particles; 20 for alpha particles) weighting the absorbed dose of radiation of a specific type and energy for its effect on tissue.

Radioactive Material—Material containing radioactive atoms.

Radioactivity—Spontaneous nuclear transformations that result in the formation of new elements. These transformations are accomplished by emission of alpha or beta particles from the nucleus or by the capture of an orbital electron. Each of these reactions may or may not be accompanied by a gamma photon.

> **Radioactivity, Artificial—**Man-made radioactivity produced by particle bombardment or nuclear fission, as opposed to naturally occurring radioactivity.
>
> **Radioactivity, Induced—**Radioactivity produced in a substance after bombardment with neutrons or other particles. The resulting activity is "natural radioactivity" if formed by nuclear reactions occurring in nature and "artificial radioactivity" if the reactions are caused by man.
>
> **Radioactivity, Natural—**The property of radioactivity exhibited by more than 50 naturally occurring radionuclides.

Radioisotope—An unstable or radioactive isotope of an element that decays or disintegrates spontaneously, emitting radiation.

Radionuclide—Any radioactive isotope of any element. Approximately 5,000 natural and artificial radioisotopes have been identified.

Radiosensitivity—Relative susceptibility of cells, tissues, organs, organisms, or any living substance to the injurious action of radiation. Radiosensitivity and its antonym, radioresistance, are used comparatively, rather than absolutely.

Reference Dose (RfD)—An estimate of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to non-threshold effects such as cancer.

Relative Biological Effectiveness (RBE)—The RBE is a factor used to compare the biological effectiveness of absorbed radiation doses (i.e., rad) due to different types of ionizing radiation. More specifically, it is the experimentally determined ratio of an absorbed dose of a radiation in question to the absorbed dose of a reference radiation (typically ^{60}Co gamma rays or 200 kVp x rays) required to produce an identical biological effect in a particular experimental organism or tissue (see Quality Factor).

Rem—The traditional unit of dose equivalent that is used in the regulatory, administrative, and engineering design aspects of radiation safety practice. The dose equivalent in rem is numerically equal to the absorbed dose in rad multiplied by the quality factor (1 rem is equal to 0.01 sievert).

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Roentgen (R)—A unit of exposure (in air) to ionizing radiation. It is the amount of x or gamma rays required to produce ions carrying 1 electrostatic unit (esu) of electrical charge in 1 cubic centimeter or 2.58×10^{-4} coulombs per kilogram of dry air under standard conditions. Named after William Roentgen, a German scientist who discovered x-rays in 1895.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Self-Absorption—Absorption of radiation (emitted by radioactive atoms) by the material in which the atoms are located; in particular, the absorption of radiation within a sample being assayed.

Short-Term Exposure Limit (STEL)—The maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily TLV-TWA may not be exceeded.

SI Units—The International System of Units as defined by the General Conference of Weights and Measures in 1960. These units are generally based on the meter/kilogram/second units, with special quantities for radiation including the becquerel, gray, and sievert.

Sickness, Acute Radiation (Syndrome)—The complex symptoms and signs characterizing the condition resulting from excessive exposure of the whole body (or large part) to ionizing radiation. The earliest of these symptoms are nausea, fatigue, vomiting, and diarrhea, and may be followed by loss of hair (epilation), hemorrhage, inflammation of the mouth and throat, and general loss of energy. In severe cases, where the radiation dose is relatively high (over several hundred rad or several gray), death may occur within two to four weeks. Those who survive six weeks after exposure of a single high dose of radiation may generally be expected to recover.

Sievert (Sv)—The SI unit of any of the quantities expressed as dose equivalent. The dose equivalent in sieverts is equal to the absorbed dose, in gray, multiplied by the quality factor (1 sievert equals 100 rem). The sievert is also the SI unit for effective dose equivalent, which is the sum of the products of the dose equivalent to each organ or tissue and its corresponding tissue weighting factor.

Specific-Activity—Radioactivity per unit mass of a radioactive element in a material expressed, for example, as Ci/gram or Bq/kilogram.

Specific Energy—The actual energy per unit mass deposited per unit volume in a small target, such as the cell or cell nucleus, as the result of one or more energy-depositing events. This is a stochastic quantity as opposed to the average value over a large number of instance (i.e., the absorbed dose).

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Stochastic Effect—A health effect that occurs randomly and for which the probability of the effect occurring, rather than its severity, is assumed to be a linear function of dose without a threshold (also called a nondeterministic effect).

Stopping Power—The average rate of energy loss of a charged particle per unit thickness of a material or per unit mass of material traversed.

Surface-seeking Radionuclide—A bone-seeking internal emitter that deposits and remains on the bone surface for a long period of time, although it may eventually diffuse into the bone mineral. This contrasts with a volume seeker, which deposits more uniformly throughout the bone volume.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Target Theory (Hit Theory)—A theory explaining some biological effects of radiation on the basis that ionization, occurring in a discrete volume (the target) within the cell, directly causes a lesion which subsequently results in a physiological response to the damage at that location. One, two, or more "hits" (ionizing events within the target) may be necessary to elicit the response.

Teratogen—A chemical that causes birth defects.

Threshold Limit Value (TLV)—The maximum concentration of a substance to which most workers can be exposed without adverse effect. TLV is a term used exclusively by the ACGIH. Other terms used to express similar concepts are the MAC (Maximum Allowable Concentration) and PEL (Permissible Exposure Limits).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Tissue Weighting Factor (W_t)—Organ- or tissue-specific factor by which the equivalent dose is multiplied to give the portion of the effective dose for that organ or tissue. Recommended values of tissue weighting factors are:

Tissue/Organ	Tissue Weighting Factor
Gonads	0.70
Bone marrow (red)	0.12
Colon	0.12
Lung	0.12
Stomach	0.12
Bladder	0.05
Breast	0.05
Liver	0.05
Esophagus	0.05
Thyroid	0.05
Skin	0.01
Bone surface	0.01
Remainder (adrenals, brain, upper large intestine, small intestine, pancreas, spleen, thymus, and uterus)	0.05

Toxic Dose (TD_{50})—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution and elimination of toxic compounds in the living organism.

Toxicosis —A diseased condition resulting from poisoning.

Transformation, Nuclear—The process of radioactive decay by which a nuclide is transformed into a different nuclide by absorbing or emitting particulate or electromagnetic radiation.

Transition, Isomeric—The process by which a nuclide decays to an isomeric nuclide (i.e., one of the same mass number and atomic number) of lower quantum energy. Isomeric transitions (often abbreviated I.T.) proceed by gamma ray and internal conversion electron emission.

Tritium—The hydrogen isotope with one proton and two neutrons in the nucleus (Symbol: ^{3}H). It is radioactive and has a physical half-life of 12.3 years.

Unattached Fraction—That fraction of the radon daughters, usually ^{218}Po and ^{214}Po, which has not yet attached to a dust particle or to water vapor. As a free atom, it has a high probability of being exhaled and not retained within the lung. It is the attached fraction which is primarily retained.

Uncertainty Factor (UF)—A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

Units, Prefixes—Many units of measure are expressed as submultiples or multiples of the primary unit (e.g., 10^{-3} curie is 1 mCi and 10^{3} becquerel is 1 kBq).

Factor	Prefix	Symbol	Factor	Prefix	Symbol
10^{-18}	atto	A	10^{3}	kilo	k
10^{-15}	femto	F	10^{6}	mega	M
10^{-12}	pico	p	10^{9}	giga	G
10^{-9}	nano	N	10^{12}	tera	T
10^{-6}	micro	M	10^{15}	peta	P
10^{-3}	milli	M	10^{18}	exa	E
10^{-2}	centi	C			

Units, Radiological—

Units	Equivalents
Becquerel* (Bq)	1 disintegration per second = 2.7×10^{-11} Ci
Curie (Ci)	3.7×10^{10} disintegrations per second = 3.7×10^{10} Bq
Gray* (Gy)	1 J/kg = 100 rad
Rad (rad)	100 erg/g = 0.01 Gy
Rem (rem)	0.01 sievert
Sievert* (Sv)	100 rem

*International Units, designated (SI)

Working Level (WL)—Any combination of short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^{5} MeV of potential alpha energy.

Working Level Month (WLM)—A unit of exposure to radon daughters corresponding to the product of the radon daughter concentration in Working Level (WL) and the exposure time in nominal months (1 nominal month = 170 hours). Inhalation of air with a concentration of 1 WL of radon daughters for 170 working hours results in an exposure of 1 WLM.

X rays—Penetrating electromagnetic radiations whose wave lengths are very much shorter than those of visible light. They are usually produced by bombarding a metallic target with fast electrons in a high vacuum. X rays (called characteristic x rays) are also produced when an orbital electron falls from a high energy level to a low energy level.

Zero-Threshold Linear Hypothesis (or No-Threshold Linear Hypothesis)—The assumption that a dose-response curve derived from data in the high dose and high dose-rate ranges may be extrapolated through the low dose and low dose range to zero, implying that, theoretically, any amount of radiation will cause some damage.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Iodine (sodium iodide, potassium iodide)
CAS Number: 7553-56-2 (7681-82-5, 7681-11-0)
Date: March 2004
Profile Status: Draft 3 Post Public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 6
Species: Human

Minimal Risk Level: 0.01 [X] mg/kg/day [ ] ppm

The administered doses of iodide (as sodium iodide) were 250, 500, or 1,500 µg I/day for 14 days (Paul et al. 1988); or 500, 1,500, or 4,500 µg I/day (Gardner et al. 1988). The pre-existing dietary iodide intakes were estimated from the reported 24-hour urinary iodide excretion rate, which was 200 µg/day (Paul et al. 1988) or 300 µg I/day (Gardner et al. 1988). The total intake of iodide was estimated as the sum of the administered iodide and the estimated dietary intake: 450, 700, or 1,700 µg/day (Paul et al. 1988); or 300, 800, 1,800, or 4,800 µg/day (Gardner et al. 1988). The estimated dosages on a per kg body weight (70 kg) were: 0.0064, 0.010, or 0.024 mg/kg/day (Paul et al. 1988); or 0.011, 0.026, or 0.069 mg/kg/day (Gardner et al. 1988).

In protecting public health ATSDR recommends using the conservative lower end of this calculated NOAEL range, 0.01 mg/kg/day, to derive an acute-duration MRL of 0.01 mg/kg/day.

Reference: Gardner DF, Centor RM, Utiger RD. 1988. Effects of low dose oral iodide supplementation on thyroid function in normal men. Clin Endocrinol 28:283-288; Paul T, Meyers B, Witorsch RJ, et al. 1988. The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism 37(2):121-124.

Experimental design: Healthy euthyroid adults (9 males, 9 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, assuming a 70-kg body weight).

Ten healthy, euthyroid, adult males 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 800, 1,800, or 4,800 µg/day or approximately 0.011, 0.026, or 0.069 mg/kg/day.

Effects noted in study and corresponding doses: In the Paul et al. (1988) study, subjects who received 1,700 µg/day (0.024 mg/kg/day) had significantly depressed (5–10%) serum concentrations of TT_4, FT_4, and TT_3 compared to pretreatment levels, and serum TSH concentrations were significantly elevated (47%) compared to pretreatment values. Hormone levels were within the normal range during treatment. In this same study, nine females received daily doses of 250 or 500 µg I/day for 14 days (total intake was approximately 450 or 700 µg/day [0.0064 or 0.010 mg/kg/day]) and there were no significant changes in serum hormone concentrations.

In the Gardner et al. (1988) study, 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 0.064 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.

Dose and end point used for MRL derivation: 0.01 mg/kg/day; reversible subclinical hypothyroidism.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[ ] 10 for human variability

Although the acute NOAEL is derived from acute studies of healthy adults, supporting studies indicate that the NOAEL would be applicable to children and elderly adults (Boyages et al. 1989; Chow et al. 1991). On this basis, an uncertainty factor is not needed to adjust the NOAEL to account for human variability in sensitivity. In the Chow et al. (1991) study, 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 elevated 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 (0.0086 mg/kg/day).

In the Boyages et al. (1989) study, thyroid status was compared in groups of children, ages 7–15 years, who resided in two areas of China where drinking water iodide concentrations were either 462 μg/L (n=120) or 54 μg/L (n=51) (Boyages et al. 1989; Li et al. 1987). Although the subjects were all euthyroid with normal values for serum thyroid hormones and TSH concentrations, TSH concentrations were significantly higher 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. 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 μg/day (0.029 mg/kg/day) and 400 μg/day (0.01 mg/kg/day) in the high and low iodide groups, respectively.

The MRL is higher than the National Research Council Recommended Dietary Allowance of 150 μg/day (0.0021 mg/kg/day for a 70-kg adult), with additional allowances of 25 μg/day (0.0025 mg/kg/day) and 50 μg/day (0.0029 mg/kg/day) during pregnancy and lactation, respectively (NRC 1989).

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No; however, urinary iodide levels were converted to estimates of iodine intakes. Steady-state baseline dietary intakes of iodide were assumed to be equivalent to the reported 24-hour urinary iodine excretion rates. This assumption is consistent with information available on the toxicokinetics of iodide that indicates nearly complete absorption of ingested iodide and that urinary excretion accounts for >97% of the absorbed dose (see Sections 3.4.1.2 and 3.4.4.2). The assumption is also supported by studies in which 24-hour urinary iodide was measured before and after supplementation (Kahaly et al. 1998; Konno et al. 1993b). For

example, 31 patients received oral supplements of 382 µg I/day for 6 months. Prior to the supplementation, the mean 24-hour urinary iodide excretion rate was 36 µg/day (range, 13–69), whereas, after 6 months of iodide supplementation, the mean 24-hour urinary iodide excretion rate was 415 µg/day (Kahaly et al. 1998). The difference between these two values, 379 µg/day, is nearly identical to the supplemental dose of 382 µg/day.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Two other acute studies reported NOAELs and LOAELs of 0.3 and 1.0 mg/kg/day, respectively (Robison et al. 1998, 1999), which are substantially higher than those from the Paul et al. (1988) and Gardner et al. (1988) studies. These suggest that doses much higher than the MRL can be tolerated in some people without producing thyroid gland suppression.

Agency Contact (Chemical Manager): John Risher, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Iodine (sodium iodide, potassium iodide)
CAS Number: 7553-56-2 (7681-82-5, 7681-11-0)
Date: March 2004
Profile Status: Draft 3 Post Public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 29
Species: Human

Minimal Risk Level: 0.01 [X] mg/kg/day [ ] ppm

Iodine intakes estimated from urinary iodine levels (see below) were 400 and 1,150 µg/day. These correspond to 0.010 or 0.029 mg/kg/day for a 40-kg child of age 11 years.

Reference: Boyages SC, Bloot AM, Maberly GF, et al. 1989. Thyroid autoimmunity in endemic goiter caused by excessive iodine intake. Clin Endocrinol 31:452-465; Li W, Qu C, Jia G, et al. 1987. Endemic goitre in Central China caused by excessive iodine intake. Lancet, August 1:257-258.

Experimental design: Thyroid status was compared in groups of children, ages 7–15 years, who resided in two areas of China where drinking water iodide concentrations 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 (29 µg/kg/day) and 400 µg/day (10 µg/kg/day) in the high and low iodide groups, respectively.

Effects noted in study and corresponding doses: 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.

Dose and end point used for MRL derivation: 0.01 mg/kg/day; subclinical hypothyroidism with thyroid gland enlargement.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[ ] 10 for human variability

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). In the Chow et al. (1991) study, 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 elevated 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 pre-existing dietary iodine intake was approximately 72–100 μg/day, based on urinary iodide measurements. Therefore, the total iodide intake was approximately 600 μg/day (0.0086 mg/kg/day).

Szabolcs et al. (1997) studied a group of 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 less than 5% is considered a NOAEL, 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 MRL is higher than the National Research Council Recommended Dietary Allowance of 150 μg/day (0.0021 mg/kg/day for a 70-kg adult), with additional allowances of 25 μg/day (0.0025 mg/kg/day) and 50 μg/day (0.0029 mg/kg/day) during pregnancy and lactation, respectively (NRC 1989).

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No; however, urinary iodide levels were converted to estimates of iodine intakes. Urinary iodide:creatinine ratios were converted to estimated iodide intake as follows assuming a constant relationship between urinary creatinine excretion rate and lean body mass. The rate of creatinine excretion (e.g., U_{Cr}, mg creatinine/day) was calculated from the relationship between lean body mass (LBM) and U_{cr}:

$$LBM = 0.0272 \cdot \dot{U}_{Cr} + 8.58$$

where the constants 0.0272 and 8.58 are the weighted arithmetic mean of estimates of these variables from eight studies reported in Forbes and Bruining (1976). Lean body mass was calculated as follows (ICRP 1981):

$$LBM = BW \cdot 0.85, females$$

$$LBM = BW \cdot 0.88, males$$

where BW is the reported body weight for children of age 11 years (40 kg) (EPA 1997). Iodide intake was calculated as:

$$Intake_I = U_{I/Cr} \cdot \dot{U}_{Cr}$$

where $U_{I/Cr}$ is the urinary iodide:creatinine ratio (μg I/g creatinine). This approach yields relationships between 24-hour urinary iodide excretion rates and the urinary iodide:creatinine ratios that are in reasonable agreement with observation (Konno et al. 1993b). The approach is consistent with

information available on the toxicokinetics of iodide that indicates nearly complete absorption of ingested iodide and that urinary excretion accounts for >97% of the absorbed dose (see Sections 3.4.1.2 and 3.4.4.2).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: One other study of elderly adults supports the MRL as being protective of this population. Thyroid status was compared in 423 residents (ages 66–70 years) of Jutland, Denmark who had iodine intakes of 40–60 µg/day (0.7 µg/kg/day) and 100 residents of Iceland who had intakes of 300–350 µg/day (5 µg/kg/day) (Laurberg et al. 1998). Subjects from the high iodine intake region had a significantly higher prevalence (18%) of serum TSH levels above the high end of the normal range (>4 mU/L) compared to subjects from the low iodine region (3.8%). The prevalence of serum TSH concentrations above 10 mU/L was 4.0% in the high iodine region and 0.9% in the low iodine region. Females in both regions had a significantly higher prevalence of elevated TSH concentrations than males. Serum concentrations of T_4 were not depressed, even in subjects with TSH concentrations that exceeded 10 mU/L. Thus, although the subjects appeared to be euthyroid, the higher iodine intakes were associated with a subclinical suppression of the thyroid gland as indicated by a high prevalence of elevated serum TSH concentrations.

Agency Contact (Chemical Manager): John Risher, Ph.D.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.10, "Interactions with Other Substances," and Section 3.11, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.5, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38r is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

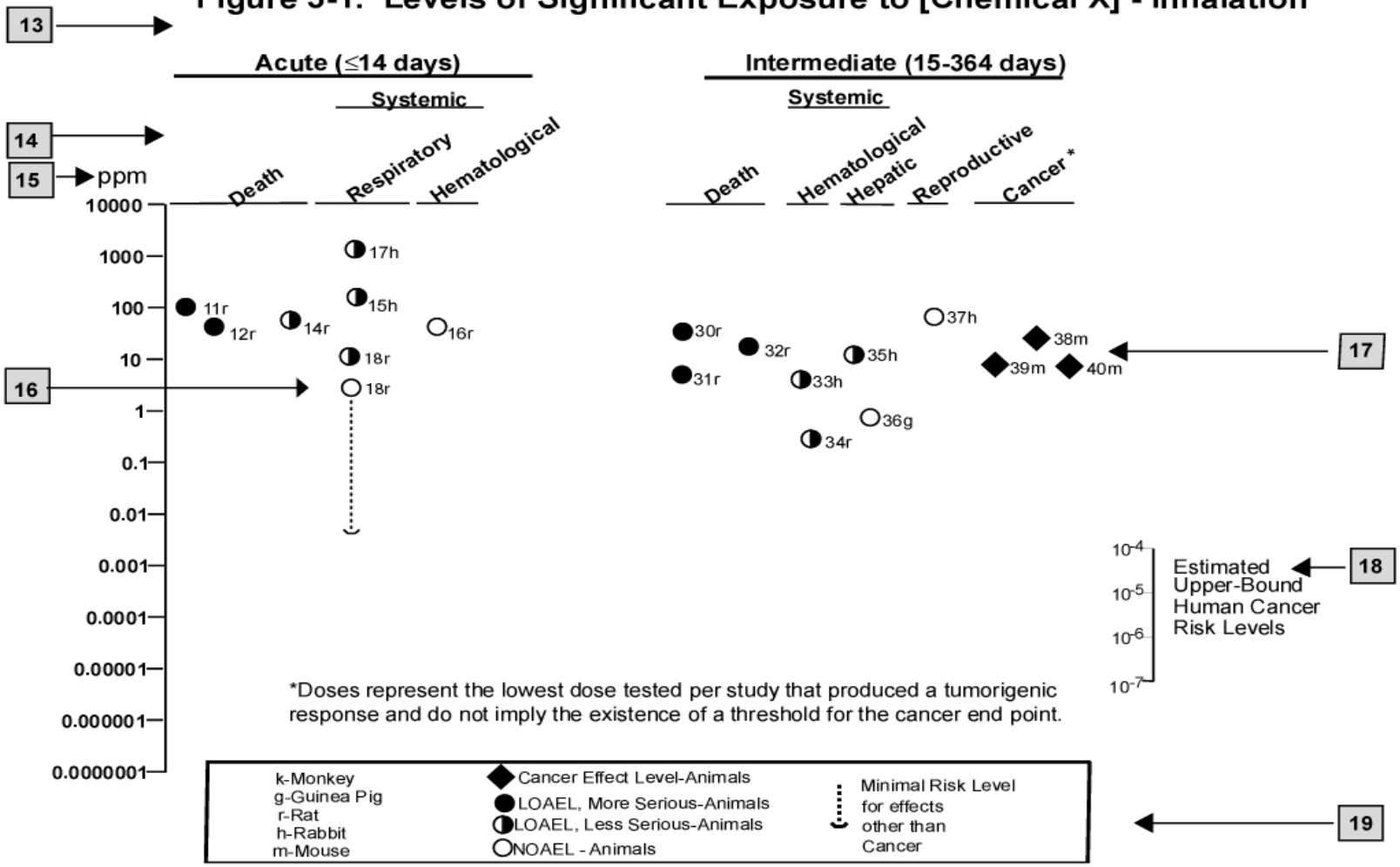
1 → **TABLE 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → a The number corresponds to entries in Figure 3-1.
b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5x10-3 ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

Some terms are generic and may not be used in this profile.

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALI	annual limit on intake
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DAC	derived air concentration
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense

DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid

MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration

OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	United States Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell

WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. OVERVIEW OF BASIC RADIATION PHYSICS, CHEMISTRY, AND BIOLOGY

Understanding the basic concepts in radiation physics, chemistry, and biology is important to the evaluation and interpretation of radiation-induced adverse health effects and to the derivation of radiation protection principles. This appendix presents a brief overview of the areas of radiation physics, chemistry, and biology and is based to a large extent on the reviews of Mettler and Moseley (1985), Hobbs and McClellan (1986), Eichholz (1982), Hendee (1973), Cember (1996), and Early et al. (1979).

D.1 RADIONUCLIDES AND RADIOACTIVITY

The substances we call elements are composed of atoms. Atoms in turn are made up of neutrons, protons and electrons: neutrons and protons in the nucleus and electrons in a cloud of orbits around the nucleus. Nuclide is the general term referring to any nucleus along with its orbital electrons. The nuclide is characterized by the composition of its nucleus and hence by the number of protons and neutrons in the nucleus. All atoms of an element have the same number of protons (this is given by the atomic number) but may have different numbers of neutrons (this is reflected by the atomic mass numbers or atomic weight of the element). Atoms with different atomic mass but the same atomic numbers are referred to as isotopes of an element.

The numerical combination of protons and neutrons in most nuclides is such that the nucleus is quantum mechanically stable and the atom is said to be stable, i.e., not radioactive; however, if there are too few or too many neutrons, the nucleus is unstable and the atom is said to be radioactive. Unstable nuclides undergo radioactive transformation, a process in which a neutron or proton converts into the other and a beta particle is emitted, or else an alpha particle is emitted. Each type of decay is typically accompanied by the emission of gamma rays. These unstable atoms are called radionuclides; their emissions are called ionizing radiation; and the whole property is called radioactivity. Transformation or decay results in the formation of new nuclides some of which may themselves be radionuclides, while others are stable nuclides. This series of transformations is called the decay chain of the radionuclide. The first radionuclide in the chain is called the parent; the subsequent products of the transformation are called progeny, daughters, or decay products.

In general there are two classifications of radioactivity and radionuclides: natural and artificial (man-made). Naturally-occurring radioactive materials (NORMs) exist in nature and no additional energy is necessary to place them in an unstable state. Natural radioactivity is the property of some naturally occurring, usually heavy elements, that are heavier than lead. Radionuclides, such as radium and uranium, primarily emit alpha particles. Some lighter elements such as carbon-14 and tritium (hydrogen-3) primarily emit beta particles as they transform to a more stable atom. Natural radioactive atoms heavier than lead cannot attain a stable nucleus heavier than lead. Everyone is exposed to background radiation from naturally-occurring radionuclides throughout life. This background radiation is the major source of radiation exposure to man and arises from several sources. The natural background exposures are frequently used as a standard of comparison for exposures to various artificial sources of ionizing radiation.

Artificial radioactive atoms are produced either as a by-product of fission of uranium or plutonium atoms in a nuclear reactor or by bombarding stable atoms with particles, such as neutrons or protons, directed at the stable atoms with high velocity. These artificially produced radioactive elements usually decay by emission of particles, such as positive or negative beta particles and one or more high energy photons (gamma rays). Unstable (radioactive) atoms of any element can be produced.

Both naturally occurring and artificial radioisotopes find application in medicine, industrial products, and consumer products. Some specific radioisotopes, called fall-out, are still found in the environment as a result of nuclear weapons use or testing.

D.2 RADIOACTIVE DECAY

D.2.1 Principles of Radioactive Decay

The stability of an atom is the result of the balance of the forces of the various components of the nucleus. An atom that is unstable (radionuclide) will release energy (decay) in various ways and transform to stable atoms or to other radioactive species called daughters, often with the release of ionizing radiation. If there are either too many or too few neutrons for a given number of protons, the resulting nucleus may undergo transformation. For some elements, a chain of daughter decay products may be produced until stable atoms are formed. Radionuclides can be characterized by the type and energy of the radiation emitted, the rate of decay, and the mode of decay. The mode of decay indicates how a parent compound undergoes transformation. Radiations considered here are primarily of nuclear origin, i.e., they arise from nuclear excitation, usually caused by the capture of charged or uncharged nucleons by a nucleus, or by the radioactive decay or transformation of an unstable nuclide. The type of radiation may be categorized as charged or uncharged particles, protons, and fission products) or electromagnetic radiation (gamma rays and x rays). Table D-1 summarizes the basic characteristics of the more common types of radiation encountered.

D.2.2 Half-Life and Activity

For any given radionuclide, the rate of decay is a first-order process that is constant, regardless of the radioactive atoms present and is characteristic for each radionuclide. The process of decay is a series of random events; temperature, pressure, or chemical combinations do not effect the rate of decay. While it may not be possible to predict exactly which atom is going to undergo transformation at any given time, it is possible to predict, on average, the fraction of the radioactive atoms that will transform during any interval of time.

The *activity* is a measure of the quantity of radioactive material. For these radioactive materials it is customary to describe the activity as the number of disintegrations (transformations) per unit time. The unit of activity is the curie (Ci), which was originally related to the activity of one gram of radium, but is now defined as that quantity of radioactive material in which there are:

1 curie (Ci) = 3.7×10^{10} disintegrations (transformations)/second (dps) or 2.22×10^{12} disintegrations (transformations)/minute (dpm).

The SI unit of activity is the becquerel (Bq); 1 Bq = that quantity of radioactive material in which there is 1 transformation/second. Since activity is proportional to the number of atoms of the radioactive material, the quantity of any radioactive material is usually expressed in curies, regardless of its purity or concentration. The transformation of radioactive nuclei is a random process, and the number of transformations is directly proportional to the number of radioactive atoms present. For any pure radioactive substance, the rate of decay is usually described by its radiological half-life, T_R, i.e., the time it takes for a specified source material to decay to half its initial activity. The specific activity is the activity of a radionuclide per mass of that radionuclide. If properly qualified, it can refer to activity per unit mass of related materials, such as the element itself or a chemical compound labeled with the radionuclide. The higher the specific activity of a radioisotope, the faster it is decaying.

The activity of a radionuclide at time t may be calculated by:

$$A = A_o e^{-0.693t/Trad}$$

where A is the activity in dps or curies or becquerels, A_o is the activity at time zero, t is the time at which measured, and T_{rad} is the radiological half-life of the radionuclide (T_{rad} and t must be in the same units of time). The time when the activity of a sample of radioactivity becomes one-half its original value is the radioactive half-life and is expressed in any suitable unit of time.

Table D-1. Characteristics of Nuclear Radiations

Radiation	Rest mass[a]	Charge	Typical energy range	Path length[b]		Comments
				Air	Solid	
Alpha (α)	4.00 amu	+2	4–10 MeV	5–10 cm	25–80 μm	Identical to ionized He nucleus
Negatron (β^-)	$5.48x10^{-4}$ amu; 0.51 MeV	–1	0–4 MeV	0–10 m	0–1 cm	Identical to electron
Positron (β^+)	$5.48x10^{-4}$ amu; 0.51 MeV	+1	0-4 MeV	0–10 m	0–1 cm	Identical to electron except for sign of charge
Neutron	1.0086 amu; 939.55 MeV	0	0–15 MeV	b	b	Free half-life: 16 min
X ray (e.m. photon)	–	0	5 keV–100 keV	b	b	Photon from transition of an electron between atomic orbits
Gamma (ρ) (e.m. photon)	–	0	10 keV–3 MeV	b	b	Photon from nuclear transformation

[a] The rest mass (in amu) has an energy equivalent in MeV that is obtained using the equation $E=mc^2$, where 1 amu = 932 MeV.
[b] Path lengths are not applicable to x- and gamma rays since their intensities decrease exponentially; path lengths in solid tissue are variable, depending on particle energy, electron density of material, and other factors.

amu = atomic mass unit; e.m. = electromagnetic; MeV = Megaelectron Volts

The specific activity is a measure of activity, and is defined as the activity of a radionuclide per mass of that radionuclide. This activity is usually expressed in curies per gram and may be calculated by

$$\text{curies/gram} = 1.3x10^8 / (T_{rad})\ (\text{atomic weight}) \quad \text{or}$$

$$[3.577 \times 10^5 \times \text{mass(g)}] / [T_{rad} \times \text{atomic weight}]$$

where T_{rad} is the radiological half-life in days.

In the case of radioactive materials contained in living organisms, an additional consideration is made for the reduction in observed activity due to regular processes of elimination of the respective chemical or biochemical substance from the organism. This introduces a rate constant called the biological half-life (T_{biol}) which is the time required for biological processes to eliminate one-half of the activity. This time is virtually the same for both stable and radioactive isotopes of any given element.

Under such conditions the time required for a radioactive element to be halved as a result of the combined action of radioactive decay and biological elimination is the effective clearance half-time:

$$T_{eff} = (T_{biol} \times T_{rad}) / (T_{biol} + T_{rad}).$$

Table D-2 presents representative effective half-lives of particular interest.

Table D-2. Half-Lives of Some Radionuclides in Adult Body Organs

		Half-life[a]		
Radionuclide	Critical organ	Physical	Biological	Effective
Uranium 238	Kidney	4,460,000,000 y	4 d	4 d
Hydrogen 3[b] (Tritium)	Whole body	12.3 y	10 d	10 d
Iodine 131	Thyroid	8 d	80 d	7.3 d
Strontium 90	Bone	28 y	50 y	18 y
Plutonium 239	Bone surface	24,400 y	50 y	50 y
	Lung	24,400 y	500 d	474 d
Cobalt 60	Whole body	5.3 y	99.5 d	95 d
Iron 55	Spleen	2.7 y	600 d	388 d
Iron 59	Spleen	45.1 d	600 d	42 d
Manganese 54	Liver	303 d	25 d	23 d
Cesium 137	Whole body	30 y	70 d	70 d

[a]d = days, y = years
[b]Mixed in body water as tritiated water

D.2.3 Interaction of Radiation with Matter

Both ionizing and nonionizing radiation will interact with materials; that is, radiation will lose kinetic energy to any solid, liquid or gas through which it passes by a variety of mechanisms. The transfer of energy to a medium by either electromagnetic or particulate radiation may be sufficient to cause formation of ions. This process is called ionization. Compared to other types of radiation that may be absorbed, such as ultraviolet radiation, ionizing radiation deposits a relatively large amount of energy into a small volume.

The method by which incident radiation interacts with the medium to cause ionization may be direct or indirect. Electromagnetic radiations (x rays and gamma photons) are indirectly ionizing; that is, they give up their energy in various interactions with cellular molecules, and the energy is then utilized to produce a fast-moving charged particle such as an electron. It is the electron that then may react with a target molecule. This particle is called a "primary ionizing particle. Charged particles, in contrast, strike the tissue or medium and directly react with target molecules, such as oxygen or water. These particulate radiations are directly ionizing radiations. Examples of directly ionizing particles include alpha and beta particles. Indirectly ionizing radiations are always more penetrating than directly ionizing particulate radiations.

Mass, charge, and velocity of a particle, as well as the electron density of the material with which it interacts, all affect the rate at which ionization occurs. The higher the charge of the particle and the lower the velocity, the greater the propensity to cause ionization. Heavy, highly charged particles, such as alpha

particles, lose energy rapidly with distance and, therefore, do not penetrate deeply. The result of these interaction processes is a gradual slowing down of any incident particle until it is brought to rest or "stopped" at the end of its range.

D.2.4 Characteristics of Emitted Radiation

D.2.4.1 Alpha Emission. In alpha emission, an alpha particle consisting of two protons and two neutrons is emitted with a resulting decrease in the atomic mass number by four and reduction of the atomic number of two, thereby changing the parent to a different element. The alpha particle is identical to a helium nucleus consisting of two neutrons and two protons. It results from the radioactive decay of some heavy elements such as uranium, plutonium, radium, thorium, and radon. The alpha particles emitted by a given radionuclide have the same energy and intensity combination. Most of the alpha particles that are likely to be found have energies in the range of about 4 to 8 MeV, depending on the isotope from which they came.

The alpha particle has an electrical charge of +2. Because of this double positive charge and their size, alpha particles have great ionizing power and, thus, lose their kinetic energy quickly. This results in very little penetrating power. In fact, an alpha particle cannot penetrate a sheet of paper. The range of an alpha particle (the distance the charged particle travels from the point of origin to its resting point) is about 4 cm in air, which decreases considerably to a few micrometers in tissue. These properties cause alpha emitters to be hazardous only if there is internal contamination (i.e., if the radionuclide is inside the body).

D.2.4.2 Beta Emission. A beta particle (&) is a high-velocity electron ejected from a disintegrating nucleus. The particle may be either a negatively charged electron, termed a negatron (&-) or a positively charged electron, termed a positron (&+). Although the precise definition of "beta emission" refers to both &- and &+, common usage of the term generally applies only to the negative particle, as distinguished from the positron emission, which refers to the &+ particle.

D.2.4.2.1 Beta Negative Emission. Beta particle (&-) emission is another process by which a radionuclide, with a neutron excess achieves stability. Beta particle emission decreases the number of neutrons by one and increases the number of protons by one, while the atomic mass number remains unchanged.[1] This transformation results in the formation of a different element. The energy spectrum of beta particle emission ranges from a certain maximum down to zero with the mean energy of the spectrum being about one-third of the maximum. The range of betas is much less in tissue than in air. Beta negative emitting radionuclides can cause injury to the skin and superficial body tissues, but mostly present an internal contamination hazard.

D.2.4.2.2 Positron Emission. In cases in which there are too many protons in the nucleus, positron emission may occur. In this case a proton may be thought of as being converted into a neutron, and a positron (&+) is emitted.1 This increases the number of neutrons by one, decreases the number of protons by one, and again leaves the atomic mass number unchanged. The gamma radiation resulting from the annihilation (see glossary) of the positron makes all positron emitting isotopes more of an external radiation hazard than pure & emitters of equal energy.

D.2.4.2.3 Gamma Emission. Radioactive decay by alpha, beta, or positron emission, or electron capture often leaves some of the energy resulting from these changes in the nucleus. As a result, the nucleus is raised to an excited level. None of these excited nuclei can remain in this high-energy state. Nuclei release this energy returning to ground state or to the lowest possible stable energy level. The

[1] Neutrinos also accompany negative beta particles and positron emissions

energy released is in the form of gamma radiation (high energy photons) and has an energy equal to the change in the energy state of the nucleus. Gamma and x rays behave similarly but differ in their origin; gamma emissions originate in the nucleus while x rays originate in the orbital electron structure or from rapidly changing the velocity of an electron (e.g., as occurs when shielding high energy beta particles or stopping the electron beam in an x ray tube).

D.3 ESTIMATION OF ENERGY DEPOSITION IN HUMAN TISSUES

Two forms of potential radiation exposures can result: internal and external. The term exposure denotes physical interaction of the radiation emitted from the radioactive material with cells and tissues of the human body. An exposure can be "acute" or "chronic" depending on how long an individual or organ is exposed to the radiation. Internal exposures occur when radionuclides, which have entered the body (e.g., through the inhalation, ingestion, or dermal pathways), undergo radioactive decay resulting in the deposition of energy to internal organs. External exposures occur when radiation enters the body directly from sources located outside the body, such as radiation emitters from radionuclides on ground surfaces, dissolved in water, or dispersed in the air. In general, external exposures are from material emitting gamma radiation, which readily penetrate the skin and internal organs. Beta and alpha radiation from external sources are far less penetrating and deposit their energy primarily on the skin's outer layer. Consequently, their contribution to the absorbed dose of the total body dose, compared to that deposited by gamma rays, may be negligible.

Characterizing the radiation dose to persons as a result of exposure to radiation is a complex issue. It is difficult to: (1) measure internally the amount of energy actually transferred to an organic material and to correlate any observed effects with this energy deposition; and (2) account for and predict secondary processes, such as collision effects or biologically triggered effects, that are an indirect consequence of the primary interaction event.

D.3.1 Dose/Exposure Units

D.3.1.1 Roentgen. The roentgen (R) is a unit of x or gamma-ray exposure and is a measured by the amount of ionization caused in air by gamma or x radiation. One roentgen produces 2.58×10^{-4} coulomb per kilogram of air. In the case of gamma radiation, over the commonly encountered range of photon energy, the energy deposition in tissue for a dose of 1 R is about 0.0096 joules (J) /kg of tissue.

D.3.1.2 Absorbed Dose and Absorbed Dose Rate. The absorbed dose is defined as the energy imparted by radiation to a unit mass of the tissue or organ. The unit of absorbed dose is the rad; 1 rad = 100 erg/gram = 0.01 J/kg in any medium. An exposure of 1 R results in a dose to soft tissue of approximately 0.01 J/kg. The SI unit is the gray which is equivalent to 100 rad or 1 J/kg. Internal and external exposures from radiation sources are not usually instantaneous but are distributed over extended periods of time. The resulting rate of change of the absorbed dose to a small volume of mass is referred to as the absorbed dose rate in units of rad/unit time.

D.3.1.3 Working Levels and Working Level Months. Working level (WL) is a measure of the atmospheric concentration of radon and its short-lived progeny. One WL is defined as any combination of short-lived radon daughters (through polonium-214), per liter of air, that will result in the emission of 1.3×10^5 MeV of alpha energy. An activity concentration of 100 pCi radon-222/L of air, in equilibrium with its daughters, corresponds approximately to a potential alpha-energy concentration of 1 WL. The WL unit can also be used for thoron daughters. In this case, 1.3×10^5 MeV of alpha energy (1 WL) is released by the thoron daughters in equilibrium with 7.5 pCi thoron/L. The potential alpha energy exposure of miners is commonly expressed in the unit Working Level Month (WLM). One WLM

corresponds to exposure to a concentration of 1 WL for the reference period of 170 hours, or more generally

WLM = concentration (WL) x exposure time (months) (one “month” = 170 working hours).

D.3.2 Dosimetry Models

Dosimetry models are used to estimate the dose from internally deposited to radioactive substances. The models for internal dosimetry consider the amount of radionuclides entering the body, the factors affecting their movement or transport through the body, distribution and retention of radionuclides in the body, and the energy deposited in organs and tissues from the radiation that is emitted during spontaneous decay processes. The dose pattern for radioactive materials in the body may be strongly influenced by the route of entry of the material. For industrial workers, inhalation of radioactive particles with pulmonary deposition and puncture wounds with subcutaneous deposition have been the most frequent. The general population has been exposed via ingestion and inhalation of low levels of naturally occurring radionuclides as well as radionuclides from nuclear weapons testing.

The models for external dosimetry consider only the photon doses (and neutron doses, where applicable) to organs of individuals who are immersed in air or are exposed to a contaminated object.

D.3.2.1 Ingestion. Ingestion of radioactive materials is most likely to occur from contaminated foodstuffs or water or eventual ingestion of inhaled compounds initially deposited in the lung. Ingestion of radioactive material may result in toxic effects as a result of either absorption of the radionuclide or irradiation of the gastrointestinal tract during passage through the tract, or a combination of both. The fraction of a radioactive material absorbed from the gastrointestinal tract is variable, depending on the specific element, the physical and chemical form of the material ingested, and the diet, as well as some other metabolic and physiological factors. The absorption of some elements is influenced by age, usually with higher absorption in the very young.

D.3.2.2 Inhalation. The inhalation route of exposure has long been recognized as being a major portal of entry for both nonradioactive and radioactive materials. The deposition of particles within the lung is largely dependent upon the size of the particles being inhaled. After the particle is deposited, the retention will depend upon the physical and chemical properties of the dust and the physiological status of the lung. The retention of the particle in the lung depends on the location of deposition, in addition to the physical and chemical properties of the particles. The converse of pulmonary retention is pulmonary clearance. There are three distinct mechanisms of clearance which operate simultaneously. Ciliary clearance acts only in the upper respiratory tract. The second and third mechanisms act mainly in the deep respiratory tract. These are phagocytosis and absorption. Phagocytosis is the engulfing of foreign bodies by alveolar macrophages and their subsequent removal either up the ciliary "escalator" or by entrance into the lymphatic system. Some inhaled soluble particles are absorbed into the blood and translocated to other organs and tissues.

D.3.3 Internal Emitters

An internal emitter is a radionuclide that is inside the body. The absorbed dose from internally deposited radionuclide depends on the energy absorbed per unit mass by the irradiated tissue. For a radionuclide distributed uniformly throughout an infinitely large medium, the concentration of absorbed energy must be equal to the concentration of energy emitted by the radionuclide. An infinitely large medium may be approximated by a tissue mass whose dimensions exceed the range of the particle. All alpha and most beta radiation will be absorbed in the organ (or tissue) of reference. Gamma-emitting radionuclide emissions are penetrating radiation, and a substantial fraction of gamma energy may be absorbed in

tissue. The dose to an organ or tissue is a function of the effective retention half-time, the energy released in the tissue, the amount of radioactivity initially introduced, and the mass of the organ or tissue.

D.4 BIOLOGICAL EFFECTS OF RADIATION

When biological material is exposed to ionizing radiation, a chain of cellular events occurs as the ionizing particle passes through the biological material. A number of theories have been proposed to describe the interaction of radiation with biologically important molecules in cells and to explain the resulting damage to biological systems from those interactions. Many factors may modify the response of a living organism to a given dose of radiation. Factors related to the exposure include the dose rate, the energy of the radiation, and the temporal pattern of the exposure. Biological considerations include factors such as species, age, sex, and the portion of the body exposed. Several excellent reviews of the biological effects of radiation have been published, and the reader is referred to these for a more in-depth discussion (Brodsky 1996; Hobbs and McClellan 1986; ICRP 1984; Mettler and Moseley 1985; Rubin and Casarett 1968).

D.4.1 Radiation Effects at the Cellular Level

According to Mettler and Moseley (1985), at acute doses up to 10 rad (100 mGy), single strand breaks in DNA may be produced. These single strand breaks may be repaired rapidly. With doses in the range of 50–500 rad (0.5–5 Gy), irreparable double-stranded DNA breaks are likely, resulting in cellular reproductive death after one or more divisions of the irradiated parent cell. At large doses of radiation, usually greater than 500 rad (5 Gy), direct cell death before division (interphase death) may occur from the direct interaction of free-radicals with essential cellular macromolecules. Morphological changes at the cellular level, the severity of which are dose-dependent, may also be observed.

The sensitivity of various cell types varies. According to the Bergonie-Tribondeau law, the sensitivity of cell lines is directly proportional to their mitotic rate and inversely proportional to the degree of differentiation (Mettler and Moseley 1985). Rubin and Casarett (1968) devised a classification system that categorized cells according to type, function, and mitotic activity. The categories range from the most sensitive type, "vegetative intermitotic cells", found in the stem cells of the bone marrow and the gastrointestinal tract, to the least sensitive cell type, "fixed postmitotic cells," found in striated muscles or long-lived neural tissues.

Cellular changes may result in cell death, which if extensive, may produce irreversible damage to an organ or tissue or may result in the death of the individual. If the cell recovers, altered metabolism and function may still occur, which may be repaired or may result in the manifestation of clinical symptoms. These changes may also be expressed at a later time as tumors or cellular mutations, which may result in abnormal tissue.

D.4.2 Radiation Effects at the Organ Level

In most organs and tissues the injury and the underlying mechanism for that injury are complex and may involve a combination of events. The extent and severity of this tissue injury are dependent upon the radiosensitivity of the various cell types in that organ system. Rubin and Casarett (1968) describe and schematically display the events following radiation in several organ system types. These include: a rapid renewal system, such as the gastrointestinal mucosa; a slow renewal system, such as the pulmonary epithelium; and a nonrenewal system, such as neural or muscle tissue. In the rapid renewal system, organ injury results from the direct destruction of highly radiosensitive cells, such as the stem cells in the bone marrow. Injury may also result from constriction of the microcirculation and from edema and inflammation of the basement membrane, designated as the histohematic barrier, which may progress to

fibrosis. In slow renewal and nonrenewal systems, the radiation may have little effect on the parenchymal cells, but ultimate parenchymal atrophy and death over several months result from fibrosis and occlusion of the microcirculation.

D.4.3 Low Level Radiation Effects

Cancer is the major latent harmful effect produced by ionizing radiation and the one that most people exposed to radiation are concerned about. The ability of alpha, beta, and gamma radiation to produce cancer in virtually every tissue and organ in laboratory animals has been well-demonstrated. The development of cancer is not an immediate effect. Radiation-induced leukemia has the shortest latent period at about 2 years, while other radiation induced cancers, such as osteosarcoma, have latent periods greater than 20 years. The mechanism by which cancer is induced in living cells is complex and is a topic of intense study. Exposure to ionizing radiation can produce cancer at any site within the body; however, some sites appear to be more common than others, such as the breast, lung, stomach, and thyroid.

DNA is the major target molecule during exposure to ionizing radiation. Other macromolecules, such as lipids and proteins, are also at risk of damage when exposed to ionizing radiation. The genotoxicity of ionizing radiation is an area of intense study, as damage to the DNA is ultimately responsible for many of the adverse toxicological effects ascribed to ionizing radiation, including cancer. Damage to genetic material is basic to developmental or teratogenic effects, as well. However, for effects other than cancer, there is little evidence of human effects at low levels of exposure.

D.5 UNITS IN RADIATION PROTECTION AND REGULATION

D.5.1 Dose Equivalent (or Equivalent Dose)

Dose equivalent (as measured in rem or sievert) is a special radiation protection quantity that is used for administrative and radiation safety purposes to express the absorbed dose in a manner which considers the difference in biological effectiveness of various kinds of ionizing radiation. ICRP (1990) changed this term to equivalent dose, but it has not yet been adopted by the USNRC or DOE.

The USNRC defines the dose equivalent, H, as the product of the absorbed dose, D, and the quality factor, Q, at the point of interest in biological tissue. This relationship is expressed as $H = D \times Q$. The dose equivalent concept is applicable only to doses that are not great enough to produce biomedical effects.

The quality factor or radiation weighting factor is a dimensionless quantity that depends in part on the stopping power for charged particles, and it accounts for the differences in biological effectiveness found among the types of radiation. Originally relative biological effectiveness (RBE) was used rather than Q to define the quantity, rem, which was of use in risk assessment. The generally accepted values for quality factors and radiation weighting factors for various radiation types are provided in Table D-3. The dose equivalent rate is the time rate of change of the dose equivalent to organs and tissues and is expressed as rem/unit time or sievert/unit time.

Table D-3. Quality Factors (Q) and Absorbed Dose Equivalencies

Type of radiation	Quality factor (Q)	Radiation Weighting Factor (w_r)*
X, gamma, or beta radiation	1	1
Alpha particles, multiple-charged particles, fission fragments and heavy particles of unknown charge	20	0.05
Neutrons (other than thermal >> 100 keV to 2 MeV), protons, alpha particles, charged particles of unknown energy	10	20
Neutrons of unknown energy	10	
High-energy protons	10	0.1
Thermal neutrons		5

*Absorbed dose in rad equal to 1 rem or the absorbed dose in gray equal to 1 sievert.

Source: USNRC. 2004. Standards for the protection against radiation, table 1004(b).1. 10 CFR 20.1004. U.S. Nuclear Regulatory Commission, Washington, D.C. NCRP 1993

D.5.2 Relative Biological Effectiveness

RBE is used to denote the experimentally determined ratio of the absorbed dose from one radiation type to the absorbed dose of a reference radiation required to produce an identical biologic effect under the same conditions. Gamma rays from cobalt-60 and 200–250 kVp x-rays have been used as reference standards. The term RBE has been widely used in experimental radiobiology, and the term quality factor (or radiation weighting factor) used in calculations of dose equivalents for radiation safety purposes (ICRP 1977; NCRP 1971; UNSCEAR 1982). Any RBE value applies only to a specific biological end point, in a specific exposure, under specific conditions to a specific species. There are no generally applicable values of RBE since RBEs are specific to a given exposure scenario.

D.5.3 Effective Dose Equivalent (or Effective Dose)

The absorbed dose is usually defined as the mean energy imparted per unit mass to an organ or tissue. This represents a simplification of the actual problem. Normally when an individual ingests or inhales a radionuclide or is exposed to external radiation that enters the body (gamma), the dose is not uniform throughout the whole body. The simplifying assumption is that the detriment will be the same whether the body is uniformly or non-uniformly irradiated. In an attempt to compare detriment from absorbed dose of a limited portion of the body with the detriment from total body dose, the ICRP (1977) has derived a concept of effective dose equivalent. ICRP (1990) changed this term to effective dose, but it has not yet been adopted by the USNRC or DOE.

The effective dose equivalent, H_E, is

$$H_E = (\text{the sum of}) \; W_t \, H_t$$

where H_t is the dose equivalent (or equivalent dose) in the tissue t, W_t is the tissue weighting factor in that tissue, which represents the estimated proportion of the stochastic risk resulting from tissue, t, to the stochastic risk when the whole body is uniformly irradiated for occupational exposures under certain conditions (ICRP 1977). Tissue weighting factors for selected tissues are listed in Table D-4.

D.5.4 SI Units

The ICRU (1980), ICRP (1984), and NCRP (1985) now recommend that the rad, roentgen, curie, and rem be replaced by the SI units: gray (Gy), Coulomb per kilogram (C/kg), Becquerel (Bq), and sievert (Sv), respectively. The relationship between the customary units and the international system of units (SI) for radiological quantities is shown in Table D-5.

Table D-4. Tissue Weighting Factors for Calculating Effective Dose Equivalent and Effective Dose for Selected Tissues

	Tissue weighting factor	
Tissue	NCRP115/ ICRP60	USNRC/ICRP26
Bladder	0.05	–
Bone marrow	0.12	0.12
Bone surface	0.01	0.03
Breast	0.05	0.15
Colon	0.12	–
Esophagus	0.05	–
Gonads	0.20	0.25
Liver	0.05	–
Lung	0.12	0.12
Skin	0.01	–
Stomach	0.12	–
Thyroid	0.05	0.03
Remainder	0.05	0.30
Total	1.00	1.00

ICRP60 = International Commission on Radiological Protection, 1990 Recommendations of the ICRP
NCRP115 = National Council on Radiation Protection and Measurements. 1993. Risk Estimates for Radiation Protection, Report 115. Bethesda, Maryland
USNRC = Nuclear Regulatory Commission, Title 10, Code of Federal Regulations, Part 20

Table D-5. Comparison of Common and SI Units for Radiation Quantities

Quantity	Customary units	Definition	SI units	Definition
Activity (A)	curie (Ci)	3.7×10^{10} transformations s^{-1}	becquerel (Bq)	s^{-1}
Absorbed dose (D)	rad	10^{-2} Jkg^{-1}	gray (Gy)	Jkg^{-1}
Absorbed dose rate ($\dot{D}$)	rad per second (rad s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	gray per second (Gy s^{-1})	Jkg^{-1} s^{-1}
Dose equivalent (H)	rem	10^{-2} Jkg^{-1}	sievert (Sv)	Jkg^{-1}
Dose equivalent rate ( )	rem per second (rem s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	sievert per second (Sv s^{-1})	Jkg^{-1} s^{-1}
Effective dose	rem	10^{-2} Jkg^{-1}	Sievert (Sv)	Jkg^{-1}
Equivalent dose (H)	rem	10^{-2} Jkg^{-1}	Sievert (Sv)	Jkg^{-1}
Linear energy transfer (LET)	kiloelectron volts per micrometer (keV μm^{-1})	1.602×10^{-10} Jm^{-1}	kiloelectron volts per micrometer (keV μm^{-1})	1.602×10^{-10} Jm^{-1}

Jkg^{-1} = Joules per kilogram; $Jkg^{-1}s^{-1}$ = Joules per kilogram per second; Jm^{-1} = Joules per meter; s^{-1} = per second

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