TOXICOLOGICAL PROFILE FOR IONIZING RADIATION

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

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Ionizing Radiation, Draft for Public Comment, was released in February 1998. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. 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
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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:

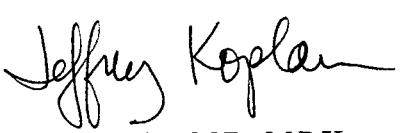
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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 3: Summary of Health Effects of Ionizing Radiation: Specific health effects of ionizing radiation are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), 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: Three new sections have been added to this Toxicological Profile to address child health issues:

Section 1.6 **How Can Ionizing Radiation Affect Children?**
Section 1.7 **How Can Families Reduce the Risk of Exposure to Ionizing Radiation?**
Section 3.2.2 **Children's Susceptibility**

Other Sections of Interest:

Section 3.2.1.4 **Teratogenic/Embryotoxic Effects**
Section 3.2.3 **Carcinogenic Effects from Ionizing Radiation Exposure**

ATSDR Information Center

Phone: 1-888-42-ATSDR or 404-639-6357 ***Fax:*** 404-639-6359
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.

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@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm

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: 847-228-6850 • FAX: 847-228-1856.

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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.

PEER REVIEW

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

1. Herman Cember, Ph.D., CHP, Consultant, Lafayette, IN;

2. Richard Toohey, Ph.D., CHP, Consultant, Oak Ridge, TN;

3. Kenneth Mossman, Ph.D., Professor, Scottsdale, AZ;

4. John Poston, Ph.D., Professor, College Station, TX; and

5. Darrell Fisher, Ph.D., Senior Scientist, Richland, WA.

These experts collectively have knowledge of ionizing radiation'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 ionizing radiation and the effects of exposure. It does not tell you about non-ionizing radiation, such as microwaves, ultrasound, or ultraviolet radiation.

Exposure to ionizing radiation can come from many sources. You can learn when and where you may be exposed to sources of ionizing radiation in Section 1.3 of this chapter. One source of exposure is from hazardous waste sites that contain radioactive waste. 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 federal cleanup. However, it's unknown how many of the 1,467 current or former NPL sites have been evaluated for the presence of ionizing radiation sources. As more sites are evaluated, the sites with ionizing radiation may increase. This information is important because exposure to ionizing radiation 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. Even in the event that you are exposed, it does not necessarily mean you will be harmed or suffer long-term health effects from exposure to ionizing radiation.

If you are exposed to ionizing radiation, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and the type of radiation. You must also consider the chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS IONIZING RADIATION?

To explain what ionizing radiation is, we will start with a discussion of atoms, how they come to be radioactive, and how they give off ionizing radiation. Then, we will explain where radiation comes from. Finally, we will describe the more important types of radiation to which you may

be exposed. Of the different types and sources of ionizing radiation, this profile will discuss the three main types: alpha, beta, and gamma radiation.

The Atom. Before defining ionizing radiation, it is useful to first describe an atom. Atoms are the basic building blocks of all elements. We have models of an atom that are supported by measurements. An atom consists of one nucleus, made of protons and neutrons, and many smaller particles called electrons. The electrons normally circle the nucleus much like the planets or comets circle the sun. The number of protons in the atom's nucleus determines which element it is. For example, an atom with one proton is hydrogen and an atom with 27 protons is cobalt. Each proton has a positive charge, and positive charges try to push away from one another. The neutrons neutralize this action and act as a kind of glue that holds the protons together in the nucleus. The number of protons in an atom of a particular element is always the same, but the number of neutrons may vary. Neutrons add to the weight of the atom, so an atom of cobalt that has 27 protons and 32 neutrons is called cobalt-59 because 27 plus 32 equals 59. If one more neutron were added to this atom, it would be called cobalt-60. Cobalt-59 and cobalt-60 are isotopes of cobalt. Isotopes are forms of the same element, but differ in the number of neutrons within the nucleus. Since cobalt-60 is radioactive, it is called a radionuclide. All isotopes of an element, even those that are radioactive, react chemically in the same way. Atoms tend to combine with other atoms to form molecules (for example, hydrogen and oxygen combine to form water). Radioactive atoms that become part of a molecule do not affect the way the molecule behaves in chemical reactions or inside your body.

What Ionizing Radiation Is. Ionizing radiation is energy that is carried by several types of particles and rays given off by radioactive material, x ray machines, and fuel elements in nuclear reactors. Ionizing radiation includes alpha particles, beta particles, x rays, and gamma rays. Alpha and beta particles are essentially small fast moving pieces of atoms. X rays and gamma rays are types of electromagnetic radiation. These radiation particles and rays carry enough energy that they can knock out electrons from molecules, such as water, protein, and DNA, with which they interact. This process is called ionization, which is why it is named "ionizing

radiation." We cannot sense ionizing radiation, so we must use special instruments to learn whether we are being exposed to it and to measure the level of radiation exposure. The other types of electromagnetic radiation include radiowaves microwaves, ultrasound, infrared radiation, visible light, and ultraviolet light. These types of radiation do not carry enough energy to cause ionization and are called non-ionizing radiation. This profile will only discuss ionizing radiation.

What Ionizing Radiation Is Not. Ionizing radiation is not a substance like salt, air, water, or a hazardous chemical that we can eat, breathe, or drink or that can soak through our skin. However, many substances can become contaminated with radioactive material, and people can be exposed to ionizing radiation from these radioactive contaminants.

How Does an Atom Become Radioactive? An atom is either stable (not radioactive) or unstable (radioactive). The ratio of neutrons to protons within the nucleus determines whether an atom is stable. If there are too many or too few neutrons, the nucleus is unstable, and the atom is said to be radioactive. There are several ways an atom can become radioactive. An atom can be naturally radioactive, it can be made radioactive by natural processes in the environment, or it can be made radioactive by humans. Naturally occurring radioactive materials such as potassium-40 and uranium-238 have existed since the earth was formed. Other naturally occurring radioactive materials such as carbon-14 and hydrogen-3 (tritium) are formed when radiation from the sun and stars bombards the earth's atmosphere. The elements heavier than lead are naturally radioactive because they were originally formed with too many neutrons. Human industry creates radioactive materials by one of two different processes. In the first process, a uranium or a plutonium atom captures a neutron and splits (undergoes nuclear fission) into two radioactive fission fragments plus two or three neutrons. In a nuclear reactor, one of these "fission neutrons" is captured by another uranium atom, and the fission process is repeated. In the second process, stable atoms are bombarded either by neutrons or by protons that are given a lot of energy in a machine called an accelerator. The stable atoms capture these bombarding particles and become radioactive. For example, stable cobalt-59, found in the steel

surrounding a nuclear reactor, is hit by neutrons coming from the reactor and can become radioactive cobalt-60. Any material that contains radioactive atoms is radioactive material.

How Does a Radioactive Atom Give off Ionizing Radiation? Because a radioactive atom is unstable, at some time in the future, it will transform into another element by changing the number of protons in the nucleus. This happens because one of several reactions takes place in the nucleus to stabilize the neutron-proton ratio. If the atom contains too many neutrons, a neutron changes into a proton and throws out a negative "beta" (pronounced bay' tah) particle. If the atom contains too many protons, normally a proton changes into a neutron and throws out a positive "beta" particle. Some atoms that are more massive than lead, such as radium, transform by emitting an "alpha" (pronounced al'-fah) particle. Any excess energy that is left can be released as "gamma" rays, which are the same as x rays. Other reactions are also possible, but the final result is to make a radioactive atom into a stable atom of a different element. For example, each atom of cobalt-60 is radioactive because it has too many neutrons. At some time in the future, one of its neutrons will change into a proton. As it changes, the atom gives off its radiation, which is a negative beta particle and two gamma rays. Because the atom now has 28 protons instead of 27, it has changed from cobalt into nickel. In this way, unstable atoms of radioactive cobalt-60 give off radiation as they transform into stable atoms of nickel-60.

How Long Can Radioactive Material Give Off Ionizing Radiation? Theoretically, it gives off ionizing radiation forever. Practically, however, after 10 half-lives, less than 0.1% of the original radioactivity will be left and the radioactive material will give off infinitesimally small amounts of ionizing radiation. The half-life is the time it takes one-half of the radioactive atoms to transform into another element, which may or may not also be radioactive. After one half-life, ½ of the radioactive atoms remain; after two half-lives, half of a half or 1/4 remain, then 1/8, 1/16, 1/32, 1/64, etc. The half-life can be as short as a fraction of a second or as long as many billions of years. Each type of radioactive atom, or radionuclide, has its own unique half-life. For example, technetium-99m and iodine-131, which are used in nuclear medicine, have 6-hour

and 8-day half-lives, respectively. The naturally occurring radionuclide, uranium-235, which is used in nuclear reactors, has a half-life of 700 million years. Naturally occurring potassium-40, which is present in the body, has a half-life of 13 billion years and undergoes about 266,000 radioactive transformations per minute in the body. Thus, technetium-99m will remain radioactive for 60 hours, and iodine-131 will remain radioactive for 3 months. On the other hand, long-lived naturally occurring uranium and potassium will remain, practically speaking, radioactive forever.

What Are the Three Types of Radiation? The three main types of ionizing radiation are called alpha, beta, and gamma radiation. These are named for letters of the Greek alphabet, and they are often symbolized using the Greek letters α (alpha), β (beta), and γ (gamma).

Alpha Radiation (or Alpha Particles). This type of radiation can be called either alpha radiation or alpha particles. Alpha radiation is a particle, consisting of two protons and two neutrons, that travels very fast and thus has a good deal of kinetic energy or energy of motion. The two protons and neutrons make an alpha particle identical to a helium atom, but without the electrons. Although it is much too small to be seen with the best microscope, it is large compared to a beta particle. The protons give it a large positive charge that pulls hard at the electrons of other atoms it passes near. When the alpha particle passes near an atom, it excites its electrons and can pull an electron from the atom, which is the process of ionization. Each time the alpha particle pulls an electron off from an atom in its path, the process of ionization occurs. With each ionization, the alpha particle loses some energy and slows down. It will finally take two electrons from other atoms at the end of its path and become a complete helium atom. This helium has no effect on the body. Because of their large mass and large charge, alpha particles ionize tissue very strongly. If the alpha particle is from radioactive material that is outside the body, it will lose all its energy before getting through the outer (dead) layer of your skin. This means that you can only be exposed to alpha radiation if you take radioactive material that produces alpha radiation into your body (for example, if you breathe it in or swallow it in food or drink). Once inside the body, this radioactive material can be mixed in the contents of

the stomach and intestines, then absorbed into the blood, incorporated into a molecule, and finally deposited into living tissue such as the bone matrix. The alpha particles from this radioactive material can cause damage to this tissue.

Beta Radiation (or Beta Particles). This type of radiation can be called either beta radiation or beta particles. Beta particles are high-energy electrons that some radioactive materials emit when they transform. Beta particles are made in one of two ways, depending on the radioactive material that produces them. As a result, they will have either a positive charge or a negative charge. Most beta particles are negatively charged. They are much lighter and much more penetrating than alpha particles. Their penetrating power depends on their energy. Some, such as those from tritium, have very little energy, and can't pass through the outer layer of dead skin. Most have enough energy to pass through the dead outer layer of a person's skin and irradiate the live tissue underneath. You can also be exposed to beta radiation from within if the beta-emitting radionuclide is taken into the body. A beta particle loses its energy by exciting and ionizing atoms along its path. When all of its kinetic energy is spent, a negative beta particle (negatron) becomes an ordinary electron and has no more effect on the body. A positive beta particle (positron) collides with a nearby negative electron, and this electron-positron pair turns into a pair of gamma rays called annihilation radiation, which can interact with other molecules in the body.

Gamma Radiation (or Gamma Rays). This type of radiation can be called either gamma radiation or gamma rays. Unlike alpha and beta radiation, gamma radiation is not a particle, but is a ray. It is a type of light you cannot see, much like radio waves, infrared light, ultraviolet light, and x rays. When a radioactive atom transforms by giving off an alpha or a beta particle, it may also give off one or more gamma rays to release any excess energy. Gamma rays are bundles of energy that have no charge or mass. This allows them to travel very long distances through air, body tissue, and other materials. They travel so much farther than either alpha or beta radiation that the source of the gamma rays doesn't have to be inside the body or near the skin. The gamma ray source can be relatively far away, like the radioactive materials in nearby

construction materials, soil, and asphalt. A gamma ray may pass through the body without hitting anything, or it may hit an atom and give that atom all or part of its energy. This normally knocks an electron out of the atom (and ionizes the atom). This electron then uses the energy it received from the gamma ray to ionize other atoms by knocking electrons out of them as well. Since a gamma ray is pure energy, once it loses all its energy it no longer exists.

More information about alpha, beta, and gamma radiation can be found in Chapter 2 of this profile.

1.2 HOW DOES RADIOACTIVE MATERIAL ENTER AND SPREAD THROUGH THE ENVIRONMENT?

Radioactive material can be released to the air as particles or gases as a result of natural forces and from human industrial, medical, and scientific activities. Everyone, with no exception, is exposed to ionizing radiation that comes from natural sources, such as cosmic radiation from space and terrestrial radiation from radioactive materials in the ground. Ionizing radiation can also come from industrially produced radioactive materials (such as iridium-192); nuclear medicine (such as thyroid cancer treatment with iodine-131 and thyroid scans using iodine-125, or bone scans using technetium-99m); biological and medical research using carbon-14, tritium, and phosphorus-32; the nuclear fuel cycle (producing fission products such as cesium-137 and activation products such as cobalt-60); and production and testing of nuclear weapons. Radioactive material released into the air is carried by the wind and is spread by mixing with air. It is diluted in the atmosphere and can remain there for a long time. When the wind blows across land contaminated with radioactive materials, radioactive particles can be stirred up and returned to the atmosphere. Radioactive material on the ground can be incorporated into plants and animals, which may later be eaten by people.

Water can contain man-made and naturally occurring radioactive materials that it dissolves from the soil it passes over or through. Rain and snow also wash man-made and naturally occurring radioactive material out of the air. Radioactive material may be added to water through planned or accidental releases of liquid radioactive material from sources such as hospitals, research universities, manufacturing plants, or nuclear facilities. Radioactive material can also reach surface waters when airborne radioactive materials settle to the earth or are brought down by rain or snow, and when soil containing radioactive material is washed away into a river or lake. The movement of liquid radioactive material is limited by the size of the bodies of water into which the radioactive materials have drained. Like silt, some radioactive material may settle along the banks or in the bottoms of ponds and rivers. In public health and ecological contexts, it is sometimes important to distinguish between dissolved radioactivity and radioactivity bound to suspended or settled solid particles. Radioactive material may also concentrate in aquatic animals and plants. Eventually, radioactive material in liquid runoff that goes into rivers and streams may reach the oceans (there are approximately one million radioactive transformations per minute of the naturally occurring radioactive potassium in one cubic meter of ocean water).

Radioactive material moves very slowly in soil compared to its speed of movement in air and water. Radioactive material will often stick to the surface of the soil. The organic material in soils can bind radioactive material, which slows its movement through the environment. If crops are watered with water containing radioactive material, the radioactive material may be taken up through the roots of the plant or may contaminate the outside of the plant. The plants may then be eaten by both animals and people. Radioactive materials that occur naturally in the soil (uranium, radium, thorium, potassium, tritium, and others) are also taken up by plants, and become available for intake by animals and people.

More information about what happens to radioactive material when it enters the environment can be found in Chapters 5 and 6 of this profile.

1.3 HOW MIGHT I BE EXPOSED TO IONIZING RADIATION?

The earth is continually irradiated with low levels of ionizing radiation, so all animals, plants, and other living creatures are exposed to small amounts of ionizing radiation from several sources every day. Figure 1-1 shows that most of your radiation dose comes naturally from the environment. Smaller portions come from medicine, consumer products and other sources.

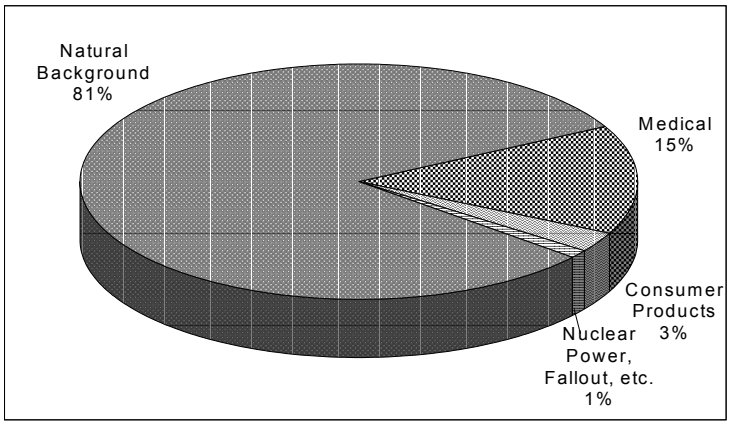


Figure 1-1. Sources of Radiation Exposure to the Average U.S. Citizen
(adapted from NCRP 1987a)

Figure 1-2 is another breakdown of the sources of radiation dose to the average American. The natural background levels (81%) shown in Figure 1-1 include the radon, terrestrial, cosmic, and natural internal sources shown in Figure 1-2. Most of your daily radiation dose is from radon (55%), which is found in all air. Higher levels are normally found indoors (especially in the basement). Figure 1-3 shows that indoor levels of radon vary depending on where you live. Higher levels can be found in underground areas, such as mines. You are always exposed to radiation from cosmic sources (mostly from outer space, some from the sun, 8%), terrestrial sources (rocks and soil, 8%), and natural internal sources (radioactive material normally inside your body, 10%). You may also be exposed to radiation from x ray exams (11%), nuclear medicine exams such as thyroid scans (4%), and consumer products including TV and smoke detectors (3%), as well as other sources.

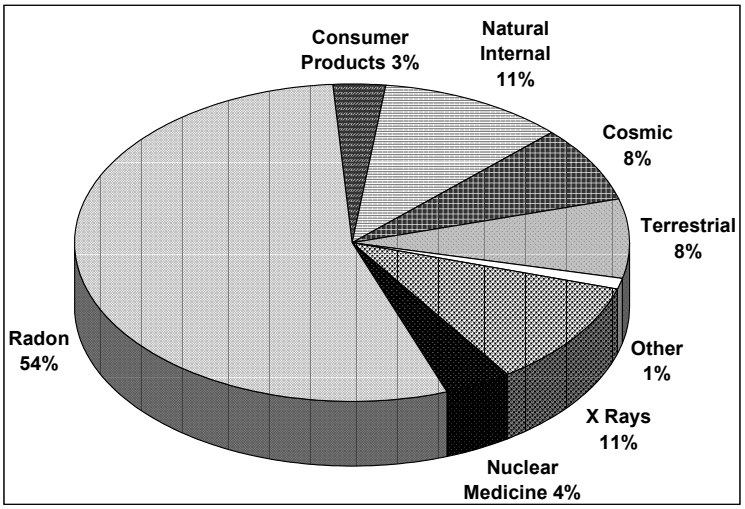


Figure 1-2. Detailed Breakdown of Radiation Exposures
(adapted from NCRP 1987a)

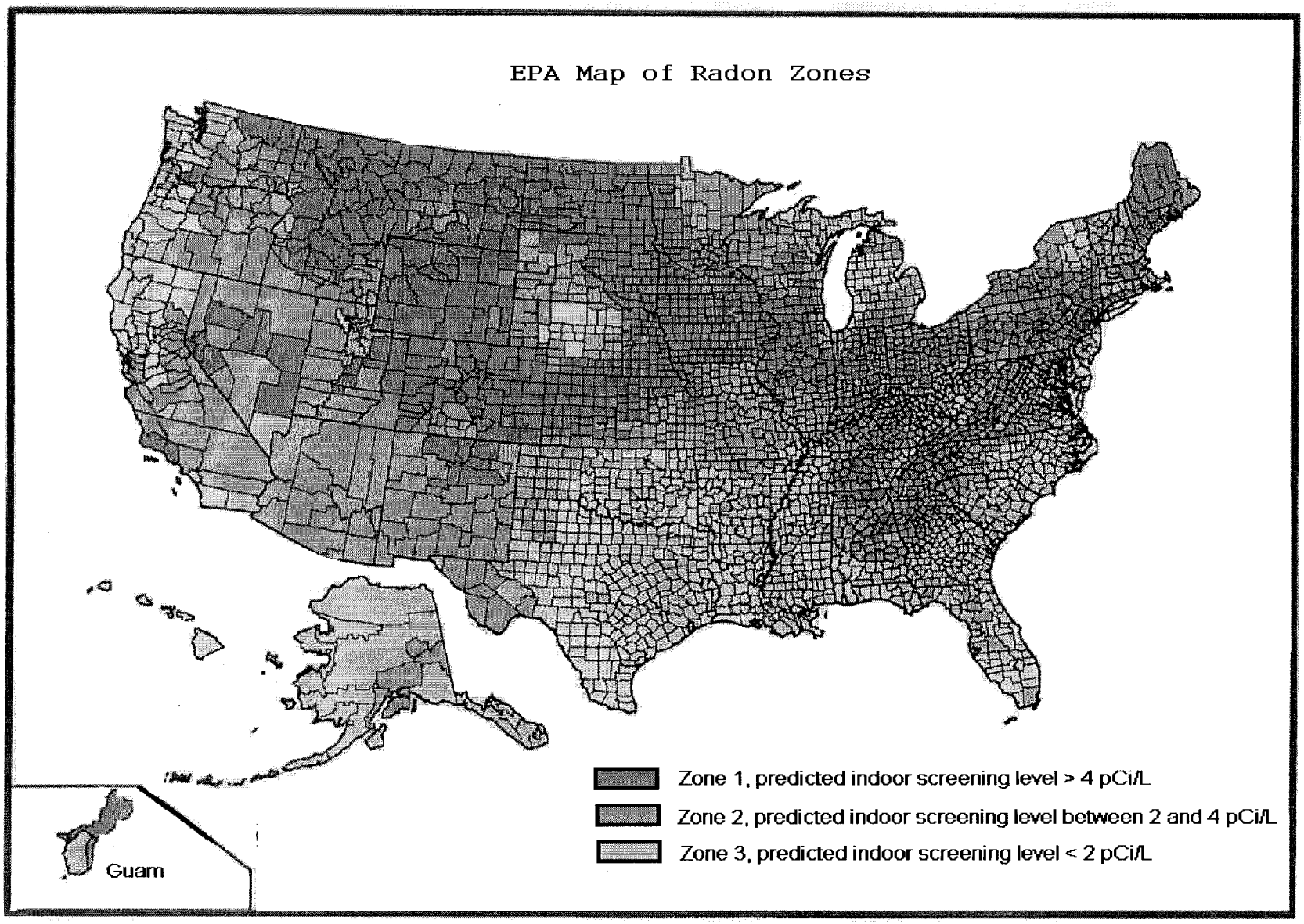


Figure 1-3. EPA Map of Indoor Radon Levels in the United States
(adapted from EPA 1999b)

Less than 1% of the total ionizing radiation dose to people living in the United States comes from their jobs, nuclear fallout, the nuclear fuel cycle, or other exposures. However, people in some types of jobs may have higher doses (pilots and flight attendants, astronauts, industrial and nuclear power plant workers, x ray personnel, medical personnel, etc.). Some groups of people have been exposed to higher-than-normal levels of ionizing radiation from weapons testing, and some individuals from accidents at nuclear facilities or in industry. Some of these exposures are discussed in Chapter 3 of this profile.

Not everyone will be exposed to every source or the same percentage of radiation shown in Figure 1-2. Since the percentages shown in Figure 1-2 are averages, half of the population will receive greater doses and half will receive smaller doses from the several sources shown in the figure. For example, if you are not regularly x rayed, you may receive less total radiation dose than what is shown. However, if you live in a town or city at a high altitude, you may receive a greater radiation dose from outer space cosmic rays than someone who lives in a town or city near the ocean at sea-level. Table 1-1 shows you that where you live and what you do determines how much ionizing radiation you will receive.

“Dose” is a broad term that is often used to mean either absorbed dose, or dose equivalent, depending on the context. The absorbed dose is measured in both a traditional unit called a rad and an International System (S.I.) unit called a gray (Gy). Both grays and rads are physical units (1 Gy = 100 rad) that measure the concentration of absorbed energy. The absorbed dose is the amount of energy absorbed per kilogram of absorber. Physical doses from different radiations are not biologically equivalent. For this reason, a unit called the dose equivalent, which considers Both the physical dose and the radiation type, is used in radiation safety dosimetry. The unit of dose equivalent is called the rem in traditional units and the sievert (Sv) in S.I. units (1 rem = 0.01 Sv). For beta and gamma radiation, 1 rad = 1 rem (1 gray = 1 sievert). For alpha radiation, however, 1 rad = 20 rem (1 gray = 20 sievert). Small radiation doses can be expressed using small dose units such as the millirem (mrem) and the millisievert (mSv), where 1 mrem = 0.001 rem and 1 mSv = 0.001 Sv.

The average annual dose to a person in the United States is about 360 mrem (3.6 mSv). An individual’s exact dose depends on several factors, such as the natural background where the

person lives, and the person's medical history and occupational experience with sources of radiation.

More information about exposure to ionizing radiation can be found in Chapters 2 and 6 of this profile.

Table 1-1. Approximate Doses of Ionizing Radiation to Individuals

Activity	Approximate doses of radiation received	Comments
Average American exposure to ionizing radiation[a]		
Total yearly dose	360 mrem/yr (3.6 mSv/yr)	
From natural sources	300 mrem/yr (3.0 mSv/yr)	
From man-made sources	60 mrem/yr (0.6 mSv/yr)	
From nuclear power	Less than 1 mrem/yr (<0.01 mSv/yr)	
Approximate doses of ionizing radiation (cosmic + terrestrial) for different locations		
Kerala, India, resident	1300 mrem/yr (13 mSv/yr)	Concentrated radioactive material in the soil
Colorado state resident	179 mrem/yr (1.79 mSv/yr)	High altitude above sea level
Boston, Massachusetts, resident	100 mrem/yr (1 mSv/yr)	
Louisiana state resident	92 mrem/yr (0.92 mSv/yr)	Low altitude above sea level
Approximate doses of ionizing radiation above background radiation and some activities[b]		
Anyone near a patient released after a nuclear medicine test.	Less than 500 mrem/patient (5 mSv/patient)	Guidance for medical facilities. Quantity depends on the quantity of radioactive material.
A person who works inside a nuclear power plant	< 300 mrem/yr (<3 mSv/yr)	
A person who gets a full set of dental x rays	40 mrem (0.4 mSv)	
A flight attendant flying from New York to Los Angeles	5 mrem/flight (0.05 mSv/flight)	
Watching a color TV set	2–3 mrem/yr (0.02–0.03 mSv/yr)	
A person who lives directly outside of a nuclear power plant	1 mrem/yr (0.01 mSv/yr)	
A person who lives in a multi-storied apartment building	~1 mrem/yr for each 5 stories above the ground floor (<0.01 mSv/yr)	Difference between Los Angeles and Denver = 87 mrem/5000 feet = 2 mrem/100 feet = 1 mrem/5 stories
A person who watches a truck carrying nuclear waste pass by	Less than 0.1 mrem/truck (0.001 mSv)	

[a]Taken from NCRP 1976a
[b]Taken from NCRP 1987b, 1987e, 1989a, 1989c

mrem = millirem for each occasion; mrem/yr = millirem per year

1.4 HOW CAN IONIZING RADIATION ENTER AND LEAVE MY BODY?

Ionizing radiation exposure can occur from a radiation source outside of the body. Exposure can also occur as a result of taking radioactive material into your body. The answer to the question of how you can be exposed to ionizing radiation can be broken into two parts. The first paragraph below describes ionizing radiation that comes from a source outside your body and some distance away (external radiation). The second paragraph describes ionizing radiation that comes from a source inside your body (internal radiation).

External radiation comes from natural and man-made sources of ionizing radiation that are *outside your body*. Part of the natural radiation is cosmic radiation from space. The rest is given off by radioactive materials in the soil and building materials that are around you. As a result of human activities, higher levels of natural radioactive material are left in products or on the land. Examples of such activities are manufacturing fertilizer, burning coal in power plants, and mining and purifying uranium. Ionizing radiation from human activities adds to your external radiation exposure. Some of this radiation is given off by x ray machines, televisions, radioactive sources used in industry, and patients who have had recent nuclear medicine tests and therapy. The rest is given off by man-made radioactive materials in consumer products, industrial equipment, atom bomb fallout, and to a smaller extent by hospital waste and nuclear reactors. Gamma rays are the main type of ionizing radiation that are of concern when you are exposed to external sources of ionizing radiation. Gamma rays (like x rays) are special bundles of light energy that you cannot see, feel, or smell. Gamma rays from natural and man-made sources pass through your body just like x rays do, at the speed of light. Gamma rays may pass directly through your body without hitting anything. When one gamma ray hits a cell, it leaves a small bit of energy behind that can cause damage. Other types of ionizing radiation, like alpha and beta particles, hit your body but normally do not have enough energy to get inside to harm you. Your external radiation dose depends on the amount of energy that ionizing radiation gives to your body as it passes through. Exposure to external radiation does not make you radioactive. The average yearly dose from external radiation in the United States is about 100 mrem per person (1 mSv/person).

Internal radiation is ionizing radiation that natural and man-made radioactive materials give off while they are *inside your body*. You take radioactive materials into your body every day since

they are in the air you breathe, the food you eat, and the water you drink. Examples of natural radioactive materials that enter, reside in, and leave your body every day include potassium-40, carbon-14, radium, and radon. Man-made radioactive materials also get into your body from the decreasing amounts of fallout from past nuclear weapons testing. Sometimes, natural conditions or industrial activities concentrate radioactive materials. If you are exposed to these, you will take in more radioactive material. Low amounts of material that act as sources of ionizing radiation may also be put into your body for medical purposes to test for or treat some types of disease, such as cancer. Scientists and clinicians have made sure that the benefits of exposing you to ionizing radiation far outweigh any bad health effects you may get from the ionizing radiation by itself. (Medical tests use small amounts of radiation or radioactive material, but some radiotherapy uses large doses that are beneficial to the patient.) Hospitals, coal-fired electricity generating plants, and nuclear reactors release radioactive materials in ways that keep your dose low. Radioactive materials build up in your body if you take them in faster than they leave in urine and feces and by radioactive transformation. If the internally deposited radioisotope is short lived and decays before the body eliminates it, then, of course, it will disappear faster from the body than by biological elimination alone. Thus, retention or elimination of internally deposited radioisotopes is measured by the effective half-life, which considers the combined effect of biological elimination and radioactive decay.

Internally deposited radioisotopes may emit gamma rays, beta particles, or alpha particles, depending on the isotope. Many gamma rays escape your body without hitting anything. When a gamma ray does hit a cell, it transfers energy to the cell. When all their energy is transferred, they vanish. Alpha and beta particles travel short distances, giving energy to cells they hit. They lose energy and quickly come to a stop. Their energy is totally absorbed inside your body. When alpha particles come to a stop, they become helium that you breathe out later. When beta particles come to a stop, they become electrons and attach to atoms near them. Your internal dose is a measure of the energy deposited by all the ionizing radiation that is produced inside your body. The average yearly dose in the United States from internal radiation is about 260 mrem per person (2.6 mSv/person).

More information about how ionizing radiation enters and leaves your body can be found in Chapters 2, 3 and 5 of this profile.

1.5 HOW CAN IONIZING RADIATION AFFECT MY HEALTH?

How radiation affects your health depends on the size of the radiation dose. Scientists have been studying the effects of ionizing radiation in humans and laboratory animals for many years. Studies so far have not shown that the low dose of ionizing radiation we are exposed to every day causes us any harm. We do know that exposure to massive amounts of ionizing radiation can cause great harm, so it is wise to not be exposed to any more ionizing radiation than necessary.

Overexposure to high amounts of ionizing radiation can lead to effects like skin burns, hair loss, birth defects, cancer, mental retardation (a complex central nervous system functional abnormality), and death. The dose determines whether an effect will be seen and its severity. For some effects such as skin burns, hair loss, sterility, nausea, and cataracts, there is a certain minimum dose (the threshold dose) that must be exceeded to cause the effect. Increasing the size of the dose after the threshold is exceeded makes the effect more severe. Psychological stress has been documented in large populations exposed to small doses of radiation (Three Mile Island and Chernobyl). Neurological injury (CNS syndrome) resulting in compromised mental function has also been documented in individuals exposed to several thousand rads of ionizing radiation.

Ionizing radiation is called a carcinogen because it may also increase your chance of getting cancer. Increasing the size of the dose increases your chance of getting cancer. Scientists base radiation safety standards on the assumption that any radiation dose, no matter how small, carries with it a corresponding probability of causing a cancer. This is called a “zero threshold” dose response relationship. Cancers that are actually caused by radiation are completely indistinguishable from those from other causes, so we can never be certain whether any individual cancer was not caused by radiation. To determine how likely it is that a certain dose of radiation will cause cancer, scientists measure the radiation dose to a group of exposed people, like the Japanese atomic bomb survivors. Then they compare the frequency of cancers (the observation period for cancer extends over decades) in this exposed group with a similar group of people who were not exposed. They also look at factors like age, sex, and time since the exposure ended. Finally, they calculate risk factors for various cancer types. Using these factors, it is possible to estimate the chance of getting cancer from a dose of radiation. Even though they assume a zero threshold, researchers have not actually seen an increase in cancer

frequency for people in the exposed Japanese group who had a radiation dose below 20 rad (0.2 Gy). No increase in any type of leukemia has been found in people whose radiation dose was below 10–40 rad (0.1–0.4 Gy).

The effects of internally deposited radioactive material are similar to those of external radiation. The effects depend on the size of the dose and factors like your sex and age when you were exposed. The radiation absorbed dose, in turn, depends on the radioactive material, the amount of activity, the type and energy of the radiation, the effective half-life of the radioactive material, its chemical form, how it was taken into your body, and how quickly it leaves your body.

Many people are exposed to radiation and radioactive materials used in medical testing and therapy. Radiation treatments for medical reasons carry the same risk as radiation from other sources. As with any medical treatment, the potential health benefits should be balanced against the potential harmful health effects.

One way to better understand the effects of radiation is to study its effects on test animals. Without laboratory animals, scientists would lose a basic method to get information needed to make informed 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.

More information about the biological effects of ionizing radiation can be found in Chapters 2, 3, and 5 of the profile.

1.6 HOW CAN IONIZING RADIATION AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Like adults, children are exposed to small background amounts of ionizing radiation that comes from the soil around where they live, in the food and water that they eat and drink, in the air that

they breathe, and from sources that reach earth from space. How much background radiation you receive depends on where you live. Some places naturally have more than others. There are no reports that say exposure to background levels of ionizing radiation causes health effects in children or adults.

If a pregnant woman is exposed to high levels of ionizing radiation, it is possible that her child may be born with some brain abnormalities. There is an 8-week period during early pregnancy when an unborn child is especially sensitive to the effects of higher than normal levels of ionizing radiation. As the levels of ionizing radiation increase, so does the chance of brain abnormalities. These abnormalities may eventually result in small head size, decreased intelligence as measured by Intelligence Quotient (IQ) tests, and other defects. These effects are not reversible.

A child will be exposed to small amounts of radiation from the environment all during prenatal development and throughout its life. There are no reports that say children suffer health effects from normal amounts of background radiation. If children are exposed to higher than background levels of ionizing radiation, they are likely to have the same possible health effects as adults exposed to similar levels.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO IONIZING RADIATION?

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

The best way to reduce your risk of exposure to higher than background amounts of radiation is to not let yourself be exposed at all. However, this is not always possible or sensible. A common way to be exposed to ionizing radiation is by receiving an x ray, but a few x rays every year will not hurt you**.** When you or your children receive an x ray, be sure to correctly wear any protective garments that are provided. The technician will make sure that only the area that needs to be x rayed will be exposed to the x ray beam.

It may be necessary to inject you with a chemical that has some amount of radioactive material in it to help a doctor diagnose or treat a disease. Many studies have shown that these drugs, used correctly, will not harm you. Be sure to follow the doctor's directions after you have been treated with these drugs.

Many places make or use various types of radioactive material or ionizing radiation for medical or research purposes. If you visit one of these facilities, be sure to follow all of the recommended safety precautions. Do not go into unauthorized areas. You may be asked to wear a special device on your shirt that records the amount of ionizing radiation you are exposed to while in the facility. This is a safety precaution. Do not put it in your pocket or let someone else wear it.

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

There are no easy or accurate medical tests to determine whether you have been exposed to low doses of ionizing radiation, but tests are available for determining whether you have been exposed to radioactive material.

Tests for Recent Exposure to Ionizing Radiation. A great degree of overexposure is necessary to cause the clinical signs or symptoms of radiation exposure. In the absence of clinical signs or symptoms there are two kinds of tests scientists use to see if you have been overexposed to ionizing radiation; they look for changes in blood cell counts and changes in your chromosomes. If you are exposed to no more than 10 rad (0.1 Gy) of ionizing radiation, there are no detectable changes in blood cell counts. The most sensitive measure of radiation exposure involves a study of your chromosomes. This is a special test for doses that are too low to produce clinically observable signs or symptoms; this test may be useful for doses greater than about 3 times the maximum annual permissible dose for radiation workers. Changes in the white blood cell count may be seen in people whose doses exceeded about 5 times the occupational maximum permissible annual dose. Radiation doses at or above these levels can be reliably estimated using these two special tests.

Tests for Radioactive Material Inside Your Body. Scientists can also examine your blood, feces, saliva, urine, and even your entire body to see if measurable amounts of radioactive material are being excreted from your body. Different tests are used for different types of radioactive material. Several types of instruments are available to look for each type of radiation. These instruments are not available at your doctor's office. They are normally large, heavy, and available only in laboratories. Equipment usually consists of a "detector," electrical cables, and a "processor." The detector contains material sensitive to one or more types of radiation, so the detector is chosen based on the type of radiation to be measured. Alpha, beta, and gamma radiation have different energies that depend upon the radioactive isotope from which they come. By determining the type and energy of the radiation, scientists can tell which radioisotope is on your skin or inside your body.

More information about the detection of ionizing radiation and biomarkers for ionizing radiation exposure can be found in Chapter 2 of this profile.

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

Recommendations and regulations are periodically updated as more information becomes available. For the most current information, check with the federal or state agency or organization that provides it.

The current federal and state regulations limit radiation workers' doses to 0.05 Sv/year (5 rem/year). The limit for the unborn child of a female radiation worker is 0.005 Sv (0.5 rem) per 9-month gestation period. For the general public, the limit is 0.001 Sv/year (0.1 rem/year), with provisions for a limit of 0.005 Sv/year (0.5 rem/year) under special circumstances. The public dose limit is set at least 10 times lower than the occupational limit to give the public an extra margin of safety. A factor of 10 is also used for public protection in other industries.

We have seen health effects from very high doses of ionizing radiation, but not at normal everyday levels. To be cautious, scientists and regulating agencies assume that there could be some harmful effects at any dose, no matter how small. Because ionizing radiation has the

potential to cause harmful health effects in overexposed people, regulations and guidelines have been established for ionizing radiation by state, national, and international agencies. The basic philosophy of radiation safety is to allow only a reasonable risk of harm using the concept of "as low as reasonably achievable" (ALARA). More specific information about the regulations in the United States and in your state can be found in Chapter 7 of this profile. Some regulations and recommendations for ionizing radiation include the following:

Radiation protection standards for radiation workers and members of the public are recommended by the International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection and Measurements (NCRP). These standards are not regulations, but they provide the scientific basis for the making of regulations by federal agencies. The ICRP and NCRP are authoritative bodies that analyze current scientific and epidemiological data and make recommendations to government and non-government organizations that set standards. ICRP and NCRP do not issue standards themselves.

Federal agencies, such as the EPA, the Nuclear Regulatory Commission (NRC), and the Department of Energy (DOE), as well as individual states are responsible for making federal and state regulations about exposure to ionizing radiation. The NRC regulates nuclear power plant operations and regulates the use of radioactive material in research and medical applications. The DOE has issued employee dose limits for its facilities.

The EPA is responsible for federal radiation protection guidance for environmental radiation standards and regulations to implement specific statutory requirements, such as the Safe Drinking Water Act and the Clean Air Act. Natural background radiation, of course, cannot be regulated but EPA recommends that the concentration of indoor radon not exceed 4 picocuries per liter (4 pCi/L) of air. EPA's National Emission Standards for Hazardous Air Pollutants (NESHAPs) contain regulations that limit the dose from radionuclides released to the air to 0.1 mSv/year (10 mrem/year). The EPA sets limits on the maximum acceptable concentration of radionuclides in public drinking water supplies. Based on the Safe Drinking Water Act, the EPA has issued drinking water standards for radionuclides, which include dose limits of 0.04 mSv/year (4 mrem/year) for man-made sources of beta and gamma emitters. EPA also sets limits on several alpha emitters in drinking water, such as radium and radon.

The NRC regulations apply to all types of ionizing radiation that are emitted from special nuclear material (such as nuclear reactor fuel) and from by-product material (materials made radioactive in the use of special nuclear material), and from source material (material from which nuclear fuel is made). The NRC sets limits on the total dose of ionizing radiation above background from these sources. It also sets limits for the amounts and concentrations of radioactive material that will give these doses if taken into the body. These are called Annual Limits on Intake (ALI) and derived air concentrations (DAC).

The NRC has also issued a standard for cleaning up sites contaminated with radioactive materials. It requires that the radiation dose to the public from these sites will not be more than 0.25 mSv per year (25 mrem per year).

Radiation doses from procedures used by licensed physicians in diagnosis and treatment of disease is not limited by regulations. However, physicians and medical technicians must be specially trained and licensed to use radiation-producing machines and licensed to use radioisotopes for these purposes. They are required to limit exposures to the members of the public who are inside their facilities to 100 mrem per year, which is the same level as required by the NRC. Also, patients with radioactive materials inside their bodies from the treatment are kept until it is likely that they will not expose anyone around them to more than 0.5 mSv (500 mrem) from that radioactive material.

States also regulate radioactive materials and other sources of radiation that are not regulated by the NRC. These include sources of natural radioactivity, such as radium, and radiation-producing machines, such as x ray machines and radioactive material produced by particle accelerators.

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 or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: (404) 639-6315 or 6324

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.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000

2. PRINCIPLES OF IONIZING RADIATION

2.1 INTRODUCTION

This chapter provides an overview of the principles of ionizing radiation before a discussion of the health effects in Chapter 3.

The primary purpose of this chapter is to provide public health officials, toxicologists, and other interested individuals and groups with an overall perspective of the health physics and toxicology of ionizing radiation. It contains descriptions and evaluations of radiological and toxicological studies and epidemiologic investigations and provides conclusions, where possible, on the relevance of health physics, toxicity, and toxicokinetic data to public health. A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile, along with an index. This profile focuses on "ionizing radiation" (alpha, beta, gamma, x ray) as opposed to "non-ionizing" radiation (radio waves, microwaves, radar, ultrasound, visible light, ultraviolet light), so the term "radiation" without further qualification refers only to ionizing radiation.

"Radioactive material" is defined as any material containing radioactive atoms that emit radiation as they transform into other radioactive or stable atoms. The frequently used terms "radiation," and "ionizing radiation" are defined in this toxicological profile as a specific form of radiation that possesses sufficient energy to remove electrons from the atoms in the tissues that they penetrate (Borek 1993). This process is called ionization and is the reason for the name "ionizing radiation." When this energy is received in appropriate quantities and over a sufficient period time, it can result in tissue damage. The clinical manifestations of radiation can be negligible (no effect), acute (occurring within several hours after very large doses), or delayed or latent (occurring several years after the exposure), depending on the dose and the rate at which it was received and the type of damage produced.

All organisms (i.e., bacteria, plants, or animals, including humans) are exposed each day to some amount of radiation. In the United States, as shown in Figure 1-2, 81% of the dose received from radiation comes from natural sources: 55% from radon; 8% from cosmic radiation; 8% from rocks and soil; and 10% from internal exposures to radiation from the radioactive materials in food and water consumed in the daily diet, such as potassium-40 (^{40}K) (NCRP 1987). The remaining 19% of the daily dose may originate from man-made sources; it is composed of medical x ray exposure (11%), nuclear medicinal exposure (4%), consumer products (3%), and other sources (<1%). This last category includes occupational sources, nuclear fallout, the nuclear fuel cycle radioactive waste, hospital radioactive waste, radioactively contaminated sites, and other miscellaneous sources.

Radiation dose is expressed in units of rad and millirad (mrad) (1 rad = 1,000 mrad), or grays (1 Gy = 100 rad) and milligrays (mGy). For administrative, regulatory, and radiation safety purposes, a unit called the rem or the sievert (Sv) (1 rem = 0.01 Sv) is used. For beta and gamma radiation, 1 rad = 1 rem, while for alpha radiation, 1 rad = 20 rem. For the population of the United States, the average annual total effective dose equivalent (natural and anthropogenic), is approximately 360 millirem (mrem) (3.6 mSv) per year (BEIR V 1990).

A survey of the open literature found comprehensive information and many discussions of the biological and toxicological effects of radiation. Much of the information on these effects was obtained from laboratory animal studies and human epidemiological studies (see Chapters 3, 4, and 5). The human data are mostly from studies of World War II atomic bomb survivors, medical patients exposed to radiation and radioactive material, uranium miners and millers, and radium dial painters. A great deal is currently known about the biological, toxicological and toxicokinetic aspects of radionuclides, as well as the general mechanisms of action of radiation. Although much remains to be learned about the specific mechanisms by which radiation exerts its effects, how these effects can be minimized in living tissues, and what the effects of very low doses of radiation over long periods of time will be (see Chapter 3), we know enough to safely use radioactive materials and radiation in commerce, industry, science, and medicine. For the purposes of this toxicologic profile, discussions on the effects of radiation will be limited to alpha (α), beta (β), and gamma (γ) radiation, since these three types of radiation are the most likely to be encountered at Department of Energy (DOE) National Priorities List (NPL) hazardous waste sites (see Chapter 3, Table 3-1). This profile provides an in-depth discussion of radiation biology and radiation toxicology. Chapters 3 and 5 provide a comprehensive overview of a representative cross-section of the available literature that pertains to the effects of radiation, both in humans and laboratory animals. Data on specific radionuclides were used to demonstrate how toxicological effects can occur, but these effects can also be caused by other radionuclides that emit the same or other types of radiation (see Chapters 3 and 5). Several excellent texts and review documents are currently available in the open literature that provide important background material used in developing other sections of this profile (BEIR IV 1988; BEIR V 1990; Cember 1996; Faw and Shultis 1993; Harley 1991; Roesch 1987; UNSCEAR 1993).

This toxicological profile contains tables that summarize the effects of radiation for both humans and laboratory animals (see Observed Health Effects from Radiation and Radioactive Material tables in Chapter 8). In radiation biology, the term "dose" has a very specific meaning. The term "dose" used in these tables refers to the amount of radiation energy absorbed per unit mass by the organ, tissue, or cell; dose is typically expressed either in grays (Gy) or in rad (1 Gy = 100 rad). For example, estimation of the dose to lung tissue or specific cells in the lung from a given exposure to plutonium-239 (^{239}Pu) is

accomplished by modeling the sequence of events involved in the inhalation, deposition, clearance, and transformation of ^{239}Pu within the lung. While based on the current understanding of lung morphometry and experimental data for other radionuclide toxicokinetics, different models make different assumptions about these processes, thereby resulting in different estimates of dose and risk coefficient. The units of measure in the studies that describe the health effects of radiation vary from one report to another. Some studies reported the amount of radioactive material introduced into the body (curies [Ci] or becquerels [Bq] where 1 Ci = 37 billion Bq) when describing the biological effects related to radiation, while other authors reported units of absorbed dose (rad, Gy) or dose equivalent (rem, Sv). Although the units did differ among the many reports, attempts were made to standardize the reporting of doses in units of rad in order to minimize confusion and provide a basis by which dose responses could be determined and evaluated.

An understanding of 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 safety principles. This chapter presents a brief overview of radiation physics, chemistry, and biology and is based to a large extent on the reviews of Eichholz (1982), Hendee (1973), Early et al. (1979), Faw and Shultis (1993), Harley (1991) and Roesch (1987).

2.2 HISTORY, BACKGROUND INFORMATION, AND SCIENTIFIC PRINCIPLES OF IONIZING RADIATION

2.2.1 Historical Perspective on Ionizing Radiation

Ionizing radiation has been present since the earth was created. Before the 1890s, there were only natural sources of radiation such as radiation from cosmic sources, and radioactive material inside the body and in rocks, soil, and air. Much of the radiation exposure was in the form of low-level cosmic and terrestrial radiation. Since radiation cannot be observed using any of the five senses, humans were not aware of its existence.

About 1,800,000 years ago, the only known natural "nuclear reactor" operated for about 100,000 years in the uranium-rich soil around what is now Oklo, Gabon. The first known use of uranium occurred in 79 AD, when Roman artisans were producing yellow-colored glass in a mosaic mural near Naples; this activity produced low levels of radiation. The first reports of adverse health effects that were probably related to radiation from inhaled radon gas and its radioactive progeny occurred around 1400 AD, when a

mysterious malady resulted in the deaths of miners at an early age in the mountains around Schneeberg and Joachimsthal in the Sudetenland (The Czech Republic). This mysterious disease was known as "mountain sickness" and is now believed to have been lung cancer. When mountain sickness was first described, radon was not known and was not linked to the disease until the 1920s, when radon gas was identified as a cause of lung cancer.

It was not until the discovery of mystery rays or "x rays" in 1895 that people began to be aware of the almost magical presence of these invisible "rays" that could allow us to see inside the body. In the summer of 1894, Wilhelm Roentgen began experiments with cathode ray tubes; on November 8, 1895, he observed that a few crystals of barium platinocyanide, which were lying on a table, produced a fluorescent glow. He subsequently discovered that some unknown component ("X") from the cathode ray tube could also penetrate solid substances, and that "x rays" had the same effect on a photographic plate as visible light. What followed was the first "Roentgen exposures," or "Roentgenograms," which were photographs that were able to show the shapes of metal objects locked in a wooden case and the bones inside his wife's hand. A month after his discovery, Roentgen sent a manuscript about his extraordinary findings to the Physical-Medical Association in Wuerzburg, titled *Concerning a New Kind of Ray: Preliminary Report*. Other periodicals such as *Nature* and *Science* published the report in the following year, and Roentgen received wide acclaim for his discovery, both in the scientific and lay communities, in the years to come. Others quickly found practical applications for x rays (also called "Roentgen rays"). In 1896, the first diagnostic x ray in the United States was performed by E. Frost. Within the next 2 years, the first x ray picture of a fetus *in utero* was taken; this was followed by the first use of an x ray in dentistry. Adverse health effects due to exposure to x rays were soon reported. These included a report by Thomas Edison asserting that eye injuries can be produced by exposure to x rays, and a report by Daniel identifying alopecia and erythema (skin reddening) 3 weeks after he radiographed the head of Edison's assistant, Mr. Dudley.

Roentgen's discovery of x rays was followed by Henri Becquerel's discovery of radioactivity in November 1896. Becquerel found that photographic plates that were lying near pitchblende (a uranium ore) were exposed despite being sealed in light-tight envelopes. The exposure, he found, was due to radiations emitted from the pitchblende. Subsequent studies showed that there were three uniquely different radiations, which he called alpha, beta, and gamma. Later, it was shown that Roentgen's x rays and Becquerel's gamma rays were the same kind of radiation.

After these discoveries, scientific interest in the properties of radiation increased dramatically. Radioactive thorium (Th) was discovered by Schmidt in 1898. A few months later, Marie and Pierre Curie isolated polonium (Po) from pitchblende, a variety of the mineral uraninite (largely UO_2), that occurs as a constituent of quartz veins and is a source of radium (Ra) and uranium (U). The Curies later isolated radioactive ^{226}Ra from pitchblende and explained the natural transformation of an unstable atom of a higher atomic number to one of a lower atomic number, referred to as transformation or "decay." The Curies ultimately coined the word "radioactivity." In the years to come, other notable scientists contributed to this new area of science: Villard discovered gamma rays; Rutherford discovered radioactive gas emanating from thorium and coined the term "half-life" and used alpha particles to develop a new theoretical model of the atom (Friedlander et al. 1964); Planck created quantum theory; Einstein discovered mass-energy relationship and photoelectric effect; and Hess reported the existence of "cosmic rays" (ionizing radiation) at high altitudes.

In 1904 Ernest Rutherford said, "If it were ever possible to control at will the rate of disintegration of radio-elements, an enormous amount of radiation could be obtained from a small amount of matter." This statement expressed the obvious implications for the use of radionuclides (in particular uranium and plutonium) in generating large amounts of electric energy in nuclear reactors and in the production of nuclear weapons approximately 40 years later. The use of the "atomic bomb" (this term is somewhat of a misnomer since it is the nucleus from which this energy derives) would make an important contribution to ending the second World War. Much scientific research was required to move from theory to application. "The Manhattan Project" was the code name for the project responsible for taking many of the theoretical ideas on atomic energy proposed since Roentgen's discovery and applying them in a real-world application that would result in the creation of the first atomic weapon.

The Manhattan Project was named for the Manhattan Engineering District of the U.S. Army Corps of Engineers, because much of the early theoretical research on the potential of nuclear energy was done at Columbia University and because the Manhattan District of the U.S. Army Corps of Engineers was located near Columbia University in New York City. Initiated by President Roosevelt on the recommendation of several physicists who had fled Europe, the program was slowly organized after nuclear fission was discovered by German scientists in 1938. Many U.S. scientists began to express the fear that the Germans, under their dictator Adolf Hitler, would attempt to build a fission bomb which would pose a serious threat to the world. It was subsequently decided that the United States must be the

first country to harness this new technology in order to maintain the future balance of world power. In 1942, General Leslie Groves was chosen to lead the Manhattan Project. He immediately purchased a site at Oak Ridge, Tennessee, and constructed the facilities to extract and purify the ^{235}U isotope fuel needed to power the weapon. He also secured a 550-square mile site in Eastern Washington State, later called the "Hanford Works," for the highly secret reactor production and chemical refinement of plutonium metal. The first plutonium in gram quantities was produced in early 1945 by the Hanford "B" reactor, which has been designated a National Historic Site. Groves appointed theoretical physicist Robert Oppenheimer as director of a weapons laboratory built on an isolated piece of land at Los Alamos, New Mexico. In 1945, ^{235}U of adequate purity was shipped to Los Alamos and was used in the testing in the first of two prototype weapons. In the first prototype, one subcritical piece of uranium was fired at another subcritical piece down a gun barrel; the combined pieces formed a supercritical, explosive mass. The second prototype was constructed using plutonium. In the plutonium prototype, the plutonium was surrounded with explosives to compress it into a superdense, supercritical mass far faster than could be done in a gun barrel. The result was tested (Pu weapon only) at Alamogordo, New Mexico, on July 16, 1945, and was the first detonation of an atomic-type weapon. Two more atomic weapons were subsequently manufactured in the United States and detonated over Hiroshima and Nagasaki, Japan, in August 1945. The use of these devices, the most destructive weapons at the time, quickly brought the war in the Pacific to an end, thus saving Allied and Japanese soldiers who would have been lost in a ground invasion of the Japanese mainland using only the conventional weapons of the time.

The two bombs detonated over Japan in the final days of World War II were made from two different types of explosive material. The Hiroshima bomb was made from the highly enriched ^{235}U, extracted from ore containing the much more abundant isotope ^{238}U. This bomb, which was released over Japan's seventh largest city on 6 August 1945, contained approximately 60 kg of highly enriched uranium; its detonation destroyed 90% of the city. The explosive charge for the bomb detonated over Nagasaki 3 days later was provided by about 8 kg of ^{239}Pu, which caused a similar amount of destruction.

Both atomic devices were detonated in the air over the cities. The devastating effects of the bombs depended essentially upon the blast, shock, and heat released at the moment of the explosion, causing immediate fires and destructive blast pressures. Since the bombs were detonated about 600 meters above the ground, only a relatively small proportion of the radioactive fission products was deposited on the ground near the "ground zero" point below the site of detonation. Some deposition occurred in areas near

each city due to local rainfall soon after the explosions, specifically at positions a few kilometers to the east of Nagasaki and in areas to the west and northwest of Hiroshima. Generally, the majority of the fission products were carried into the upper atmosphere by the heat generated by the explosion. When the fallout returned to earth, it contributed to global human radiation exposure.

In Hiroshima, with a resident civilian population of about 250,000 people, an estimated 45,000 died on the first day after the bombing and an additional 19,000 died during the subsequent 4 months. In Nagasaki, with a resident population of about 174,000, an estimated 22,000 died on the first day and an additional 17,000 deaths were reported within the next 4 months. Actual totals may be higher due to unrecorded deaths of military personnel and foreign workers. Teratogenic effects on fetuses were severe among those heavily exposed, resulting in many birth deformities and stillbirths over the next 9 months. No genetic damage has been detected in the survivors' children and grandchildren, despite careful and continuing investigation by the Radiation Effects Research Foundation (RERF), which is a joint Japanese-U.S. foundation. Since then, some of the surviving adults developed leukemias and other cancers (see Chapter 3). The major source of radiation dose to the population in both cities was from the penetrating gamma radiations. The study of the Japanese survivors has proven to be an important historical confluence for major health effects studies at low doses. Prior to World War II, radiation mutagenesis, teratogenesis, and carcinogenesis studies developed along separate lines. The study of the atomic bomb survivor populations allowed these separate lines of research to converge with studies in a single population.

The atomic bombs used in Japan in 1945 and the bombs tested during the following 7 years used ^{235}U or ^{239}Pu. The explosive power of the Hiroshima bomb was about 15 kilotons (equivalent to 15,000 tons of trinitrotoluene [TNT]) and that of the Nagasaki bomb was approximately 25 kilotons. For comparison, the total TNT equivalent explosive power of all atmospheric weapon tests made by the end of 1951 was approximately 600 kilotons.

After 1951, the atomic bombs being tested included hydrogen bombs, which became more sophisticated and had explosive effects about a thousand times greater than those of the Hiroshima and Nagasaki type bombs; by the end of 1962, the total of all atmospheric tests had risen from the 1951 value of 0.6 million tons of TNT equivalent, to about 500 million tons of TNT equivalent. This vast increase in scale was due to the testing of the “thermonuclear” weapons or (hydrogen bombs or “H-bombs”), which depended not on the fission of a critical mass of fissile material alone, but on a two- or three-stage process initiated by a

fission reaction. Briefly, the hydrogen bomb uses the same process that the sun uses to release its tremendous amounts of energy. In the hydrogen bomb, the nuclei of two light atoms (usually hydrogen) are fused together to form a heavier atom, helium. A fission reaction, in which a heavier atom is split into lighter ones, generates the energy to trigger the fusion reaction. The United States exploded its first hydrogen bomb in November 1952 at Eniwetok Atoll in the South Pacific. Atomic weapons development by the United States and other nations continues in the 1990s.

The development of the “atomic bombs” has frequently received more attention than the peaceful use of atomic energy and radiation. Peaceful uses of radiation have also been developed quite successfully. An important application has been in the generation of safe, controlled and long-term power sources for the civilian population. On December 20, 1951, the first usable electricity produced from nuclear energy was manufactured at the National Reactor Testing Station, now called the Idaho National Engineering and Environmental Laboratory (INEEL), in Idaho Falls, Idaho. The electricity produced lit four light bulbs across a room of the Experimental Breeder Reactor I (EBR-I). In 1953, these scientists demonstrated that a reactor could create more fuel than it used, "breeding" fuel from ^{238}U as it created electricity with ^{235}U. EBR-I operated as a research reactor until 1963, at which time EBR-II became active; EBR-II is now a historical monument. In July 1955, Arco, Idaho, became the first U.S. town to be powered by nuclear energy, supplied by power from the Borax-III reactor, an early prototype of a boiling water-type nuclear reactor. The Sodium Reactor Experiment in Santa Susanna, California, generated the first power from a civilian nuclear reactor on July 12, 1957, using sodium instead of water as the primary coolant. The first large-scale nuclear power plant in the world began operating in Shippingport, Pennsylvania, in December 1957. Today, nearly 25% of the electricity generated in the United States (75% in Maine and Illinois and 50% in South Carolina) comes from nuclear power. Other countries generate much larger proportions of their electricity with nuclear energy. In oil-poor countries, such as France, 80% of the electricity is generated with nuclear energy and in Japan nuclear energy accounts for 30% of the electricity generated. Other countries using nuclear power include Canada (17%), Germany (29%), Sweden (47%), and the former Soviet Union (42%) (USNRC 1997b). Although nuclear reactors continue to be used as a source of power for many states and countries, public concerns about nuclear reactor safety have intensified due to well-publicized accidents (see Chapters 4 and 6). However, only two of these accidents involved nuclear power reactors: Three Mile Island and Chernobyl. At Three Mile Island, although the reactor melted down, no one was overexposed or injured, and there was no significant contamination outside the

containment and auxiliary buildings. At Chernobyl, the reactor melted down, causing serious public health consequences which could have been prevented if the reactor design had included a containment building.

Medical uses of machine-produced radiation and radionuclides emitting radiation have also been developed that play a significant role in medical diagnosis and treatment. Controlled amounts of radiation in the form of x rays have been used for a century, and beta particles have used more recently, as an aid in the diagnosis and treatment of diseases in humans and animals. Today, much is known about the health effects of high doses of x rays, as well as other radiation; however, this has not always been the case. In 1947, doctors in Israel and many other countries treated ringworm of the scalp with up to 400 rad (4 Gy) of x rays to cause the hair to fall out (alopecia); it was later found that this treatment regimen led to a greater than expected incidence of thyroid tumors and brain cancers. Radium-224 (^{224}Ra) was used in the treatment of ankylosing spondylitis in Germany in the 1940s; these treatments later were associated with an increased incidence of bone cancers. In addition to x rays, radionuclides such as iodine-131 (^{131}I) and metastable technetium 99 (^{99m}Tc) are being used to successfully diagnose and/or treat a wide range of diseases. Laboratory research has benefitted from the use of radionuclides, typically in the form of radiolabeled tracers that enabled us to learn the details of the biochemistry of health and disease, and to develop new diagnostic techniques and new (non-radioactive) drugs for treatment of disease. Carbon 11 is a short half-life (20 minutes) radionuclide produced in cyclotrons in conjunction with several medical facilities and used in positron emission tomography (PET) studies that enable physicians to see inside the body and precisely locate sites of medical concern.

2.2.2 Basic Information on Ionizing Radiation

Ionizing radiation is any of several types of particles and rays given off by radioactive material, nuclear reactions, and radiation producing machines. Those that are primarily addressed in this profile because of their relevance to public health are alpha particles, beta particles, and gamma rays, which are also called alpha, beta, and gamma radiation. The term “ionizing” refers to the ions or charged atoms and molecules that radiation produces along its path by knocking electrons from atomic orbits. The term “radiation” refers to the way these particles and rays move away or radiate from their sites of production at speeds ranging from a few tenths of the speed of light to the speed of light. Our senses cannot detect radiation since it is odorless, tasteless, and invisible, and cannot be heard or felt. All life on earth is

exposed to low levels of ionizing radiation from terrestrial and cosmic sources every day. This profile will not address non-radiation, such as radiowaves, microwaves, infrared light, visible light, ultrasound, and ultraviolet light.

To explain exactly what radiation is, we begin at the atomic level with atoms, how they come to be radioactive, and how they give off radiation. The materials we call elements are composed of atoms, which in turn are made up of neutrons, protons, and electrons. Protons (positively charged particles) and neutrons (neutral particles with no charge) reside in and primarily comprise the nucleus of any atom, while electrons exist in a "cloud" of orbits around the nucleus. Nuclide is a general term referring to any atom. All atoms of an element have the same number of protons (the number of protons = the atomic number) but may have different numbers of neutrons (this is reflected in the atomic mass or atomic weight of the element). Atoms with the same atomic number but different atomic masses are referred to as isotopes of an element. An isotope is a specific nuclide that is characterized by the composition of its nucleus (by the number of protons and neutrons in the nucleus).

Radioactivity is the characteristic of any atom that is unstable due to the binding of the protons and neutrons within its nucleus. If the number of neutrons is too small or too large for the number of protons, the nucleus is unstable and the atom is said to be radioactive. Radioisotope refers to any radioactive isotopes of an element, and radionuclide is a generic term applying to any radioactive species of any element. Every radioactive nucleus will eventually change its neutron/proton ratio by one of four basic methods and simultaneously emit radiation to obtain a more stable energy configuration. These methods can involve the ejection of an alpha particle (a 2-proton 2-neutron packet) directly from the nucleus, the conversion within the nucleus of a neutron to a proton or a proton to a neutron with the emission of a beta particle and gamma rays, or the splitting or spontaneous fission of the nucleus. Each radionuclide has a unique configuration, so the radiation types, energies, and intensities are unique to it, and these are keys to its identification. The unstable radionuclide is transformed during this process into a new nuclide, which is typically stable. Radionuclides that are still radioactive after one transformation, continue through a series of one or more further transformations until a stable atom is formed. This series of transformations, called a "decay" chain, is typical of the very heavy natural elements like uranium and thorium. The first radionuclide in the chain is called the parent radionuclide, and the subsequent products of the transformation are called progeny, daughters, or transformation products. To summarize, radioactive decay results in a stable nuclide or a less unstable nuclide than the parent.

2. PRINCIPLES OF IONIZING RADIATION

Naturally-occurring radionuclides can be classified as either primordial (present from ancient times) or cosmogenic (produced by cosmic rays). Primordial radionuclides include ^{40}K, ^{238}U, ^{235}U, and ^{232}Th, which have existed since the earth was formed, and the series of radionuclides which each of the last three isotopes transform through before becoming stable isotopes of lead. ^{40}K and about half of the decay chain radionuclides emit beta and gamma radiation while ^{238}U, ^{235}U, ^{232}Th and the other half of their decay chain isotopes emit alpha particles. Cosmogenic radionuclides (^{3}H, ^{7}Be,^{14}C, etc.) are those which are constantly being formed in the atmosphere as cosmic rays and particles from space interact with and transform atmospheric gases. All of these transform by emitting beta and gamma radiation.

Natural background radiation is the combined radiation field produced by the primordial and cosmogenic radioactive materials that are around us plus cosmic radiation from space. Everyone is exposed to this background radiation throughout their lives, at levels that depend on the ambient concentration of those radioactive materials and the altitude at which we live. This background radiation is the major source of radiation exposure to humans and arises from several sources. Natural background dose rates are frequently used as a standard of comparison for doses from various man-made sources of radiation. Man-made radiation is that which is produced by machines, such as x ray machines, and from the decay of radioactive materials that we make. Man-made radioactive materials are those associated with nuclear reactor operation (fission products of uranium and plutonium, and neutron activated by-product material) and high-energy physics equipment (cyclotrons and particle accelerators that bombard targets with charged particles). A number of short-lived radionuclides are produced and used daily in the medical field to diagnose and treat illness. Currently-available equipment and methods can be used to produce radionuclides of any known element, and to even create new elements as scientists attempt to understand the atom more completely. Both naturally occurring and anthropogenic radionuclides have numerous applications in diagnostic and therapeutic medicine, industrial products, consumer products, and in scientific and industrial research. Trace amounts of some specific radionuclides remain in the environment, or have been redistributed in the environment, as a result of these applications and also from the production, testing, and use of nuclear weapons.

2.2.3 Principles of Radioactive Transformation

The stability of an atom is the result of the balance of the forces among the components of the nucleus. High-energy physicists exploring the nucleus have developed the field of quantum mechanics and semiempirical equations to express the binding energies or stability of nucleons in the nucleus. One general finding of those studies is that a nucleus with too many or too few neutrons for a given number of protons is unstable (radioactive) and will eventually undergo transformation to achieve a more stable energy state. Most radioactive atoms can achieve stability in one transformation, but most with atomic masses greater than lead require several successive transformations and are said to be in a decay chain. Any radionuclide can be uniquely characterized by its rate of transformation and the types, energies, and intensities of its radiations. Table 2-1 summarizes the basic characteristics of the more common types of radiation.

Table 2-1. Characteristics of Nuclear Radiations

Radiation	Rest mass[a]	Charge	Typical energy range	Path length		Comments
				Air	Solid	
Alpha (α)	4.0026 amu	+2	4–10 MeV	3–10 cm	25–80 μm	An electron-stripped He nucleus
Negatron (β^-)	5.48×10^{-4} amu; 0.51 MeV	–1	0–4 MeV	0–15 m	0–1 cm	Identical to electron
Positron (β^+)	5.48×10^{-4} amu; 0.51 MeV	+1	0-4 MeV	0–15 m	0–1 cm	Identical to electron except for sign of charge
Neutron	1.0086 amu; 939.55 MeV	0	0–15 MeV	b	0–100 cm	Free half-life: 10.4 min
x ray $_{(e.m.\ photon)}$	–	0	5 keV–100 keV	b	b	Photon from transition of an electron between atomic orbits
Gamma $(p)_{(e.m.\ photon)}$	–	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 = 9 32 MeV.
[b]Path lengths are not applicable to x- and gamma rays since their intensities decrease exponentially

amu = atomic mass unit; e.m. = electromagnetic; keV = KiloElectron Volts; MeV = MegaElectron Volts

The mode of transformation refers to the way the parent radionuclide undergoes its transformation. The modes that are most significant to public health are alpha and beta decay with the subsequent emission of gamma radiation, although others, such as electron capture and spontaneous fission, also occur in certain radionuclides. Alpha decay occurs among those radionuclides, such as the uranium isotopes, with sufficient excess nuclear energy to eject part of their mass, which is always a packet containing two protons and two neutrons, called an alpha particle. One of two types of beta decay occurs among the other radionuclides, and the type (negatron or positron) depends on the availability of neutrons to stabilize the nucleus. For neutron-rich nuclei, like those formed in nuclear reactors, a neutron converts to a proton and a negatively charged beta particle called a negatron, or simply a beta particle. For neutron-poor radionuclides, such as those produced using particle accelerators, a proton converts to a neutron and the nucleus emits a positively-charged beta particle called a positron. The two types of beta decay are often referred to generically as beta decay. One reason is that both positrons and negatrons are the same particle, an electron, but with different charges. Another mode of transformation for a neutron-poor nucleus is electron capture, in which the nucleus captures an orbital electron and uses it to convert a proton into a neutron. A transformation that is available to only a few radionuclides, such as ^{238}U, is spontaneous fission in which the nucleus splits into two fragments of unequal mass releasing a few neutrons and a large amount of energy. Spontaneous fission neutrons can be used to induce the chain reactions in nuclear reactors. Some radionuclides, such as ^{238}U, follow multiple modes with specific frequencies. The various decay modes often leave the nucleus with a small amount of excess energy that is released as a gamma ray. When alpha, beta, or gamma radiation interact with atoms along their paths, the electrons they knock from interior orbitals produce vacancies which the atom corrects by cascading electrons down from higher energy orbitals to fill the inner ones. In doing so, each electron drops to a lower energy state and the atom emits the energy difference in the form of a photon, called an x ray. X and gamma rays are different in their origin (electron shells or nucleus) but are indistinguishable in their characteristics. Both are massless bundles of electromagnetic energy with sufficient energy to ionize matter. During these transformations, the atom changes from one element into another, modifying the structure of the electron orbitals, and in some cases emitting x rays with energies characteristic of the new element. Characteristic x rays are useful in determining a material's elemental makeup.

The type of radiation may be categorized as charged particle (alpha, negatron, positron), uncharged particle (neutron), or electromagnetic radiation (gamma and x ray). The type of radiation can also be characterized as directly ionizing (alpha, negatron, positron, or proton) or indirectly ionizing (neutron,

gamma, or x ray). X- and gamma rays are categorized as indirectly ionizing radiation because they have no charge and it is the electrons that they liberate from atoms that produce most of the ionization.

Except for delayed neutrons emitted during the nuclear fission process, no radionuclides emit neutrons. For example, californium-252 (^{252}Cf), which undergoes spontaneous nuclear fission as well as alpha transformation, emits neutrons during the fission process. When neutrons are needed for neutron activation analysis or for radiography, they can be produced by a nuclear reactor, a sealed ^{252}Cf source, or a neutron generator (an alpha emitter surrounded by an appropriate target element). An example of such a neutron source is a mixture of a finely powdered alpha emitter, such as ^{210}Po and beryllium (Be). The alpha particle bombards the ^{9}Be isotope to produce ^{12}C and a neutron.

Each radionuclide has a characteristic rate of decay called the half-life, which is the time it takes for 50% of its atoms to decay. Each radionuclide transforms at a constant rate, which is independent of the temperature, pressure, or chemical form in which it exists. A high rate of transformation leads to a short half-life, while a long half-life means a slow rate of transformation. During one half-life, 50% of the radioactive atoms transform; during the next half-life, 50% of the remaining radionuclide transforms, and so on. For example, ^{32}P has a half-life of about 14 days. If one starts with 100 µCi of ^{32}P on day 1, on day 14 there will be exactly one-half, or 50 µCi of ^{32}P remaining. After another 14 days pass, exactly 25 µCi of ^{32}P will remain, and so on. This decrease in radioactivity is illustrated in Figure 2-1.

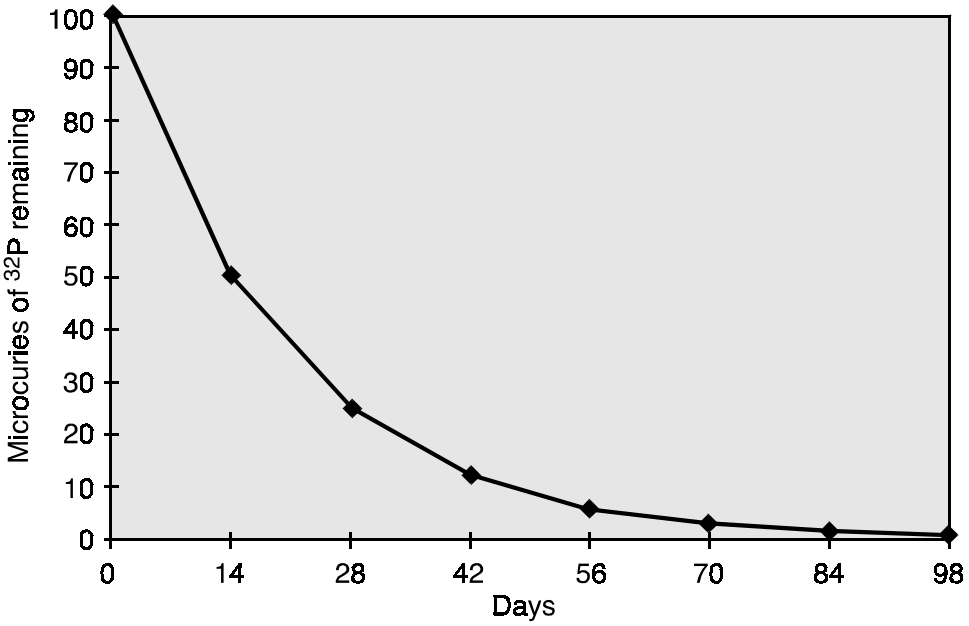


Figure 2-1. Transformation of 100 µCi of ^{32}P

Half lives of the various radionuclides range from fractions of a second to billions of years. The amount of radioactive material is expressed in terms of activity, which is defined as the number of disintegrations (or transformations) in the radioactive material during 1 second or 1 minute. The traditional unit for measurement of activity is the curie (Ci). The curie was originally defined as the activity of 1 gram of ^{226}Ra, which is about 3.69×10^{10} transformations or disintegrations per second (dps). Now it is defined as that quantity of radioactive material in which an average of 3.7×10^{10} atoms transform in 1 second. In the International System (SI), the unit of activity is the becquerel (Bq). One Bq is defined as the amount of radioactive material in which an average of 1 atom disintegrates in 1 second.

The activity of a radionuclide at time t may be calculated by the equation:

$$A = A_o e^{-0.693t/T(phys)}$$

where A is the activity in appropriate units, such as Ci, Bq, or dps; A_o is the activity at time zero; t is the time that has elapsed; and T_{phys} is the physical radioactive half-life of the radionuclide. T_{phys} and t must be in the same time units.

2.2.4 Interaction of Radiation with Matter

Radiation will interact with matter: it will lose kinetic energy to any solid, liquid, or gas through which it passes; this occurs by several mechanisms and at different rates. The partial or complete transfer of energy to a medium by either electromagnetic (gamma) or particulate (alpha or beta) radiation may be sufficient to excite electrons or to "knock out" electrons from the absorber atoms or molecules. For those electrons that are knocked out of the atom, the process is called ionization and is the source of the name "ionizing radiation." Compared to other types of radiation that may be absorbed (e.g., ultraviolet radiation), ionizing radiation deposits a relatively large amount of energy into a small volume of matter, possibly resulting in harmful biological effects.

Radiation may interact with a biological medium to cause damage either directly or indirectly. A direct effect occurs when an ionizing event disrupts a critical molecule (such as an enzyme, DNA, or RNA) by knocking out an intramolecular bonding electron. Indirect effects occur when ionized or disrupted molecules, mainly water (since the body is about 80% water), recombine to form chemically toxic compounds, such as hydrogen peroxide (H_2O_2) (Casarett and Doull 1996). Indirect effects also involve

free radicals. Indirect effects occur when these radiolysis products diffuse and damage a nearby biological molecule along their path. Further discussion of the direct and indirect effects of radiation is presented in Chapter 5.

Each type of radiation is also classified as to its directness (directly or indirectly ionizing) and its ionizing density (linear energy transfer). Radiations that produce significant ionization themselves (alpha, beta) are called directly ionizing radiation, while those that produce minimal primary ionization (gamma, x ray, neutron) are called indirectly ionizing radiation. The amount of energy that the radiation transfers per unit of path length is called its linear energy transfer (LET) and is measured in units of MeV/μm. This feature reflects a radiation's ability to produce biological damage. Radiation is classified as either high linear energy transfer (high LET) or low linear energy transfer (low LET), based on the amount of energy it transfers per unit path length it travels. Alpha radiation is high LET; beta and gamma radiation are low LET. Alpha particles are classified as high LET radiation because their large +2 charge and relatively large mass (about 7,200 times that of an electron) cause them to move relatively slowly and interact strongly with any material they pass through, producing dense ionization along its path. Beta particles, which are energetic electrons, are classified as low LET radiation. Even though they interact with matter in a manner similar to alpha particles, their smaller +1 or -1 charge and smaller mass result in a greater distance between ionizing collisions and, thus, a lower rate of energy transfer. Gamma rays are indirectly ionizing radiation. Depending on its energy and the atomic number of the absorbing material, a gamma ray photon interacts with an absorber atom by one of three primary mechanisms (photoelectric interaction, Compton scattering, and pair production), which results in the production of highly energetic electrons, which dissipate their energy by interacting with other atoms in their path in exactly the same manner as beta particles (which are electrons) and excite and ionize these atoms. Since the ionizations resulting from gamma radiation are due to electrons, gamma radiation is a low LET radiation.

Both high and low LET interactions can cause significant damage to the DNA and can result in a wide array of biological effects. Radiation can also react with molecules other than DNA (lipids, proteins, water, etc.) to produce free radicals, which can then go on to adversely react with the DNA molecule. Regardless of the method of energy transfer, DNA is the primary molecule of concern for effects from low level radiation because DNA damage from radiation and from other sources is cumulative and can (but does not always) result in carcinogenesis or other adverse cellular events months or years after exposure.

2.2.5 Characteristics of Emitted Radiation

2.2.5.1 Alpha Radiation

Alpha radiation has little penetrating power compared with other types of radiation. The alpha particle is hazardous only if there is internal exposure (i.e., from a radionuclide that has been ingested, inhaled, or otherwise absorbed internally) (see Table 2-2).

An alpha particle is composed of two protons and two neutrons, and thus is a helium nucleus. When a parent radionuclide emits an alpha particle, its atomic mass number (number of protons plus neutrons) decreases by four and its atomic number (number of protons) decreases by two, resulting in the formation of a different element. In nature, alpha particles come from the radioactive transformation of heavy elements (e.g., uranium, radium, thorium, and radon) where long transformation chains produce several successive alpha and beta particles until the resulting nuclide has a stable configuration. A specific alpha emitting radionuclide emits monoenergetic alpha particles of discrete energies and relative intensities, making it possible to identify each alpha emitting radionuclide by its alpha energy spectrum.

The alpha particle's electrical charge of +2 and mass number of 4, both of which are larger than most other types of radiation, cause it to interact strongly with matter. This relatively slow-moving, highly charged, high LET particle spends a relatively long time in the vicinity of each atom it passes; this enables it to pull electrons easily off those atoms. With a mass about 7,200 times that of each electron, each interaction has only a small effect on its velocity, but the strong interaction with each atom it encounters causes it to lose energy very quickly. As a result of these characteristics, the alpha particle has less penetrating power than other types of radiation. Typically, an alpha particle cannot penetrate an ordinary sheet of paper. Its range in air (the distance the charged particle travels from the point of origin to its resting point) is approximately 3–10 cm; in biological tissue, the range decreases dramatically to 25–80 μm (see Table 2-1). Thus, alpha particles deposit all of their energy in a small volume. Once its energy is expended, the alpha particle will combine with two electrons to become a helium atom, which does not chemically react with biological material.

Table 2-2. Effective Half-Lives of Selected Radionuclides in Major Adult Body Organs

Radionuclide	Critical organ	Half-life		
		Physical	Biological	Effective
Tritium (^{3}H) [a]	Whole body	12.3 yr	12 d	12d
Iodine-131 (^{131}I)	Thyroid	8 d	138 d	7.6 d
Strontium-90 (^{90}Sr)	Bone	28 yr	50 yr	18 yr
Plutonium-239 (^{239}Pu)	Bone	24,400 yr	200 yr	198 yr
	Lung	24,400 yr	500 yr	500
Cobalt-60 (^{60}Co)	Whole body	5.3 yr	9.5 d	9.5 d
Iron-55 (^{55}Fe)	Spleen	2.7 yr	600 d	388 d
Iron-59 (^{59}Fe)	Spleen	45.l d	600 d	41.9 d
Manganese-54 (^{54}Mn)	Liver	303 d	25 d	23 d
Cesium-137 (^{137}Cs)	Whole body	30 yr	70 d	. 70 d

[a] Mixed in body water as tritiated water
d = days; yr = years

2.2.5.2 Beta Radiation

A beta particle is a high-velocity electron ejected from a transforming nucleus. This occurs when a nuclide has a nucleus that is very unstable because it has too many or too few neutrons to stabilize the number of protons. The particle may be either a negatively charged electron, called a negatron (β^-), or a positively charged electron, called a positron (β^+).

Beta minus or negatron (β^-) transformation is a process by which a radionuclide with too many neutrons achieves stability. It does not stabilize by emitting an extra neutron; instead, a neutron changes into a proton and the nucleus emits a negatron (β^-) and an antineutrino (see glossary). This nuclear transformation results in the formation of a different element with one more proton, one fewer neutron, and the same mass number as the original nucleus. The energy spectrum of a beta particle ranges from zero to a specific maximum, which is a characteristic of that particular radionuclide, with the mean energy of the beta spectrum being about one-third of the maximum. Overexposure to negatron-emitting radionuclides outside the body can cause more injury to the skin and superficial body tissues than alpha particles or gamma radiation. They are even more harmful as an internal radiation hazard when excessive amounts are taken into the body.

Beta positive (β^+), or positron, transformation occurs when there are not enough neutrons (or too many protons) in the nucleus. In this case, a proton changes into a neutron and the nucleus emits a positron (β^+)

and a neutrino (see glossary). This nuclear transformation results in the formation of a different element with one more neutron, one less proton, and the same atomic mass number as the original nucleus. The positron is a very reactive species; when sufficiently slowed through successive ionizing collisions, it will combine with an electron. At this point, the electron-positron pair is annihilated (their combined mass is converted into energy in the form of two gamma ray photons of 0.51 MeV each). 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 negatron (β^-) emitters of equal energy. The neutrino in β^+ transformation and the antineutrino in β^- transformation are not known to produce any biological damage.

2.2.5.3 Gamma Radiation

Gamma radiation is the main source of external radiation hazard because it is highly penetrating. Radioactive transformation by alpha or beta emission often leaves the nucleus in an excited energy state with some residual energy. The nucleus cannot remain in this elevated energy state indefinitely, and will eventually release this energy and achieve ground state, or the lowest possible stable energy level. The energy is released in the form of gamma radiation (high-energy photons) and is equal to the change in the energy state of the nucleus. Gamma rays are low LET because the average distance between ionizations is large and they liberate energetic electrons when absorbed in matter. The liberated electrons are also low LET.

Gamma radiation and x rays are types of electromagnetic radiations that behave identically but differ in their origin; gamma emissions originate in the nucleus while x rays originate in the orbital electron structure, or from the slowing down or stopping of highly energetic beta particles or electrons. The x rays that originate in the orbital structure are called *characteristic* x rays, and are useful in chemical analysis while those due to stopping high speed electrons are called *bremsstrahlung*.

2.2.6 Estimation of Energy Deposition in Human Tissues

Humans can be exposed externally from radiation sources outside the body, or internally from radioactive material deposited inside the body. Internally deposited radioactive material is more hazardous than external (superficial or skin) deposition. Internal exposures occur when radionuclides that have entered the body through the inhalation, ingestion, or dermal pathways undergo radioactive transformation

resulting in the deposition of energy to internal cells and organs. This radioactive material may be eliminated quickly (hours to days) or may result in a long-term retention pattern of the radionuclide (weeks to years).

When radioactive material is inside a living organism, either naturally or as the result of an accidental intake, the radioactive material is eliminated by both radioactive transformation and biological removal. A rate constant called the biological half-time (T_{biol}) is the time required for the sum of all of the available biological processes to eliminate one-half of the retained radioactivity. This time is the same for both stable and radioactive isotopes of any given element since they behave identically in the body. The time required for a radioactive element to be halved as a result of the combined action of radioactive transformation and biological elimination is the effective half-time (T_{eff}), and is described in the equation:

$$T_{eff} = (T_{biol} \times T_{phys})/(T_{biol} + T_{phys}).$$

This basic equation is typically more complicated in reality because the biological half-time can differ from one organ to another within the body. In addition, radioactive material distributes throughout the body and its radiations may penetrate to and expose tissues other than those in which it was deposited. Current internal dosimetry methods account for these multiple clearance rates and the distribution of radioactive material in the body. (See Table 2-2 for representative effective half-times of some radionuclides.)

External exposures occur when the body is irradiated directly from sources located outside the body, such as radiation from radionuclides on ground surfaces, dissolved in water, or dispersed in the air. In general, external exposures are from gamma-emitting radionuclides, from which the radiation readily penetrates 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. High levels of beta contamination of the skin may lead to skin burns. However, while the skin dose from beta radiation may be very high, the beta contribution to the total body dose from external radiation, compared to that contributed by gamma rays, may be small.

Characterizing the radiation dose to persons or laboratory animals from external radiation is relatively simple, but determining the dose from internal radiation is a complex issue. However, through the use of physiologically-based mathematical models, the dose from internal exposure can be estimated with a sufficient degree of accuracy to establish reliable radiation safety standards.

2.3 FUNDAMENTALS OF IONIZING RADIATION DOSIMETRY

2.3.1 Dose Units

In radiation biology, the term “dose” refers to the amount of energy that radiation deposits in an organ or tissue as it passes through rather than to the energy of that radiation or the quantity of radioactive material that is present.

Absorbed dose is the energy absorbed per unit mass of the absorber. The traditional unit of absorbed dose is the rad, with 1 rad = 100 ergs of energy deposited in 1 gram = 0.01 joule of energy/kg in any irradiated medium. The SI unit of absorbed dose is the gray (Gy), which is equivalent to 100 rad or 1 J/kg. External radiation dose is obtained by multiplying the radiation dose rate (measured using instruments) by the exposure time. Internal radiation dose at different sites within the body can be obtained from a knowledge of the quantity of radioactive material present; the uptake fraction and the distribution and retention kinetics of the chemical species involved; the type, energy, and intensity of its radiations; and the energy transfer parameters for those radiations to the tissues involved; and the radioactive half-life. An exposure is classified as "acute" or "chronic" depending on how long an individual or organ was exposed to the radiation. For internally deposited radionuclides, it is the effective half-life (which accounts for clearance by radioactive decay and chemical elimination) which determines whether the radiation dose is of acute, intermediate, or chronic duration. For an acute-duration intake of a radioactive material, a very short effective half-life results in an acute-duration radiation dose, but a very long effective half-life results in an intermediate- or chronic-duration radiation dose.

The roentgen (R) is the unit of x ray or gamma radiation exposure related to the intensity of an x ray or gamma radiation field, and is measured by the amount of ionization caused in air by x ray or gamma radiation. One roentgen produces 2.58×10^{-4} coulomb per kg of air. In the case of gamma radiation, over the commonly encountered range of photon energy, the energy deposition in tissue for an exposure of 1 R is 0.0096 J/kg of tissue (0.96 rad) which for most purposes is about equal to 1 rad. Thus, although the roentgen is a unit of x ray exposure (not dose), it continues to be used for radiation safety measurements because an exposure of 1 R leads to a dose of approximately 1 rad. An exposure of 1 R is considered a dose equivalent of 1 rem (0.01 sievert). The dose equivalent units, the rem and the sievert, are discussed

below in Section 2.3.3. Health physics survey meters that are used to measure external x ray or gamma radiation are usually calibrated in units or subunits of R (roentgens) per hour.

External doses are measured directly with radiation dosimeters or calculated from hand-held survey meter readings as the product of the exposure time and the dose rate in rad/unit time. Internal doses, however, are not measured directly; they are calculated with data obtained from measurements of radiation emissions from the body or from the radioactivity in excreta samples in counts/unit time. The radioactive material(s) are identified and their radiation characteristics are used to calculate the activity inside the body in curies or becquerels. Physiologically based biokinetic models are then used to calculate the dose from the radioactive materials take into the body. For radiation safety purposes and for regulatory requirements, the dose is multiplied by the quality factor Q rem/rad, for that specific radiation to convert rad to rem. Special units are used to describe the concentration and exposure to radon and its progeny.

Certain types of radiation with short-lived progeny are measured in units called working levels (WL). The potential inhalation hazard from atmospheric radioisotopes ^{222}Rn and ^{220}Rn (thoron) is due to their short-lived progeny. The concentration of these short-lived progeny (^{218}Po through ^{214} Po from ^{222}Rn and ^{216}Po through ^{212}Po from ^{220}Rn) is measured by the working level (WL). One WL is defined as any combination of short-lived radon daughters per L of air that will result in the emission of 1.3×10^5 MeV of alpha energy. An activity concentration of 100 picocuries (pCi) of ^{222}Rn per L of air, in equilibrium with its daughters, corresponds to 1 WL. The WL unit for thoron (^{220}Rn) daughters at 50% equilibrium is 14.8 pCi/L. Thoron daughters in radioactive equilibrium with thoron at a concentration of 7.43 pCi/L represents 1 WL. The total radiation dose to radon progeny is commonly expressed in working level months (WLM) units. One WLM corresponds to exposure to a concentration of 1 WL for the reference period of 170 working hours per month, or to a concentration of 0.5 WL for 340 hours, etc.

2.3.2 Dosimetry Models

Physiologically based biokinetic dosimetry models are used to estimate the dose from radioactive material taken into the body. The models for internal dosimetry consider the quantity of radionuclides entering the body, the factors affecting their movement or transport through the body, the distribution and retention of radionuclides in the body, and the energy deposited in organs and tissues from the radiation that is emitted during spontaneous transformation processes. The dose pattern for radioactive materials in the

body may be strongly influenced by the route of entry of the material. The most frequent exposure routes for industrial workers have been inhalation of radioactive particles with pulmonary deposition and puncture wounds with subcutaneous deposition.

Ingestion. Ingestion of radioactive materials is most likely to occur from contaminated food and water, or by eventually swallowing inhaled compounds initially deposited in the lung but transported to the throat by the mucociliary clearance pathway. Ingestion of an excessive amount of radioactive material may result in toxic effects as a result of either absorption of the radionuclide from the intestine, irradiation of the gastrointestinal tract during passage through the tract, or a combination of both. The fraction of radioactive material absorbed from the gastrointestinal tract is variable, depending on the specific element, its chemical and physical form, the diet, and the individual's own metabolic and physiological factors. The absorption of some elements is influenced by age, usually with higher absorption rates in very young animals. These factors are quantitatively considered in the model that describes the gastrointestinal tract in terms of four compartments—stomach, small intestine, upper large intestine, and lower large intestine—and a fifth compartment that includes all the body fluids (NCRP 1988).

Inhalation. The inhalation route is a major route of exposure for radioactive materials. The deposition site 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, the physiological status of the lung, and the site of deposition. There are at least three distinct mechanisms that operate simultaneously to remove or clear radioactive material from the lung. Ciliary clearance acts only in the upper respiratory tract (i.e., trachea and the major and minor conducting airways of the lung). Cilia, short hairlike filaments growing out of the lining cells of the upper respiratory tract, are covered by the layer of mucous in the upper respiratory tract. The cilia move in a synchronized beating motion that pushes the mucous blanket, on which the large sized inhaled particles are deposited, upwards into the throat. There the particles can be coughed up or swallowed. The second and third mechanisms, phagocytosis and systemic absorption following dissolution of a particle, act mainly in the deep respiratory tract. 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. These factors are considered by the biokinetic model of the respiratory tract. This model includes four major compartments— extra-thoracic region (nasal airways and throat), tracheo-bronchial region (windpipe and bronchi), pulmonary region (alveolar area from which oxygen and carbon dioxide diffuse into and out of

the blood), and pulmonary lymph node region. Dosimetric lung models are reviewed by NCRP (1994), James (1987, 1994) and James and Roy (1987).

Internal emitters. When a radionuclide is ingested or inhaled, it becomes an internal emitter. The absorbed dose from an internally deposited radionuclide is determined by the concentration of absorbed energy in the tissue. Thus, the dose to an organ or tissue depends on its mass, the quantity of radioactive material introduced into the organ, the length of time that the radioactivity remains in the organ (represented by the effective half-life), and the energy and type of radiation. Since alpha and beta particles travel only short distances, all alpha particle energy and all or most beta particle energy is absorbed in the tissue that contains the radioactive material. Many common radionuclides also emit gamma rays that are so penetrating that a significant number escape from that tissue and interact with remote portions of the body, or pass out of the body entirely without interacting. For this reason, the gamma radiation dose to an organ considers both the dose from radioactive material in that organ plus the exposure from the gamma emitter deposited in other organs in the body. 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 isotope. An infinitely large medium may be approximated by a tissue mass whose dimensions exceed the range of the particulate radiation. All of the alpha radiation (due to its very short traveling distance in biological tissue) and most of the beta radiation will be absorbed in the organ (or tissue of reference).

2.3.3 Terms Used in Radiation Safety Practice and Regulation

The terms defined below are also included in the glossary in Chapter 9.

Absorbed dose. The energy imparted by radiation per unit mass of irradiated material is called the absorbed dose. The units of absorbed dose are the rad, in traditional units, and the gray (Gy), in SI units. (See “Units of radiation dose” for more information on absorbed dose).

ALARA. This acronym for “As Low As is Reasonably Achievable” refers to the practice of making every effort to keep exposure to radiation as far below the dose limit as possible while still achieving the purpose for which the radiation is intended to be used. It takes into account the state of technology, the economics of improvements in relation to state of technology, the economics of improvements in relation

to benefits to the public health and safety, and other societal and socioeconomic considerations. In addition, ALARA is applied to the utilization of nuclear energy and licensed materials in the public interest.

ALI. This acronym for "Annual Limit on Intake" is the derived limit for the amount of radioactive material taken into the body of an adult worker by inhalation or ingestion in a year. For a given radionuclide, ALI is defined as the smaller of the intakes that would result in a committed effective dose equivalent of 5 rem (0.05 Sv) or a committed dose equivalent of 50 rem (0.5 Sv) to any individual organ or tissue. Committed dose equivalent is the total dose equivalent that radioactive material internalized in a particular year will deliver to the body in that and all subsequent years out to 50 years after the intake. For radionuclides with effective half-lives of a month or less, essentially all the radiation dose will be delivered in the same year as the radioactive material intake, and the committed dose equivalent equals the dose equivalent received that year. However, radionuclides with longer half-lives remain in and expose the body for more than 1 year, and the committed dose equivalent accounts for this by summing the estimated dose equivalents produced by the radioactive material during the current year and every year out to 50 years.

Dose equivalent (H). The dose equivalent is used in radiation safety dosimetry to account for differences in biological effectiveness among the various radiations. The same energy imparted (absorbed dose) may result in different levels of biological effects for α, β, and γ rays. To account for the differences in biological effectiveness, a normalizing factor is used. The normalizing factor (Q) is used as a multiplier of the radiation absorbed dose (D) to give the *dose equivalent*. The dose equivalent, symbolized by H, is expressed in units of rem in the traditional system of units and in sievert (Sv) units in the SI (international) measuring system (100 rem = 1 sievert). This relationship is expressed as

$$H = D \times Q$$

Effective dose equivalent (H_E). The effective dose equivalent is used for radiation safety purposes and for regulatory purposes to account for the relative susceptibility of the various organs and tissues to radiation-induced non-deterministic or stochastic effects (principally cancer) in cases of non-uniform irradiation. The basis for the effective dose equivalent concept is that the probability of a non-deterministic effect from non-uniform irradiation should be equal to that due to uniform whole body irradiation. The effective dose equivalent is found by multiplying the dose equivalent (H_T) to each irradiated tissue or organ by a tissue weighting factor, W_T, and then summing these products for all the irradiated tissues, as shown in the equation

$$H_E = G(W_T \times H_T)$$

W_T represents the fraction of the probability of a non-deterministic effect resulting from irradiation of that tissue to the total probability of a non-deterministic effect when the whole body is uniformly irradiated. The values for W_T used by the USNRC and ICRP are listed below in Table 2-3.

For occupational exposure, the USNRC specifies an upper limit of 5 rem (0.05 Sv) in 1 year for the effective dose equivalent. The regulations also specify an upper annual limit of 50 rem (0.5 Sv) for all organs and tissues except the lens of the eye, for which an annual maximum of 15 rem (0.15 Sv) is prescribed.

Table 2-3. Tissue Weighting Factors Used by the USNRC and ICRP to Calculate Effective Dose

Tissue	USNRC Weighting factor for Effective Dose Equivalent (ICRP 1977; USNRC 1997a)	ICRP Weighting factor for Effective Dose (ICRP 1991)
Whole body	1.00 [a]	–
Gonads	0.25	0.20
Breast	0.15	0.05
Red bone marrow	0.12	0.12
Lung	0.12	0.12
Thyroid	0.03	0.05
Bone surface	0.03	0.01
Colon	–	0.12
Stomach	–	0.12
Bladder	–	0.05
Liver	–	0.05
Esophagus	–	0.05
Skin	–	0.01
Remainder	0.30 [b]	0.05

[a]The whole body weighting factor was introduced by the USNRC and is not addressed by either the ICRP or the NCRP.
[b]0.30 results from 0.06 being assigned to each of the five remaining organs (excluding the skin and lens of the eye) that receive the highest doses.

External dose. Radiation dose from a radiation source originating from outside of the body.

Health physics. Health physics is the science concerned with recognition, evaluation, and control of health hazards from ionizing and non-ionizing radiation. Health physics covers environmental, occupational, and medical areas, and includes radiobiology and the study of mechanisms of health effects.

The scientific and engineering aspects of health physics deal with the measurement of radiation and radioactivity, the establishment of dose-response relationships for radiation exposure, movement of radioactivity through the body and the environment, the design of radiologically safe processes and equipment, and the maintenance of a radiologically safe environment. The health physicist is the professional who deals with radiation safety.

Internal dose. Radiation dose from radioactive material inside the body.

Quality factor (Q). For health physics purposes, a normalizing factor, called the *quality factor* (Q), is applied to the radiation absorbed dose to account for the relative biological effectiveness (RBE) of the different radiations. The numerical values for the quality factors are determined by a committee of experts, and are based on a conservative upper limit of the RBE for the biological effect believed to be of the greatest interest to humans. Values for Q that are used in the USNRC safety standards in the Code of Federal Regulations (CFR) 10, Part 20, are listed below in Table 2-4.

Table 2-4. Quality Factors Used in USNRC Radiation Safety Regulations

Type of radiation	Quality factor (Q)
Alpha particles, multiple charged particles, fission fragments, and heavy charged particles	20
x rays, gamma rays, electrons, negatrons, or positrons	1
Thermal neutrons	2
Fast neutrons, neutrons of unknown energy, or high-energy protons	10

Source: USNRC 1997a

Relative biological effectiveness (RBE). The toxicity of a given absorbed radiation dose depends on the LET of the radiation: the higher the LET, the more toxic is the radiation and the smaller is the dose needed to produce a specific biological end point. To account for this LET effect, radiobiologists use the term *relative biological effectiveness* (RBE). The RBE for any radiation is typically defined as the ratio of the dose from 200 keV x rays required for a given biological effect to the dose that would produce the same effect with that radiation. RBEs can also be defined for specific scenarios that compare the effects of different radiation types or energies on producing the same end point. The term RBE is restricted in application to radiobiology.

Units of radioactive material. The following two units of radioactivity are commonly used when describing the quantity of radioactivity:

Becquerel (Bq). The SI unit of measure for radioactive material; one becquerel equals that quantity of radioactive material in which one atom disintegrates in one second.

Curie (Ci). The conventional unit used to measure the quantity of radioactive material. The curie is equal to that quantity of radioactive material in which 37 billion atoms transform per second. This is approximately the activity of 1 g of radium.

Units of radiation dose. The International Commission on Radiation Units and Measurements (ICRU 1980), International Commission on Radiological Protection (ICRP 1984), and National Council on Radiation Protection and Measurements (NCRP 1985) now recommend that the traditional units: rad, roentgen, curie, and rem be replaced by the SI units: gray (Gy), coulomb per kilogram (C/kg), becquerel (Bq), and sievert (Sv), respectively. However, the regulations used in the United States are written with the traditional units or with both traditional and SI units. The following four dosimetric units are commonly used:

Gray (Gy). The SI unit of absorbed dose. One gray = 1 J/kg = 100 rad.
Rad. The unit of absorbed dose. One rad = 100 erg/g = 0.01 Gy.
Sievert (Sv). The SI unit of dose equivalent, equal to absorbed dose in gray multiplied by the quality factor. One Sv = 100 rem.
Rem. The conventional unit of dose equivalent. One rem = 0.01 Sv.

The relationship between the traditional units and the international system of units (SI) for radiological quantities is shown in Table 2-5.

Table 2-5. Common and SI Units for Radiation Quantities

Quantity	Traditional units	SI units	Relationship
Activity (A)	curie (Ci)	becquerel (Bq)	1 Ci = 3.7×10^{10} Bq 1 Bq = 1 dps, 1 S^{-1}
Absorbed dose (D)	rad	gray (Gy)	1 rad = 0.01 Gy 1 Gy = 1 Jkg^{-1}
Dose equivalent (H)	rem	sievert (Sv)	1 rem = 0.01 Sv 1 Sv = 1 Jkg^{-1}

dps = transformations per second; Jkg^{-1} = Joules per kilogram; S^{-1} = per second

Source: Shleien 1992

Weighting factor (W_T). This factor is used for radiation safety purposes to account for the different sensitivities of the various organs and tissues to the induction of non-deterministic radiation effects.

Other terms used in discussions of radiation protection and regulation include: bioassay, collective dose, embryo/fetus, eye dose equivalent, public dose, shallow dose equivalent, total effective dose equivalent, whole body, and working level. These terms and their definitions may be found in Chapter 9.

2.4 BIOLOGICAL EFFECTS OF RADIATION

Radiation interactions within the body produce microscopic subcellular-level effects that may result in cellular responses and, in the aggregate, may ultimately produce macroscopically observable effects on specific organs or tissues, such as the skin, eye lenses, and thyroid.

Irradiation of biological tissue sets into motion a series of intracellular biochemical events that start with ionization of a molecule, and which may ultimately lead to cellular injury. Injury to a large number of cells may, in turn, lead to further injury to the organ and to the organism. Many factors may modify the response of a living organism to a given dose of radiation. Factors related to the dose include the dose rate, the energy and type of radiation, and the temporal pattern of the exposure. Biological factors include species, age, sex, the portion of the body tissues exposed, and repair mechanisms. A generally applicable rule of thumb is the Law of Bergonie3 and Tribondeau, based on their research in 1906, which states that cells are sensitive to radiation damage if they have a high mitotic rate, a long mitotic cycle, and are not specialized (undifferentiated) (Casarett and Alison 1968). In addition, the concurrent exposure to

radiation and other substances may result in antagonistic, additive, or synergistic effects, such as the synergism between ionizing and ultraviolet radiation to produce skin cancer.

The DNA is considered to be the primary target molecule for radiation toxicity. Molecular damage, which includes damage to the DNA, can occur in one of two ways from an exposure to radiation. First, radiation can interact directly with the DNA, resulting in single or double-strand DNA breaks or unbonding base pairs. Second, radiations can interact directly with other surrounding molecules within or outside of the cell, such as water, to produce free radicals and active oxygen species. These reactive molecules, in turn, interact with the DNA and/or other molecules within the cell (cell membranes, mitochondria, lipids, proteins, etc.) to produce a wide range of damage at the cellular and tissue levels of the organism. High LET radiation is an efficient producer of free radicals and H_2O_2, both of which can act directly on macromolecules. About 66% of the damage from low LET radiation and about 50% of the damage from high LET radiation comes from aqueous radiolytic products.

Regardless of how the DNA is damaged, the mammalian body has remarkable abilities to repair its damaged DNA. Mammalian DNA repair schemes, classified as either direct or indirect repair mechanisms, include many mechanisms such as nucleotide excision (via endonuclease), base excision (via DNA glycosylase), and mismatch repair. The success or failures of these inherent DNA repair systems depend on many factors, such as the dose and dose rate of radiation received and the tissue that received the radiation. Depending on the dose and the tissue exposed, inherent DNA repair mechanisms may be highly successful, resulting in total repair of the DNA. These mechanisms may fail completely if the repair mechanism is overwhelmed with very high doses of radiation, or may fail to repair all of the DNA damage caused by lower doses of radiation. This failure can result in necrosis due to cell death, apoptosis (programmed cell death), altered cell function, or the development of neoplastic cells several years after the damage occurred. DNA repair systems may be able to adequately repair the radiation damage to the DNA itself, but may do nothing to protect the irradiated cell from damage to other cellular structures (membranes, mitochondria, etc.) by the radiation (Zajtchuk 1989). Other repair mechanisms must be employed to protect the cell against these injuries.

Several protective strategies are used to minimize the damage from free radicals and reactive oxygen species that occur in cells exposed to high acute doses of radiation. Some of these methods include hypoxia (protective at high dose; can be observed for cell killing at doses >1 Gy), which decreases the

amount of oxygen available to form such reactive species; hypothermia; the use of free radical scavenging agents (aminothiols, vitamins A, E, and C); and eicosanoids. These methods have been used in special cases, such as in radiation therapy of tumors, to protect the surrounding healthy tissue. Genetic methods (repair by hydrogen transfer, regeneration) are also being investigated (Zajtchuk 1989).

The study of the mechanisms by which radiation exerts its toxicological effects is an important and constantly evolving field of toxicology. More information on the mechanisms of action of radiation can be found in Chapter 5 of this toxicological profile. 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 (BEIR V 1990; ICRP 1984; Kondo 1993; Rubin and Casarett 1968). A general overview of the health effects of alpha, beta, and gamma types of radiation in some types of biological tissue is presented below; more in-depth information on the health effects of radiation is presented in Chapters 3 and 5 of this toxicological profile (UNSCEAR 1993).

2.4.1 Radiation Effects at the Cellular Level

According to Mettler and Moseley (1985), at acute doses up to 10 rad (0.1 Gy), single-strand breaks in DNA may be produced. These single-strand breaks may be repaired rapidly. With doses in the range of 50 to 500 rad (0.5–5 Gy), irreparable double-strand DNA breaks are likely, resulting in cellular reproductive death after one or more divisions of the irradiated 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 is dose-dependent, may also be observed at this dose level. Specific clinical symptoms and other health effects associated with different doses of radiation are discussed in Chapter 3 of this profile.

The sensitivity of various cell types within an organism may vary widely, depending on specific cell and tissue characteristics. According to the Law of Bergonie and Tribondeau, 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). This means that cells that undergo frequent mitosis under normal physiologic circumstances or are not well-differentiated in histologic cell-type characteristics will tend to be more susceptible to the effects of radiation than those cells in which the converse is true. Rubin and Casarett (1968) devised a classification system that categorized cells

according to type, function, and mitotic activity. The five 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. This classification system is shown in Table 2-6.

Cellular changes in susceptible cell types may result in cell death; extensive cell death may produce irreversible damage to an organ or tissue, or may result in the death of the individual. If the cells recover, altered metabolism and function may be the ultimate sequelae, and the damage imposed may be repaired to a normal state, produce some characteristic manifestation of clinical symptoms, or result in apoptosis (programmed cell death). If the cells are adequately repaired and relatively normal function is restored, the more subtle DNA alterations may also be expressed at a later time as mutations and/or tumors. More information on the genetic effects of radiation is presented in Chapter 5 of this profile.

Table 2-6. Relative Radiosensitivity of Mammalian Cells

Class	Category	Characteristics	Cell types
I	Vegetative intermitotic cells	Rapidly dividing, short-lived; daughter cells will either differentiate or form more cells like the parent cell	Hemocytoblast, lymphoblast, erythroblast, myelobalst, primitive intestinal crypt cell, type A spermatogonia, primitive oogonia, lymphocytes
II	Differentiated intermitotic cells	Somewhat less radiosensitive than Class I cells; rapid proliferation rates, but daughter cells become more radioresistant than the parent cell	Type B spermatogonia, oogonia, cells of the intermediate stages of erythropoiesis and myelopoiesis
III	Multipotential connective tissue cells	Cells divide regularly in response to injury and irritation	Endothelium, fibroblast, mesenchymal cells.
IV	Reverting postmitotic cells	Normally do not undergo cell division	Epithelial cells of salivary glands, liver, kidney, pancreas, lung; parenchymal cells of sweat glands and endocrine glands. Interstitial cells of testis and ovary
V	Fixed postmitotic cells	Cells that will not divide; highly radioresistant	Mature nerve cells, muscle cells, sperm, erythrocytes.

Source: Sanders and Kathren 1983

2.4.2 Radiation Effects at the Organ Level

In most organs and tissues, the injury and the underlying mechanism for that injury are complex and involve a combination of events. The extent and severity of this tissue injury depend on the dose and 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 mucous; a slow renewal system, such as the pulmonary epithelium; and a nonrenewable 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, which is called the histohematic barrier (HHB); the injury may progress to fibrosis. In slow renewal and nonrenewable systems, the radiation may have little effect on the parenchymal cells, but ultimate parenchymal atrophy and death over several months may result from HHB fibrosis and occlusion of the microcirculation.

2.4.3 Acute and Delayed Somatic Effects

2.4.3.1 Acute Effects

The result of acute overexposure to radiation is commonly referred to as Acute Radiation Syndrome (ARS). This effect is seen only after whole-body exposures to relatively high doses (>100 rad, >1.0 Gy) such as might occur in a serious nuclear accident, close to a nuclear weapon detonation, or after a period of exposure to the high radiation field of irradiator sources, such as occurred to Chernobyl on-site responders and individuals in Goiania, Brazil (see Chapter 4). The four stages of ARS are prodrome (or initial), latent stage, manifest illness stage, and recovery or death. The probability of the prodromal phase is characterized by nausea, vomiting, malaise and fatigue, increased temperature, and blood changes. The latent stage is similar to an incubation period. Subjective symptoms may subside, but changes may be taking place within the blood-forming organs and elsewhere that will subsequently give rise to the next stage. The manifest illness stage gives rise to signs and symptoms specifically associated with the radiation injury: hair loss, fever, infection, hemorrhage, severe diarrhea, prostration, disorientation, and cardiovascular collapse. Convulsions are possible at extremely high doses. The severity and time of onset of the signs and symptoms depend upon the radiation dose received (see Chapter 3), with the time of onset decreasing with increasing dose.

2.4.3.2 Delayed Effects

The level of exposure to radiation and radioactive materials that may be encountered in the environment, even large exposures spread over a long enough period of time, is expected to be too low to result in the acute effects described above. Occupational and medical radiation may produce long-term effects that manifest themselves years after the original exposure and may be due to a single elevated exposure or a continuous low-level exposure.

Exposure to radiation has resulted in a number of adverse health effects. The rapidly dividing cells in the developing fetus put it at a higher risk of the adverse biological effects of radiation than a post-partum child, who in turn is more radiosensitive than an adult. External alpha (because it is non-penetrating) and beta radiation are of little concern due to the protection afforded by the mother's body tissues and the placental sac; however, gamma radiation can provide a more uniform exposure to the fetus. Analysis of the human data from the children exposed *in utero* by the bombing of Hiroshima and Nagasaki suggests that the cells of the developing central nervous system are the cells most sensitive to the effects of radiation in the developing human fetus. The major clinical effect on these susceptible cells is impaired intelligence and mental retardation that is observed during childhood development, mainly for those fetuses exposed to doses of radiation during weeks 8–15 after conception. A "no observable effect" threshold exists for doses in the range of 20–40 rad (0.2–0.4 Gy); at a dose of 100 rad (1 Gy), the frequency of observed mental retardation was 43% (BEIR V 1990).

The lens of the eye is also susceptible to the effects of radiation. Sufficient exposure of the lens to radiation results in cataract formation, ranging from mild visual impairment to blindness. The lens fibers are normally transparent and function in focusing light entering from the pupil onto the retina; however, after exposure to large doses of radiation, these cells fail to divide to produce lens fibers of the appropriate length or transparency. This results in increased opacity of the crystalline lens of the eye (cataracts). Cataracts have been induced by as little as 200 rad (2 Gy) of acute gamma or x ray exposure of the eye (Adams and Wilson 1993), but 500 rad (5 Gy) is required when fractionated over 5 weeks. Chronic occupational exposures to 70–100 rad (0.7–1.0 Gy) of gamma and x ray radiation have not caused cataracts, and the higher doses at which they have been observed require the dose to be delivered at a threshold dose rate of greater than 15 rad/yr (0.15 Gy/yr) (UNSCEAR 1993; NRC 1990). Data from victims exposed to large doses of radiation after the bombings of Hiroshima and Nagasaki give a cataract threshold of 60–150 rad (0.6–1.5 Gy); however, typical human exposure over a long period of time is thought to have a threshold greater than 800 rad (8 Gy) (BEIR V 1990). This is an established example of a radiation effects threshold that does not follow the standard linear, no-threshold theory that is applied

only to non-deterministic effects (cancer). This observation may mean that the effect on the lenses is actually below an effects threshold, or it could mean that the latency period for developing the effect is longer than the current human life span.

Sufficient evidence exists from high dose studies of both human populations and laboratory animals to establish that radiation can be carcinogenic and that the incidence of cancer increases with the dose of radiation. Human data are extensive and include epidemiological studies of atomic bomb survivors, many types of radiation-treated patients, underground miners, and radium dial painters. Reports on the survivors of the atomic bomb explosions at Hiroshima and Nagasaki, Japan (with whole-body external radiation doses up to 200 rad [2 Gy]), indicate that cancer mortality has increased in that exposed population compared to control (non-exposed) individuals (BEIR V 1990; Kato and Schull 1982; NCRP 1990b,1993; NRC 1990; UNSCEAR 1993). The use of x rays (at doses of approximately 100 rad [1 Gy]) in the medical treatment for ankylosing spondylitis and other non-cancerous conditions, and for diagnostic purposes has resulted in excess cancers in the irradiated organs (BEIR 1980, 1990; UNSCEAR 1977, 1988). Leukemia has been observed in children exposed *in utero* to doses of 0.2 to 20 rad (0.02–0.2 Gy) (BEIR 1980, 1990; UNSCEAR 1977, 1988). The medical use of Thorotrast (colloidal thorium dioxide) resulted in increases in the incidence of cancers of the liver, bone, and lung (ATSDR 1990b; BEIR 1980, 1990). Occupational exposure to radiation provides further evidence of the ability of radiation to cause cancer. Numerous studies of underground miners exposed to radon and radon daughters (which are α emitters), in combination with silica dust, diesel fumes, and other potential toxicants in uranium and other hard rock mines, have demonstrated increases in lung cancer in exposed workers, especially smokers (Harley 1990b, 1996c). Workers who ingested ^{226}Ra while painting watch dials had an increased incidence of osteogenic sarcoma (ATSDR 1990d). Animal studies indicate that, depending on the radiation dose and the exposure schedule, radiation can induce cancer in nearly any tissue or organ in the body. However, radiation has not been shown to cause cancer of the prostate, uterus, testis, and mesentery in humans (Sanders and Kathren 1983). Radiation-induced cancers in humans are found to occur in the hemopoietic system, lung, thyroid, hepatic, bone, skin, and many other tissues.

The effects of sex, age, smoking, and other susceptibility factors have also been reviewed (BEIR V 1990). Generally, cancer rates after exposure to radiation are age-dependent and increase with age. The effect of smoking on lung cancer incidences in those individuals who also have prolonged exposure to inhaled alpha emitters indicates a multiplicative risk (or near multiplicative risk); however, this may not be the case for acute exposures to x rays or gamma rays. In contrast, the data on lung cancer and smoking in the Japanese atomic bomb survivors indicate an additive risk (no interaction between radiation and smoking).

It is not presently clear how a person's sex influences cancer rates. Males appear to be more susceptible to lung and non-sex-specific cancers than are females; however, this may be related to the male's increased exposure to carcinogens and promoting agents in occupational situations, as well as a number of lifestyle factors, and not necessarily due to increased radiation dose.

Laboratory animal data show that high doses of radiation are carcinogenic and mutagenic, and can result in cell lethality. These effects are not seen at low doses. This raises a question about the relationship between high and low doses. There is uncertainty regarding the shape of the dose response curve with regard to extrapolating from high-dose effects to effects of low doses or doses received over protracted periods of time, where no effects have been seen. If the dose-response relationship is assumed to be linear all the way down to zero dose, then a proportional decrease in the incidence of the effect being measured (cancer, reciprocal chromosome translocations, locus mutations, life-span shortening, etc.) would be expected as the dose or dose rate of radiation decreases. However, in laboratory studies with high doses, a dose rate effect was found. That is, an acute-duration exposure delivered over several days required a higher dose to produce a given effect than if delivered within hours. To account for this, a compensation factor or Dose Rate Effectiveness Factor (DREF) can be incorporated into the dose response models to extrapolate cancer risk from high to low doses or low dose rates. For low LET radiation, DREF factors from 2 to 10 have been suggested, with a DREF of 2.5 for human leukemia. Assumptions about DREF are largely based on laboratory animal data. A comprehensive discussion of radiation-induced cancer is found in BEIR IV (1988), BEIR V (1990), and UNSCEAR (1988) and in Chapters 3 and 5 of this toxicological profile.

Lifetime radioactive material feeding studies using Beagle dogs indicate that radiation effects may be viewed from a perspective of life-span shortening which is linear with dose rate rather than with dose. Time-to-death plots as a function of dose rate show three separate sections, representing mortality from acute radiation syndrome, cancer, and old age, each with separate linear slopes that intersect at points of equal competing causes of death. At extreme dose rates, death is caused exclusively by acute radiation syndrome, with time-to-death increasing with a steep linear slope as the dose rate decreases. At a low enough dose rate, cancer replaces ARS as the primary cause of death, and the time to death curve assumes a shallower slope. At a low enough dose rate, cancer deaths are replaced by the limit of the normal life span (Raabi 1993, 1996).

2.4.4 Genetic Effects

All genes have a natural and spontaneous mutation rate, but radiation can induce additional genetic damage, such as gene mutations and a variety of chromosomal aberrations, by causing changes in the structure, number, or genetic content of chromosomes in the cell nucleus. Radiation increases the mutation rate. No new types of mutations are known to be produced by radiation. The evidence for the mutagenicity of radiation is derived from studies in laboratory animals, primarily mice (BEIR 1980, 1988, 1990; UNSCEAR 1982, 1986, 1988, 1993). Evidence for genetic effects in humans is derived from tissue cultures of human lymphocytes from persons exposed to ingested or inhaled radionuclides (ATSDR 1990d, 1990e). Evidence for mutagenesis in human germ cells (cells of the ovaries or testis) is not conclusive (BEIR 1980, 1988, 1990; UNSCEAR 1977, 1986, 1988,1993). Chromosome aberrations following radiation exposure have been demonstrated in humans and in experimental animals (BEIR 1980, 1988, 1990; UNSCEAR 1982, 1986, 1988,1993). This finding is not thought to be in conflict with results of animal studies that indicate induction of mutations by radiation; instead, the finding may result from the difficulty of demonstrating a slight increase of effects of this type in a human population (UNSCEAR 1993). However, no genetic effects have been observed in any human population exposed to any radiation at any dose level. An important source of data on genetic effects in humans are Japanese survivors of the atomic bombs and their offspring. More information on the genetic effects of radiation can be found in Chapters 3 and 5 of this toxicological profile.

2.4.5 Teratogenic Effects

There is sufficient evidence from x ray and gamma ray studies to suggest that some forms of radiation produce teratogenic effects in animals. Rapidly multiplying cells tend to be more sensitive to the adverse effects of radiation than slowly multiplying cells. Leukemia and other childhood cancers are the principle effects of *in utero* exposure at low doses (<100 rad [<1 Gy]). It appears that the developing fetus is more sensitive to radiation than the mother and is most sensitive to radiation-induced damage during the early stages of organ development (first trimester) due to the rapid cellular proliferations occurring at that time. The type of malformation depends on the stage of development and the cells that are undergoing the most rapid differentiation at the time. Studies of mental retardation, intelligence reduction, microcephaly, and growth retardation in children exposed *in utero* to high doses of radiation from the atomic bombs at Hiroshima and Nagasaki provide evidence that radiation can produce teratogenic effects in human fetuses if delivered in large enough doses during weeks 8 through 25 after conception (Otake and Schull 1984; Zajtchuk 1989). The damage to the child was found to be related to the dose that the fetus received *in utero*. In addition, numerous studies have been conducted on the carcinogenicity of *in utero* irradiation,

and some appear to indicate that *in utero* exposure may produce a larger cancer risk per unit dose than postnatal irradiation (NCRP 1995). Chapters 3 and 8 contain more information on the teratogenic effects of radiation.

2.4.6 Internal Exposure to Ionizing Radiation

For the purposes of this profile, internal exposure is defined as the energy deposited in the body by the transformation of radioactive material that is inside the body. The pathways by which radioactive materials enter the body include inhalation, ingestion, dermal absorption, and injection. The material's solubility and chemical nature, and not its radioactive properties, determine the degree to which the material will stay in one place or redistribute throughout the body. Thus, the internal radiation dose is determined from the types and energies of emitted radiation, the rates of radioactive transformation and biological elimination, and the distribution of the material throughout the body. The dose to one part of the body is the sum of the doses to that part from radiation emitted from all other organs and tissues that contain the radionuclide.

2.4.6.1 Inhalation

Inhalation is an important route by which internal exposure to radionuclides can occur. Many of the inhalation studies discussed in Chapter 3 are further indexed by no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) in Chapter 8 of this toxicological profile. The total absorbed radiation dose to a specific site, such as the lungs and any surrounding structures, is dependent on the physicochemical characteristics of the radioactive element, the molecule in which it is present, or the particle to which the radioactive element is bound or incorporated when deposited in the respiratory tract. In many of the studies reported in Chapters 3 and 8 of this profile, laboratory animals were exposed to a radionuclide that was bound to a particle of some type. The radionuclide "piggy-backing" on that particle was inhaled, the initial lung burden was determined, and the health effects on the animal observed over a period of days or over its lifespan. Particle kinetics are a major determinant in the size of the total absorbed radiation dose that lung tissue and other tissues and organs receive from inhaled radioactive material. Several excellent reviews are available that discuss the deposition and clearance of inhaled particles in humans and in laboratory animals (Gore and Patrick 1978; Lippmann and Esch 1988; Lippman and Schlesinger 1984; Schlesinger 1989; Snipes 1989; Stahlhofen et al. 1980, 1981). A brief review is presented below. Internal radionuclide exposures may occur from direct medical administration for diagnosis or treatment of disease, or from passive inhalation of radionuclides that are present in normal breathing air.

Particle deposition and clearance mechanisms in the respiratory tract are complex. The patterns of deposition and clearance differ among animal species, but some generalities have been reported (Snipes 1989). As a rule of thumb, the larger the particle inhaled, the more likely that particle will be deposited in the upper airways (nasal tract and upper conducting airways); the smaller the particle, the more likely that alveolar and deep penetration of the particle into the lung will occur, regardless of the particle's solubility. Particles that are soluble in the lung fluid milieu generally have shorter residence times or biological half-lives than those that are insoluble in lung fluid. These concepts are important when considering inhaled radioactive particles. For example, particles that are 3 μm in diameter and that are also insoluble (such as fused aluminosilicate particles [FAP]) containing a radionuclide such as ^{144}Ce are likely to be largely deposited deep in the lung (bronchioles and alveoli). Retention of particles deep within the lung may be due to a number of factors, including the lack of cilia and less mucous in the smaller airways than in larger airways (trachea and bronchi) (Snipes et al. 1996). These insoluble particles are also likely to be cleared slowly from the respiratory tract over a period of several months or years, thereby subjecting the tissues around that particle to long-term exposure to radiation. On the other hand, particles that are very large (10–12 μm and above) may not reach the deep lung and will either lodge in the nasal cavity or be cleared by mucociliary clearance from the conducting airways, resulting in a low radiation dose to the respiratory tract (but may increase the dose to the gastrointestinal tract or nasal passages). Soluble particles will dissolve, releasing the material into the surrounding tissue, where it will behave toxico-kinetically like its nonradioactive counterpart. Leaching of radionuclides from insoluble particles has also been reported to occur.

Factors that influence particle clearance include: (1) particle characteristics, such as geometric size, shape, density, hygroscopicity, and electrical charge; (2) respiratory tract characteristics, such as the individual airway caliber, branching patterns of the conducting (tracheobronchial) airway tree, and the path length to the terminal airways, all of which contribute further to the disposition of particles in the respiratory tract; (3) mode of breathing (oral, nasal, oronasal), respiratory rate, tidal volume, interlobular distribution of ventilated air, length of respiratory pauses, etc; and (4) other factors (lung disease, age of the animal, irritant exposure, etc.) which also play significant roles in how long a particle remains lodged in the respiratory tract. Several natural body mechanisms function to clear the respiratory tract of these foreign bodies. Such mechanisms include sneezing, coughing, mucociliary transport, dissolution (for highly as well as slightly soluble particles), and removal by macrophages; these decrease the particle residence time in the respiratory tract, thereby decreasing the total radiation dose to the tissues (Schlesinger 1989). Deposition and clearance mechanisms are important factors influencing radiation dose from a radionuclide to lung tissue and in relating that dose to a corresponding health-related effect.

2.4.6.2 Ingestion

Oral exposure to radionuclides may occur with the ingestion of contaminated food or water. There is little literature available that describes the toxicity of ingested radioactivity in humans. The main source of information on oral toxicity of a radionuclide is the experience of the radium dial painters who "tipped" their paint brushes with their lips and/or tongues, subsequently ingesting radioactive radium. The radium in the paint contained both the long-lived ^{226}Ra and the shorter-lived ^{228}Ra isotopes. Some of these exposed individuals later developed bone sarcomas and head carcinomas that appeared from 5 to 50 years after their first exposure to these isotopes (Mays 1988; Spiess and Mays 1970). On the other hand, millions of people have been given individual administrations of 200–500 MBq (5–14 mCi) of radioiodine orally to aid in the diagnosis of thyroid disorders, with no apparent harmful effects. Although a number of radionuclides are in widespread use, the use of ^{131}I to treat thyroid conditions predominates worldwide, and radiopharmaceuticals administered by various routes currently produce an estimated population dose of 930,000 man-rem/yr (9,300 man-Sv/yr) (UNSCEAR 1993).

For most radionuclides present at chemical waste sites containing low-levels of radioactive isotopes, oral exposure is not a major route of exposure; however, the oral exposure route cannot be disregarded because of the potential for groundwater contamination, consumption of animals that have ingested radioactive compounds in their diet, and uptake by plants following erosion of ground cover from a contaminated site.

2.4.6.3 Dermal

Dermal exposure to radionuclides is a minor route of exposure at low-level radioactive waste sites. Swimming or bathing in water containing soluble radioactive compounds in the water itself or water-insoluble radioactive compounds in sediment or sludge are potential sources of dermal exposure in highly contaminated areas. Contact with tritiated water is another situation in which skin absorption of a radionuclide can be significant. Depending on the specific physical properties of the radionuclide that may reside on the skin, the percutaneous absorption of radionuclides from particles is usually negligible (especially if the skin is thoroughly washed immediately following exposure), with long-term biological effects being demonstrated locally at the level of the dermis (and its vasculature) and epidermis; however, these effects depend greatly on the size of the dose and length of exposure. More soluble forms of the radionuclides may result in a small percentage of the nuclide being absorbed if it was not removed from the skin's surface. This absorption may, in turn, affect tissues other than the skin.

2.4.7 External Exposure to Ionizing Radiation

External radiation is also a major source of exposure to radiation. External radiation is defined here as radiation exposure from a radioactive source that is outside of the body. Common natural sources are terrestrial radiation (originating from the soil, water, building materials, and air) and cosmic radiation from outer space. Common sources of man-made external radiation include medical and dental x rays, consumer products, licensed radioactive sources, and being near someone undergoing a medical radionuclide treatment. Technologically enhanced sources consist of concentration of naturally radioactive elements, such as uranium mine and mill tailings or the uranium-containing slag from phosphate rock processing.

In situations involving external exposure to radiation, radionuclides that are gamma emitters are of greatest importance. Alpha particles travel only a few inches in the air and are not capable of penetrating a piece of paper or the stratum corneum (the dead outer layer of the skin); beta particles are less energetic and have only limited penetrating ability. In contrast, gamma radiation is highly penetrating, and thus more capable of irradiating the whole body from distant sources.

2.5 MEASURING INTERNAL AND EXTERNAL SOURCES OF IONIZING RADIATION

The radiation from some internally deposited radionuclides cannot be measured directly. The radioactivity of such radionuclides within the body is determined by bioassay methods, and the data obtained are applied to physiologically-based biokinetic models to calculate the dose.

Dose rates for external radiation can be directly measured with appropriate instruments; the total dose is determined by multiplying the dose rate by the exposure time. Total dose from external sources can be easily measured. This is usually done with a personal monitoring device, such as an electronic dosimeter, a pocket dosimeter and film badge, or a thermoluminescent dosimeter (TLD). Table 2-7 lists some of the methods and instruments used by the health physicist to determine a person's radiation dose. The Multi-Agency Radiation Survey and Site Investigation Manual (MARSSIM) manual provides information on how various types of field and laboratory equipment are used to measure radiation dose rates and quantities of radioactive material (MARSSIM 1997).

2.5.1 Internal Radiation Measurements

The amounts of radioactive material in the body are measured by *in vivo* or *in vitro* methods or a combination of *in vivo* and *in vitro* techniques. These types of measurements, called bioassays, are used to determine the type, quantity, location, and retention of radionuclides in the body. *In vivo* techniques measure the quantities of internally deposited radionuclides directly, while *in vitro* analyses are performed on the materials excreted or removed from the body. A synopsis of the analytical methods used to measure the quantity of radioactivity both inside and outside of the body is presented in Table 2-7.

Table 2-7. Common Analytical Methods for Measuring Radioactive Material Inside and Radiation Outside the Body

Sample matrix	Preparation method	Device used	Reference
Whole body, portion of body, or organ (x or γ radiation)	Position individual in front of detector with area of interest shielded from extraneous radiation	Multichannel analyzer with NaI detector for up to a few γ-emitters, a germanium detector for any number of γ-emitters, or a planar germanium detector for α-emitters that also emit x rays.	NCRP 1978
Urine, blood or feces	Put any solids into solution; do chemical separation if multiple radioactive elements are present; deposit thin layer on a planchet or mix with liquid scintillation cocktail.	Liquid scintillation for α- or β-emitters; alpha spectroscopy for α-emitters; GM counter for high-energy β- or γ-emitters; multichannel analyzer for γ-emitters.	Jia et al. 1994
Personal monitoring: external radiation dose (β- and γ-radiation)	Heat dosimeter to produce thermoluminescence	TLD	Lynch et al. 1994
	Develop film	Film badge	Shapiro 1990c
	None	Electronic dosimeter	
Contamination monitoring: surfaces, skin, clothing, shoes (β- and γ-radiation)	None	GM counter	NCRP 1978
Contamination monitoring: surfaces, skin, clothing (α-radiation)	None	Proportional counter	NCRP 1978

α = alpha; β = beta; γ = gamma; GM = Geiger-Mueller; TLD = thermoluminescent dosimeters

One *in vivo* or direct method of measuring radionuclides in the body is performed with a radiation detection system and its associated electronics, called a whole-body counter (see Figure 2-2). Equipment for whole-body counting varies from facility to facility and is selected based on the needs of each facility. Equipment changes also continue as the state of the art advances. Commonly, the subject is seated in front of a single large detector; however, the subject can remain standing during the count, as shown in Figure 2-2. This system measures the emission of gamma rays or x rays from internally deposited radionuclides. The use of whole-body counters is limited to assessment of radionuclides that emit x ray or gamma radiation as these counters are insensitive to the alpha and beta particles emitted from radionuclides. Whole-body counting systems can vary from single, unshielded detectors that can be used in the field to shielded multi-detector scanning systems (NCRP 1987).

Figure 2-2. Whole Body Counter. The linear geometry NaI based WBC pictured here is designed to maximize sensitivity and accuracy for internally deposited fission/activation products such as isotopes of Cs and Co. (Photograph courtesy of Canberra Nuclear/Packard BioScience Co.)

The complexity of whole-body counting systems depends on their intended uses and the radionuclides to be measured, as well as the accuracy and precision required of the measurement. Multiple, fixed position detectors may also be used for simultaneously assessing multiple areas of the body (e.g., lung and thyroid detectors). The detector is placed a short distance from the body, such as over the chest when a lung count is desired. Examples of types of detectors used include solid, inorganic scintillators (e.g., sodium iodide), and semiconductors (e.g., germanium detectors).

Examples of radionuclides that may be readily identified and quantified using whole-body counting techniques are ^{134}Cs, ^{137}Cs, ^{58}Co, ^{60}Co, ^{131}I, ^{99m}Tc, and ^{133}Xe. If a particular portion of the body requires monitoring after exposure to alpha particle emitters that also emit x rays or gamma rays, such as uranium, plutonium, and americium, a low-energy germanium lung counter can be used to maximize detection sensitivity for x rays or gamma rays that are emitted from such internally deposited radionuclides (see Figure 2-3). Typical count time for the instrument shown in Figure 2-3 is 15–30 minutes. Another detector variation consists of moving one or several detectors along the length of the subject, or moving the subject in relation to a fixed detector, and determining radioactivity in the body as a function of the position of the detector (NCRP 1987). Photons from the radionuclides in the body enter the detector and interact with the detection medium. In the case of a sodium iodide detector, this interaction produces flashes of light (scintillations). The intensity of each scintillation is proportional to the interaction energy of the photon producing it. Photomultiplier tubes convert the light energy to an electrical pulse with an output voltage proportional to the intensity of the scintillation. The output pulses are then amplified and sorted by energy level. If a germanium semiconductor detector is used, the photon interaction directly produces an electrical impulse whose magnitude is proportional to the photon's energy. With either detector, qualitative and quantitative analyses of the energy profiles are then performed to identify the radionuclides present and their activities.

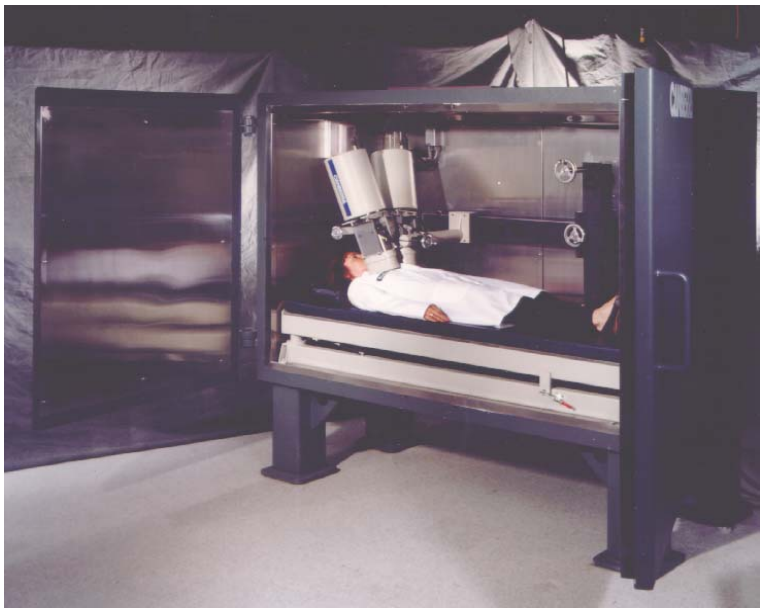


Figure 2-3. Low Energy Germanium (LEGe) Based Lung Counter. This instrument is designed to maximize sensitivity for internally deposited U, Pu and Am isotopes. Germanium is used to provide the system with the ability to resolve the differences between photons which are close in energy to each other. (Photograph courtesy of Canberra Nuclear/Packard BioScience Co.)

In vivo counting systems are calibrated using tissue-equivalent phantoms. These phantoms have shapes similar to the human torso and are made of polystyrene or other tissue equivalent material. Standard radioactive sources of known activities are inserted into the phantom at locations or geometries approximating internal depositions of particular radionuclides in the human body. Relationships are thus determined between the radiations detected and the known activity in the phantom (DOE 1988; HPS 1996).

The Health Physics Society developed the American National Standard on Performance Criteria for Radiobioassay (HPS 1996) to establish performance criteria for accuracy, bias, and precision for

bioassays. The sensitivity of a whole-body counting system is specified by the acceptable Minimum Detectable Amount (MDA) which is the smallest activity or mass of an analyte in a sample or the body that will be detected, given assigned type I and type II error limits. The criterion imposed on a participating laboratory is the Minimum Testing Level (MTL) or the amount of radioactive material that the service laboratory should be able to measure. When the analysis facility can measure an acceptable MTL with acceptable bias and precision, the performance requirements of the ANSI standard are considered to have been met. Some examples of MTLs are 9 kBq (0.24 μCi) of ^{239}Pu or 3 kBq (81 nCi) of ^{60}Co in the lung by direct test methods, or 0.01 Bq (0.27 pCi) of ^{239}Pu or 2 Bq (54 pCi) of ^{60}Co per liter of biological material by indirect methods (HPS 1996).

For radionuclides that transform by alpha or beta particle emission and do not emit readily measurable gamma rays, *in vitro* or indirect analyses can be performed. *In vitro* analyses may also be performed in support of an *in vivo* monitoring program, or in cases where the size of an operation does not justify the cost of a whole-body counting facility. These analyses usually involve measurement of radionuclides in urine, but other body materials such as feces, blood, or tissue samples may also be measured. Urine sample analysis is a rapid way to determining whether an intake of radioactive material has occurred. Urine samples are easily obtained and easy to analyze; however, fecal, blood or tissue samples are difficult to obtain, and thus these analyses are not routinely performed. ^{3}H, ^{14}C, various isotopes of uranium and plutonium, and many other β- or α-emitting radionuclides are often assessed by *in vitro* techniques.

Gamma ray measurements of excreta may not require chemical processing and separation prior to counting due to the penetrating characteristic of gamma radiation. For alpha and beta radiation measurements, the energy spectra of the various radionuclides overlap. In such cases, chemical separation of samples prior to quantification of the radioactivity may be required. If only the total activity, not the identity of the radionuclide, is needed, gross alpha and gross beta quantification can be performed with minimal sample preparation. There are no standard chemical separation or preparation procedures for *in vitro* analysis that are recommended by any recognized authority; however, many acceptable procedures are available and in use at a large variety of laboratories and facilities, and DOE and EPA laboratories have some standard procedures that they routinely follow. Regardless of the procedures used by each laboratory, the methods should be capable of meeting the acceptable MTLs identified by HPS (1996).

Detectors commonly used to quantify alpha, beta, and gamma radiation in *in vitro* samples include scintillation (Figures 2-4) and liquid scintillation detectors (Figure 2-5), Geiger-Mueller (GM) detectors, gas-filled proportional counters, and semiconductor detectors. In scintillation counters, photons from the

radionuclides exit the sample (i.e., urine, feces, tissue) and interact with the scintillator (e.g., zinc sulfide for α-emitters, toluene for α- and β-emitters; NaI crystals for γ-emitters) to produce flashes of light (scintillations). Photomultiplier tubes convert the light energy into an electrical pulse with an output voltage proportional to the energy of the radiation interaction. The output pulses are then amplified and sorted by energy level. Gamma rays interact, producing a broad energy spectrum from Compton interactions superimposed by peaks from photoelectric events. The peak centroids and areas are used to identify the isotopes and their activities.

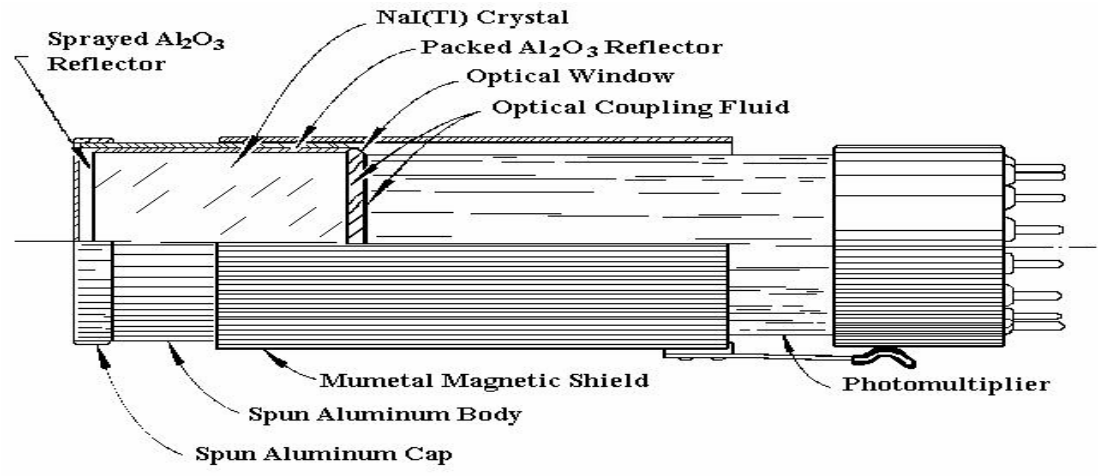


Figure 2-4. Components of a Scintillation Detector (adapted from http://tweedledee.wonderland.caltech.edu/-derose/labs/exp12.html)

Liquid scintillation counters (Figure 2-5) are used to isotopically identify and measure the activity of alpha or beta radionuclides in a range of sample matrices. This method is useful in avoiding some of the difficulties that arise when analyzing alpha or low-energy beta emitters, such as ^{3}H and ^{14}C, where self-absorption within the sample matrix can be significant. The sample is dissolved directly into a liquid scintillator and placed inside a light-tight system. The radiation from the sample activates the scintillator, causing flashes of light (scintillations) whose intensities are proportional to

Figure 2-5. Liquid Scintillation Counting (LSC) System. Shows system (left) and closeup view of sample vials to be loaded (right). (from Canberra/Packard Bioscience Co.)

the radiation energy. These scintillations are measured by an integral photomultiplier tube. The counting efficiency of current generation photomultiplier tubes is about 90%. Most liquid scintillation fluids (cocktails) are organic-based solvents, such as toluene. The signal from the dissolved sample is reduced or quenched through partial absorption of the light by the dissolved sample, so an optical comparison of pure and sample laden scintillation cocktail is made to correct for this phenomenon (Knoll 1989).

GM counting systems consist of a gas-filled detector tube, associated electronics, and counting circuit and display. The tube end can have a thin covering (window) that allows low-energy beta particles to enter the tube. When an incident particle from a radionuclide enters the tube window and interacts with at least one gas molecule, it initiates a series of ionizations that result in generation of a voltage pulse of about 1 volt. These radiation-induced electrical pulses trigger a circuit which counts the pulses. The GM counter is not capable of discriminating among various types of radiation (alpha, beta, gamma); the instrument simply records the number of pulses. However, the use of different window thicknesses allows the user to discriminate among the different radiations. An aluminum window 0.1 mm thick will stop all beta particles emitted from ^{14}C; to measure alpha particles, an aluminum window thickness of less than 0.02 mm is required. Gamma radiation does not require a special window because gamma rays will penetrate the tube from all directions (Shapiro 1990).

Gas-filled proportional counters are used to measure alpha and beta particles; they are particularly well-suited for low-level alpha measurements due to their large counting areas and low background. Like the GM counters, the voltage pulse output signal produced in proportional counters is a result of an electrical charge resulting from the ionization of the gas by the incident particle. Electrons released by the ionization are drawn toward the positively charged central wire. As they travel toward the wire, the electrons collide with other gas molecules, producing more ionizations and an amplification effect. At certain counter operating voltages, the amplified charge produced is proportional to the energy absorbed in the detector and facilitates energy discrimination techniques. Alpha particles, due to their larger size, large charge, and lower speed, interact with more gas molecules over a given path-length than beta particles. Thus, the alpha-to-beta particle pulse height ratio is substantial (Shapiro 1990). Proportional detectors use this difference to distinguish between alpha and beta particles, based on pulse-height discrimination.

Semiconductor detectors are characterized by their use of crystalline silicon or germanium as the ionization medium. A sensitive volume is produced in the crystal by electrochemical means. The interaction of radiation with the crystalline lattice within the sensitive volume generates electrons by ionization, and the collection of these electrons leads to an electrical output pulse whose size is proportional to the energy of the radiation. A semiconductor detector requires only about one-tenth as much energy to produce an ionization as other types of detectors. This leads to a great increase in the detector's resolving power (i.e., in the ability

of the detector to separate pulses from particles whose energy differences are very small). For this reason, semiconductor detectors find their main use in nuclear spectroscopy, where they can simultaneously separate, accurately identify, and quantify various radionuclides. Several types of semiconductor systems are available, including *in-situ* spectrometers and both portable and stationary systems equipped with multichannel analyzers (Cember 1996; Shapiro 1990).

2.5.2 External Radiation Measurements

People who could be occupationally exposed to radiation are routinely monitored for external radiation dose by several different devices called dosimeters. The most commonly used personal monitoring dosimeters are thermoluminescent dosimeters (TLDs) and nuclear emulsion monitors (film dosimeters), which can be used to measure exposure to β, x ray, and γ radiation doses. The TLDs and the film dosimeters are integrating devices that measure the total dose over the period that the TLD or film badge is used or worn.

The most widely used thermoluminescent material for measuring beta and gamma radiation is a lithium fluoride crystal. The energy absorbed from the radiation raises the electrons in the lattice structure of the crystal to a higher energy level, where a portion are trapped by added impurities. The electrons remain in these excited states until the TLD is heated to temperature high enough to return the material to its normal energy level (Lynch et al. 1994). Light is emitted which can be measured; the amount of light is proportional to the radiation dose to which the TLD was exposed. Automated systems called TLD readers for measuring the light output from the heated TLDs are commercially available. TLDs are normally worn from 1 day to 1 quarter before results are processed; TLDs posted around occupied areas to assess doses to unmonitored individuals are normally posted for 1 month to 1 year; the TLD can be used again (Shapiro 1990).

When individuals are exposed to mixed radiation fields (e.g., mixtures of beta/gamma radiation), measurements for each radiation type must be performed. Either film badges or TLDs can be made to distinguish among various radiations, and are commonly used to monitor personal exposures to β, x, and γ radiation, but not α radiation. Due to the limited range of beta particles in tissue, the exposure of concern is primarily to the skin, although beta particles whose energy exceeds 0.8 MeV can penetrate to the lens of the eye. Penetrating x ray and gamma radiation can expose the whole body, including the lens of the eye. These types of radiation are assessed simultaneously using multiple TLDs individually covered with absorbers of various materials, or a strip of film with sections covered with absorbers that separate the radiations according to their penetrability. The skin dose, called the shallow dose equivalent (SDE), is measured with the dosimeter behind a very thin absorber that is 7 mg/cm^2 thick and represents the dead skin layer above live tissue. The dose to the lens of the eye, called the eye dose equivalent (EDE), is measured behind 300 mg/cm^2 of material

equal to the thickness of the cornea plus liquid that covers the lens. The whole-body dose, called the deep dose equivalent (DDE), is measured behind an absorber whose thickness of 1,000 mg/cm^2 which is equal to about 1 cm of tissue or the depth inside the body where the dose from high energy gamma rays tends to be the highest. For example, most TLDs and film badges have a small beta window shielded only by a thin sheet of mylar, and a gamma ray detection area consisting of one or more sections shielded with thin sheets of plastic, metal (like copper, aluminum, steel, tin, or lead), or combinations of these. The radiation exposure of the film is determined by the degree of darkening of the photographic film. A densitometer is used to read the film darkening, which is proportional to the absorbed dose in the tissue (Shapiro 1990).

In addition to wearing TLDs and film badges, many radiation workers also carry self-reading pocket dosimeters to provide the wearer an indication of the radiation dose received during the day. Because the pocket dosimeters may be read by the individual locally, it gives the worker the necessary information to prevent an overexposure and the worker can leave an area before a particular radiation dose is exceeded. The dosimeters are usually worn beside the primary dosimeter and typically measure x ray or γ radiation. They respond to betas but are not meant to measure betas. By lining the interior of the chamber with boron, the devices may also be made to monitor thermal neutron exposure. In this instrument, a quartz fiber is electrostatically displaced by charging the dosimeter to a potential of about 200 volts. As with other dosimeters, ionizations caused by radiation discharge the dosimeter which returns the fiber to its usual position as it loses its charge. The relative position of the fiber is calibrated to an exposure scale, usually in the range of 0 to 200 mR. The position of the fiber against the scale may be viewed through the end of the instrument.

There are two type of pocket dosimeters. The second type, called a condenser-type dosimeter, is an indirect reading dosimeter. An additional device, referred to as a charger-reader, is needed to charge and read the dosimeter. The dosimeter is basically a capacitor with an exterior wall made of an electrically conducting plastic or metal and an interior central wire which is insulated from the outer wall. Using the charter-reader, a positive charge is placed on the central wire. When exposed to x or gamma radiation, the ionizations discharge the unit. The amount of charge remaining in the dosimeter at any point is inversely proportional to the ionization produced in the cavity. The degree of discharge, and therefore the exposure, is measured by attaching the dosimeter to the charger-reader. Pocket dosimeters gradually discharge over time due to cosmic radiation and charge leakage across the insulating material. Because of the natural discharging and the potential for malfunction due to dropping the device, they are typically worn in duplicate with a film badge or TLD and are read and recharged daily (Cember 1996)

Electronic dosimeters are now widely used. These dosimeters feature solid-state detectors and a microprocessor to monitor x and gamma ray dose, dose rate, and dose history. Also, these small, programmable, lightweight dosimeters feature audible and vibrating alarms and visible digital readouts that keep the wearer informed of their radiation dose status at all times. Units with telemetric capabilities can be monitored at stations outside the work area where the dosimetry of a number of individuals can be simultaneously viewed and assessed to facilitate a higher degree of radiological control, such as for activities involving high intensity radiation sources. These dosimeter can be retained indefinitely by the individual and the person's dose history can be accumulated remotely, stored digitally in database fashion, and used to produce computer generated dosimetry reports on demand.

Figure 2-6. Geiger-Mueller Counter with an Energy-compensated Gamma Probe. (Photo courtesy of Ludlum Measurements, Inc.)

2.5.3 Field Radiation and Contamination Surveys

Environmental radiation arises from four basic sources: (1) natural radioactivity from uranium, thorium, and other primordial radionuclides; (2) cosmic rays and radionuclides produced by cosmic-ray interactions in the atmosphere; (3) contaminants from nuclear-weapons fallout; and (4) effluent from nuclear and medical facilities (NCRP 1985). Two methods are routinely used for measuring environmental radiation: (1) field surveys using portable survey instruments, and (2) analysis of samples procured in the field that are returned to the laboratory for quantification.

Figure 2-7. Geiger-Mueller Counter with a Beta/gamma Pancake-type Detection Probe. (Photo courtesy of Ludlum Measurements, Inc.)

2.5.3.1 Field Measurements of Ionizing Radiation

External radioactivity and radiation measurements can be made with portable, hand-held survey instruments. The primary purpose of some types of survey instruments is to measure the radiation levels to which people

are exposed, while others detect any contamination that may be present on an individual's skin, clothing, shoes or in the environment.

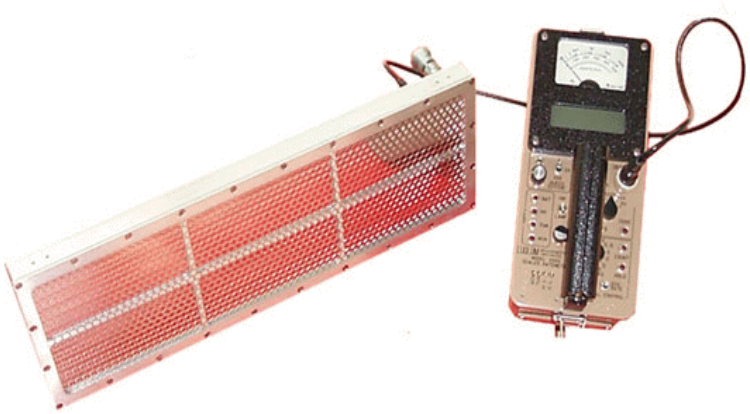


Figure 2-8. Large Area Alpha Radiation Detector with Digital/Analog Survey Meter (photo courtesy of Ludlum Measurements, Inc.)

Various types of radiation detectors (e.g., Geiger-Mueller or scintillation) are coupled with a count rate meter designed to detect alpha, beta, and gamma radiation. The count rate meter has a scale with a needle indicator or digital display that provides an immediate readout of levels of radiation or contamination that may be present in units of milliroentgens per hour (mR/hr) (1 mR ≈ 1 mrem = 0.01 mSv) or counts per minute (cpm). Two frequently used GM survey meters are the energy compensated GM detector (Figure 2-6) and the GM thin window "pancake" type detector (Figure 2-7). The energy compensated type of GM detector surrounds the detector chamber with a material of density and thickness that somewhat normalizes the dose response over a range of energies, which sacrifices some sensitivity for accuracy. The pancake detector typically has a very thin window and a relatively large detection area. The typical survey meter for identifying alpha contamination uses a zinc sulfide scintillator material that can reliably detect 200–500 dpm per 100 cm^2 (DOE 1988). Disintegrations per minute per 100 cm^2 of contaminated area is the criterion that has been chosen by regulatory agencies for control purposes. The alpha reading may be inaccurately low if the surface is irregular, porous, or damp since these conditions can attenuate the alpha particles. Recent developments in large area gas and gas-flow proportional counter technology, which have enabled these detectors to achieve higher sensitivities than alpha scintillator detectors, have made them acceptable for use in decommissioning operations. Figure 2-8 is an example of a current generation large area detector with digital survey meter. Figure 2-9 is a floor monitor system with multi-detector array that covers a wide path. The detector is slowly moved over a building or roadway surface to locate radioactive contamination and then held in place to quantify the level. Floor monitors with drive, data recording, and positioning systems are used to develop digitized reports and plots of alpha and beta contamination levels; these units can quantify contamination levels while continuously moving.

Figure 2-9. Floor Monitor System with Multi-detector Array. (Photo courtesy of Ludlum Measurements, Inc.)

Field surveys can be either qualitative (to provide a go/no-go indication for excess radiation levels) or quantitative (to provide a numerical value for the level and possible identification of the radionuclides present). Most field surveys involve the use of calibrated, portable, hand-held survey meters equipped with count-rate meters or digital displays that provide an immediate reading of the radiation field strength or the surface contamination level.

The radiation detector used in a survey must be appropriate to the type of radiation being measured. Typical alpha radiation detectors use the alpha scintillator material ZnS, as well as gas-flow surface contamination monitors. Typical beta radiation detectors are pancake type GM detectors and gas-flow surface contamination monitors. Gamma radiation detectors include a wide range of equipment types, including the GM and sodium iodide scintillation counters. Counter-type survey instruments are highly sensitive and are used mainly to search for and detect radiation. Ion chambers are used for measuring the radiation dose rate, with pressurized ion chambers being used for very low radiation levels.

Specialty instruments are available for more detailed field work, but their use generally requires special skills and training. The *in-situ* germanium spectrometer is a multichannel analyzer with a germanium detector that can identify a range of γ-emitting isotopes and quantify their concentration in surface soil. The Laser Ablation Inductively Coupled Plasma mass spectrometer (LA-ICP-MS) can measure 0.3 pCi/g of ^{238}U in soil. The Long Range Alpha Detector (LRAD) can measure alpha soil contamination down to 10 pCi/g. The Field Instrument for Detection of Low Energy Radiation (FIDLER) is used to measure plutonium and americium surface contamination. The field x ray fluorescence spectrometer can measure the relative concentration of metal atoms in soil or water down to the parts per million (ppm) range.

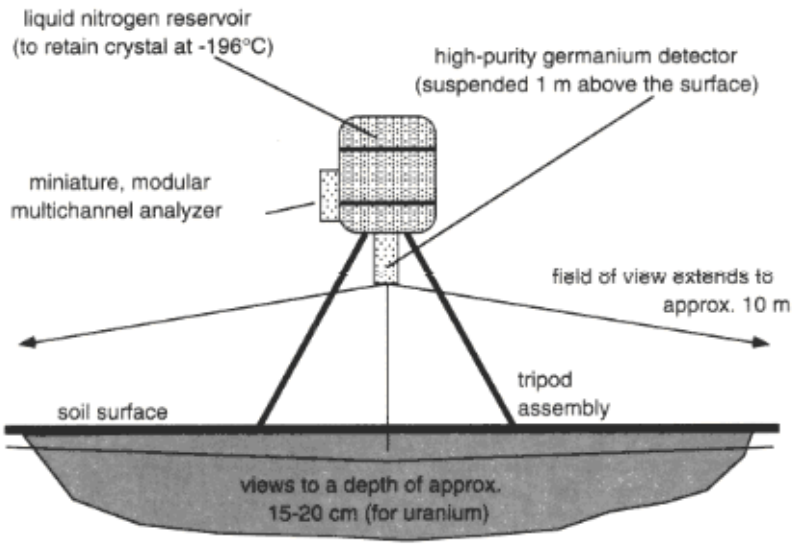


Figure 2-10. *In-Situ* Gamma Ray Spectrometer
(adapted from http://www.em.doe.gov/rainplum/fig16.html)

Field survey instruments provide timely information on the presence and levels of radiation fields or radioactive materials.

Measurements of radiation fields or loose radioactive material can be made in the field with portable instrumentation (Figure 2-10). Similar surveys can also be performed on people when contamination is suspected since both environmental surveys and personnel surveys use many of the same types of portable instrumentation.

Semi-permanent instruments or instruments placed in the field for extended periods of time are sometimes used to measure ambient environmental radiation levels or to detect changes in ambient environmental radiation levels (for example, around nuclear facilities). Pressurized ionization chambers (PICs) are used as a standard for measuring gamma radiation levels. Readings are recorded on a real-time strip chart recorder or on a magnetic card, and can be arranged to transmit these data to a central site for computer processing. Several types of portable survey instruments using ionization chamber detectors are also available. Ionization chamber detectors can only be used for ambient environmental radiation monitoring, if the detection sensitivity is several μrad/hour (Kathren 1984). Ion chamber survey meters typically exhibit long response times, particularly at low radiation levels, requiring up to several minutes to record a detectable measurement above background levels at low radiation levels.

GM counters and both plastic and NaI scintillators have also been used for field measurements of ambient radiation. These instruments have detection capability down to several μrad/hour (nGy/hr). They are rugged and have a shorter time constant than a pressurized ion chamber (PIC), making them more suitable than PICs when numerous environmental measurements are to be made. Counter-type survey meters, such as GM and scintillation counters, are very energy dependent when used to measure dose. They can be used to reliably measure dose or dose rate only for radiation whose energy is the same as the energy of the calibration source. Energy flattening filters are sometimes used in GM survey meters to compensate for the energy dependence (Kathren 1984; NCRP 1976, 1985). The energy response problem can largely be overcome by taking paired PIC and GM or NaI readings at several points to develop factors for converting GM or NaI readings to true exposure levels in mR/hr (EPA 1994).

Scintillation detectors and semiconductor detectors, when used in conjunction with a multichannel analyzer and computing capabilities, make it possible to determine whether the radiation fields originate from terrestrial radiation, cosmic radiation, or anthropogenic radiation, or from a combination of these sources. These instruments are useful for environmental monitoring around reactor sites and sites undergoing remediation for unrestricted use by the public.

The very short range of the alpha particle makes it necessary for the distance between the α-emitting source and the alpha detector to be very small. It also requires that the detector window be very thin to enable passage of the alpha particle into the detector. A scintillation detector that is frequently used is silver-activated ZnS. The ZnS scintillation detector is relatively insensitive to beta or gamma radiation and exhibits a low background count, thus permitting measurement of alphas in the presence of high beta or gamma radiation fields. Gas-filled proportional counters are particularly well-suited for low-level alpha measurements due to their large counting areas and low background. Proportional detectors can distinguish between alpha and beta particles based on differences in the size of the output voltage pulses from alphas and betas (NCRP 1978; Shapiro 1990).

Awareness of the need for detection of plutonium in the environment has increased due to several accidents that have occurred in the past (see Section 3.5). Plutonium transforms by α emission with a small percentage of accompanying x rays with energies in the region of 17 keV from the excited ^{237}Np daughter. Due to the difficulties associated with measurement of alpha particles, an instrument called a FIDLER (Field Instrument for Detection of Low Energy Radiation) was developed. This instrument measures the 17 keV photons associated with the transformation of ^{239}Pu using a 5-inch diameter crystal of NaI, 1/16th of an inch thick. FIDLER measurements are also made of the 60 keV photons from americium-241 (^{241}Am), which is often associated with plutonium as an impurity (Kathren 1984).

Large-scale environmental monitoring for contamination is sometimes carried out on roads and railroad tracks using scintillation detectors mounted on vehicles. The detectors are shielded on the sides and tops and are suspended above the ground surface. In addition, aerial surveys for radioactivity are useful for mineral exploration, special studies of uranium fields, nuclear facilities monitoring, fallout measurements, etc. The detector of choice for most of these measurements is the scintillator, usually a large single crystal (Kathren 1984) or multiple smaller detectors with summed responses. The correlation of airborne measurements with ground-level data indicates agreement to within about ± 20% in a strip of land 400 meters wide under the flight lines (NCRP 1976).

In addition to the use of survey instruments, environmental radiation is also measured with passive integrating detectors such as film badges or TLDs. TLDs are superior to film badges in energy dependence, angular dependence of radiation incident upon the dosimeter, permissible time in the field, resistance to environmental conditions, and lower limit of detection (10 mrad for film compared with 1 mrad for TLD)

(Kathren 1984; NCRP 1976). Several different thermoluminescent phosphors are available for environmental measurements, including LiF, CaF_2, $CaSO_4$ (Kathren 1984; NCRP 1976) and Al_2O_3. In the field, TLDs do not require a great deal of protection; however, some phosphors may exhibit sensitivity to light and humidity. Consequently, it is useful to package the TLD in some sort of light and water-tight material.

A good source of information on the performance of field radiation surveys, the collection and processing of samples and the applicability, operation, specificity, sensitivity, cost, and cost of operation of field and laboratory equipment is the Multi-Agency Radiation Survey and Site Investigation Manual (MARSSIM) prepared by EPA, NRC, DOD, and DOE as a consensus guide for conducting the final status survey in releasing a radiation site for unrestricted public use (MARSSIM 1997).

2.5.3.2 Laboratory Analysis of Environmental Samples

There are standardized analytical methods for the quantification of radioactive material in air, water, sediment, food, vegetation, and other biota (DOE 1997a); however, current philosophy supports performance-based rather than prescriptive methods. In many cases, particularly in occupational settings, the radionuclide(s) are known so the analysis can be confined to that particular radionuclide(s). If the radioactivity in a sample is from an unknown radionuclide(s), the sample should be examined for α and β/γ-emitting nuclides. Environmental samples usually involve measurement of low levels of specific radionuclides in the presence of naturally occurring radionuclides. Consequently, the analyzing analytical instrumentation is sensitive and the effect of natural background radiation levels on the detectors should be minimized. Background reductions are usually achieved mechanically by the use of shields around the detectors and electronically by pulse size discrimination (NCRP 1978).

Preparation of various environmental media for analysis of radioactive content may require concentrating the radioactive material from a large sample into a small volume to increase the sensitivity of the analysis or to reduce the sample to a form more suitable for counting. For example, solvent extraction may be used for samples with high salt content whereas ion exchange chromatography may be used for samples with low salt content. However, some standardized methods for environmental sample preparation have been developed in laboratories for analysis of radionuclides in various matrices (EPA 1984) and in drinking water (EPA 1980). Chemical separation techniques and nuclear instrumentation for assessment

of several radionuclides in various matrices can be found in the ATSDR profiles for plutonium, radium, and uranium (ATSDR 1990c, 1990d, 1999b).

There are several methods in use for quantification of alpha particles. If the identity of the α-emitting radionuclide is not needed or is already known, alpha activity of samples can be quantified by gross or "total" alpha counting (NCRP 1985). However, the short range of alpha particles in liquid and solid samples usually requires physical and/or chemical separation of the radionuclide from the matrix as described by EPA procedures (EPA 1980, 1984). Since the energies of the radiations from radionuclides are specific for those radionuclides, alpha spectroscopy, using a high-resolution silicon diode surface barrier detector with a resoulution of 10–20 keV, is used when it is necessary to determine both the identity and the quantity of the α-emitting radionuclide(s) in a sample (Knoll 1989; NCRP 1985); procedures manuals of the DOE's Environmental Measurements Laboratory and the Los Alamos National Laboratory contain example procedures for such analyses (DOE 1997a).

For environmental samples containing radionuclides that emit gamma rays, scintillation detectors (sodium iodide) and semiconductor detectors (germanium) are commonly used. These detectors, along with the appropriate electronics, computers and software, can be used to simultaneously identify and quantify a number of γ-emitting radionuclides (Kathren 1984; Knoll 1989; NCRP 1985). Germaniuim detectors have superior resolution and are more suitable if more than a few radionuclides are present in the sample.

A number of radionuclides, including ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{45}Ca, ^{89}Sr, ^{90}Sr, and ^{90}Y, emit only beta radiation (NCRP 1985). Liquid scintillation counting systems are widely used for the assay of low levels of β-emitting radionuclides and can be used to quantify all of the radionuclides listed above. GM detectors are also used for quantification of beta particles; however, GM detectors are not used to quantify ^{3}H because of its very low beta energy. Another instrument used for assessment of beta particles in environmental samples is the gas-flow proportional counter. Gas-flow proportional counters can readily quantify the β-emitting radionuclides identified above, as well as ^{3}H and ^{14}C, either when the detector window is very thin (in the case of ^{14}C) or when the detector is windowless (in the case of ^{3}H). In general, liquid scintillation, gas-flow proportional and GM counters provide data on total beta activity, although some liquid scintillation counters have some ability to resolve energy spectra. Also, solid organic scintillators, which are usually made from plastic or crystals of anthracene and trans-stilbene, may be used to quantify and identify beta particles (Knoll 1989).

2.6 CONCLUSIONS

The study of the effects of radiation is a highly specialized area of toxicology that requires knowledge and understanding of radiation physics and radioactivity, radiation dose, and biology. Radiation interacts in unique ways with matter to yield carcinogenic and non-carcinogenic effects after acute and chronic exposures.

Low levels of radiation have always been present in the environment. Only in the past 100 years have humans discovered its ubiquitous presence. During the 20th century, scientists and governments have developed uses for radionuclides both for peaceful purposes, such as medical diagnosis and treatment and electrical power generation, and for military purposes, such as weapons technology. Much research has been performed to define the different types of radiation, to explain how radiation interacts with matter, and to determine how to measure both the radioactivity and the radiation dose from a given exposure. This and other information has been used to correlate absorbed dose (from short-term high doses to long-term low doses) with toxicological diseases ranging from almost immediate death after an initial exposure to the induction of carcinogenesis years after a non-lethal exposure. This chapter summarized some of the information about radiation and methods for measuring radiation and radiation exposure. The remainder of this toxicological profile discusses in more depth the biological and toxicological effects and mechanisms of action of radiation (Chapters 3 and 5), sources of population exposure (Chapter 6), and regulatory situation specific to ionizing radiation (Chapter 7). Observed Health Effects from Radiation and Radioactive Material tables for ionizing radiation are presented in Chapter 8.

2.7 OTHER SOURCES OF INFORMATION

The Internet sites listed in Table 2-8 provide information on the general principles and health effects of the different forms and doses of radiation. Information obtained from internet sources should not be considered to have been peer reviewed unless separately authenticated.

Table 2-8. Some Internet Sites Related to Ionizing Radiation

HyperText Transfer Protocol (HTTP) address	Web page contents
http://www.uic.com.au/ral.htm	A beginner's reference for radiation.
http://www.dne.bnl.gov/CoN/index.html	Radionuclide information on half-life, transformation energies, etc.
http://www.nih.gov/health/chip/od/radiation	Summary information on radiation and its health effects
http://www.umich.edu/~radinfo/introduction	Introduction to radiation; professional, research and educational resources
http://radefx.bcm.tmc.edu/	Baylor College of Medicine Radiation Effects Homepage. Health effects documents, downloadable software, Chernobyl information, links to other radiation-related sites.
http://www.em.doe.gov/cgi-bin/tc/tindex.html	DOE Environmental Management. Public information access and links to DOE research laboratories
http://www.rerf.or.jp/	Radiation Effects Research Foundation. Human health impact of the atomic bomb release on Hiroshima and Nagasaki, Japan.
http://www.ohre.doe.gov/	DOE "cold war" radiation research using human subjects.
http://www.hps.org	Health Physics Society. Involved in the development, dissemination, and application of radiation protection. Concerned with understanding, evaluating, and controlling the risks from radiation exposure relative to the benefits derived.
http://www.epa.gov/narel/index.html http://www.epa.gov/narel/erd-online.html	Reports nationwide radionuclide concentrations in air, drinking water, surface water, precipitation, and milk.
http://www.aapm.org	American Association of Physicists in Medicine. Concerned with the safe use of radiation and radioactive materials in medicine.
http://law.house.gov/4.htm	U.S. House of Representatives internet law library of the Code of Federal Regulations. Provides CFR text.
http://www.nrc.gov/	USNRC. Nuclear waste, nuclear reactors in operation, and rule-making procedures.

3. SUMMARY OF HEALTH EFFECTS OF IONIZING RADIATION

3.1 INTRODUCTION

Ionizing radiation is a form of radiation with sufficient energy to remove electrons from their atomic or molecular orbital shells in the tissues they penetrate (Borek 1993). These ionizations, received in sufficient quantities over a period of time, can result in tissue damage and disruption of cellular function at the molecular level. Of particular interest is their effect on deoxyribonucleic acids (DNA).

A special issue to consider when examining the health effects caused by ionizing radiation is the concept of dose and dose rate. The dose delivered to tissue from ionizing radiation can either be acute (the energy from the radiation is absorbed over a few hours or days) or chronic (the energy is absorbed over a longer period of months, years, or over a lifetime). The dose becomes particularly important when the individual is exposed is to radioactive materials inside the body. In distinguishing between acute and chronic exposure, both the intake rate and the physical, chemical, and biological aspects of the radionuclide kinetics must be considered. For radioactive materials with effective half-lives longer than a day, even if the intake is brief (minutes to a few days), the energy is deposited in tissue where it remains over a period longer than a few days, so that the exposure to the surrounding tissue is of a chronic duration. Depending on the size of the dose and the dose rate, the effects of ionizing radiation can either be acute (occurring within several hours to several months after exposure) or delayed (occurring several years after the exposure).

The principles of dose are important to the interpretation of Tables 8-1 through 8-4, found in Chapter 8 ("Levels of Significant Exposure to Radiation and Radioactive Material") in this profile. For example, Table 8-1 lists the observed health effects from radiation and radioactive material using inhalation as the route of exposure. Entry 109 shows a study in which Beagle dogs were exposed for 2 to 22 minutes to $^{90}SrCl_2$. Although these animals received the total amount of radionuclide within 2 to 22 minutes (an acute duration of exposure), the radionuclide was absorbed and redistributed to other tissues (in this case, bone), where it remained for a protracted period of time (chronic exposure). Delayed effects of osteosarcoma and other tumors were found in almost half of these animals (Gillett et al. 1987b). Without a clear understanding of both the dose and the toxicokinetics of the radionuclide, one might conclude from this table that a 2- to 22-minute dose of radiation from $^{90}SrCl_2$ will cause bone cancer in dogs. The more appropriate conclusion to draw from this study is that after a 2- to 22-minute intake, $^{90}SrCl_2$

appeared to have redistributed from the lungs to the bones and, given its long physical half-time ($t_{1/2}$) of 28.6 years, would have irradiated the surrounding tissues for a lengthy period of time to produce a cancerous end point.

Sources of ionizing radiation can be found at many waste sites in the United States and other countries. Exposure to these sources may have potential adverse health effects, depending on the isotope, the absorbed dose, and the dose rate. The predominant radionuclides found currently or in the past at Department of Energy (DOE) National Priorities List (NPL) waste sites are listed in Table 3-1.

Table 3-1. ATSDR Priority Listing of Radionuclides Present at Department of Energy NPL Sites

Ranking #	Isotope	Primary emission	Physical half-life	Target tissue(s) for soluble forms
1	Thorium-232	α	1.4×10^{10} years	
2	Uranium-235	α	7.04×10^{8} years	Renal (proximal tubules)[a]
3	Radium-228	β	5.76 years	Skeleton
4	Uranium-238	α	4.46×10^{9} years	Renal (proximal tubules)
5	Radium-226	α	1600 years	Skeleton
6	Cobalt-60	β, γ	5.271 years	Whole body
7	Krypton-85	β	10.72 years	
8	Americium-241	α	432.2 years	Lung
9	Uranium-234	α	2.45×10^{5} years	Renal (proximal tubules)
10	Potassium-40	β	1.26×10^{9} years	Skeleton
11	Europium-152	β	13.5 years	
12	Neptunium-237	α	2.14×10^{6} years	
13	Cesium-137	β,γ	30 years	Whole body
14	Protactinium-231	α	3.25×10^{4} years	
15	Strontium-90	β	28.6 years	Skeleton
16	Krypton-88	β	2.84 hours	
17	Thallium-208	β	3.053 minutes	
18	Thorium-228	α	1.913 years	
19	Protactinium-234	β	6.69 hours	
20	Argon-41	β	1.82 hours	
21	Plutonium-239	α	24,131 years	Bone surface
22	Krypton-87	β/γ	76.3 minutes	Whole body
23	Thorium-230	α	77,000 years	Bone surface
24	Uranium-236	α	2.3415×10^{7} years	Bone surface
25	Plutonium-238	α	87.75 years	Bone surface

[a]Renal toxicity is more likely due its heavy metal properties rather than its radioactive properties.
Source: Lide 1996; Schleien 1992

The scientific literature is filled with in-depth discussions and reviews on the effects of ionizing radiation in humans and animals, and it would be difficult, if not impractical, to summarize all of the known information about the effects of each radionuclide in every animal. Although the database of biological, radiological, toxicological, and toxicokinetic information is substantial and much is known, much remains to be learned about the specific mechanisms by which ionizing radiation produces its effects, how these effects can be minimized in living tissues, and what the long-term effects of very low doses of ionizing radiation are over the normal human lifespan. In this profile, some of the information about the effects of ionizing radiation has been obtained from human epidemiological and medical studies, but a sizable portion has come from studies conducted in laboratory animals and then extrapolated to humans. In addition to data from epidemiological studies, there is a substantial human database derived from therapeutic applications of radiation. Because of this large database of information, and in an effort to provide a useable overview of the health effects caused by exposure to radionuclides, this toxicological profile will summarize the adverse effects of ionizing radiation from alpha (α), beta (β), and gamma (γ) radiation, using representative radionuclides to illustrate the effects on specific organs and tissues. Other radionuclides with similar emissions and kinetics may produce similar end points. This profile will not provide an in-depth discussion of the more subtle points of radiation biology and toxicology. It will, however, provide the reader with a comprehensive and informative overview of a cross-section of the scientific literature that pertains to the potential adverse carcinogenic and non-carcinogenic effects of α, β, and γ radiation, focusing on key human and animal studies and using representative radionuclides for illustration purposes. Readers are encouraged to consult both the glossary and Chapter 2 of this profile to become familiar with the terminology used in discussing exposure to ionizing radiation and the characteristics of these three radiations. Several excellent texts and review papers are also available in the open literature that provide the salient background material for many of the sections of this profile (BEIR IV 1988; BEIR V 1990; Faw and Shultis 1993; Harley 1991; Roesch 1987; UNSCEAR 1993; Raabe 1994).

3.2 HEALTH EFFECTS FROM EXPOSURE TO IONIZING RADIATION

High doses of ionizing radiation can lead to various effects, such as skin burns, hair loss, birth defects, illness, cancer, and death. The basic principle of toxicology, “the dose determines poison,” applies to the toxicology of ionizing radiation as well as to all other branches of toxicology. In the case of threshold effects (“deterministic effects” in the language of radiation toxicology), such as skin burns, hair loss, sterility, nausea, and cataracts, a certain minimum dose (the threshold dose), usually on the order of hundreds or thousands of rad, must be exceeded in order for the effect to be expressed. An increase in the size of the dose above the threshold dose will increase the severity of the effect.

For cancer induction, increasing the radiation dose does not increase the severity of the cancer; instead it increases the chance of cancer induction. In the case of carcinogens generally, whether chemical or radiological, safety standards are based on a postulated zero threshold (i.e., any increment of carcinogen, no matter how small, is assumed to carry with it a corresponding increase in the chance of causing cancer). Increasing the size of the dose increases the probability of inducing a cancer with that carcinogen. Cancers that are, in fact, caused by radiation are completely indistinguishable from those that seem to occur spontaneously or are caused by other known or suspected carcinogens. In a given population, such as the Japanese survivors of the atomic bombings of 1945, investigators identified the carcinogenicity of ionizing radiation only by measuring the frequency of occurrence of cancer. In the case of the survivors of the atomic bombings in Japan, there was no observed statistically significant increase in cancer frequency among people whose radiation dose did not exceed 0.4 Gy (40 rad) and no increase in leukemia among those whose radiation dose did not exceed 0.1 Gy (10 rad). Because investigators could not uniquely identify any cancer as having been caused by the radiation, and because there was no observed increase in cancer frequency following low-level irradiation, the calculated cancer risk coefficient (i.e., the probability of getting cancer per unit of radiation dose) is usually estimated by extrapolation of data from observations on populations that received high doses of radiation.

For the purposes of this profile, we have divided the end points produced by ionizing radiation into effects that were (at least initially) non-carcinogenic and carcinogenic effects. The non-carcinogenic effects were further subdivided by major organ systems affected plus teratogenic effects. This was done primarily to help the reader understand the broad scope of adverse health effects that can be produced by ionizing radiation. This approach was also necessary to facilitate evaluating study designs found in the literature. Some studies exposed laboratory animals to radiation, determined the non-cancerous end points, and then sacrificed the animals to complete the study objectives. These studies imply that cancer did not or would not develop after exposure to this radiation, which certainly may not be the case. Other studies exposed animals to radiation, observed the non-carcinogenic end points (if any), and then allowed the animals to live out their normal lifespans to determine if cancer would develop. These latter studies provided more complete information on the overall effects of exposure to ionizing radiation.

No acute-, intermediate-, or chronic-duration inhalation, oral, or dermal Minimal Risk Levels (MRLs) were developed for internal exposure to alpha, beta, or gamma radiation. Radiation effect(s) on a biological system during an acute, intermediate, or chronic duration of exposure depend on the radiation dose; the dose, in turn, depends on several variables. For airborne radioactivity, these include physical form (gas versus particle), particle solubility, particle size, type of radiation (alpha, beta, gamma, or combinations), and energy of the radiation. For oral and dermal exposure, toxicity is influenced by

solubility, metabolism within the body, and the type and energies of the radiation. Since there is a biological equivalence of internal and external dose equivalent in units of sievert and rem, an MRL for external radiation should be appropriate for internal radiation.

Two MRLs have been derived for exposures to ionizing radiation:

- An MRL of 0.004 Sv (0.4 rem) has been derived for acute-duration external ionizing radiation exposure (14 days or less).

The acute MRL is based on results from two studies, one by Schull et al. (1988) and one by Burt (1966). Schull et al. (1988) evaluated the quantitative effect of exposure to radiation on the developing fetal and embryonic human brain. The end point measured was change in intelligence test scores. Broadly speaking, a large body of literature shows the effects of radiation on the embryonic and fetal brain. ATSDR recognizes that there is considerable public interest in and debate about the interpretation of intelligence scores and that government agencies have been very careful in setting health benchmarks for chemicals whose effects are measured by intelligence testing. ATSDR is basing the MRL on the published results from relevant IQ studies and applies a conservative factor to account for uncertainties. Underlying assumptions in the MRL development are stated as clearly as possible.

Schull et al. (1988) evaluated effects on individuals exposed *in utero* during the atomic bombing of Hiroshima and Nagasaki, based on the original PE86 samples (n=1,759; data on available intelligence testing) and the clinical sample (n=1,598). The original PE86 sample included virtually all prenatally exposed individuals who received tissue-absorbed doses of 0.50 Gy or more, and many more individuals in the dose range 0–0.49 Gy than in the clinical sample. The clinical sample does not include children prenatally exposed at distances between 2,000–2,999 meters in Hiroshima and Nagasaki. Children prenatally exposed at greater distances or not present in the city were selected as controls. In 1955–1956, Tanaka-B (emphasis on word-sense, arithmetic abilities, and the like, which were associated with the more subtle processing of visual clues than their simple recognition and depended more on connectedness) and the Koga (emphasis on perception of spatial relationships) intelligence tests were conducted in Nagasaki; the Koga test was conducted in Hiroshima. No evidence of radiation-related effect on intelligence was observed among individuals exposed within 0–7 weeks after fertilization or after the 25th week. The highest risk of radiation damage to the embryonic and fetal brain occurred 8 to 15 weeks after fertilization under both T65DR and DS86 dosimetric systems (Otake and Schull 1984). The regression of intelligence score on estimated DS86 uterine absorbed dose is more linear than with T65DR fetal dose, and the diminution in intelligence score under the linear model is 21–29 points at 1

Gy. The regression of intelligence score on estimated fetal absorbed dose was linear for the exposed 8–15 weeks after fertilization and possibly linear for the 16–25-week group. The cumulative distribution of test scores suggested a progressive shift downwards in individual scores with increasing exposure in the 8–25-week exposure group. The mean IQ scores decrease significantly and systematically with uterine or fetal tissue dose within the groups exposed at 8–15 and 16–25 weeks.

The linearity of the response over the exposure ranges does not mean that there is no threshold for ionizing radiation's neurological effects. A threshold response (i.e., deterministic response) in the case of ionizing radiation involves damage to brain stem cells or to cells that differentiate into brain cells. This threshold, however, is indeterminate and therefore, there is no readily available lowest-observed-adverse-effect level (LOAEL). However, a no-observed-adverse-effect level (NOAEL) is taken from a study by Burt (1996). Results from the Schull et al. (1998) study are used in conjunction with the Burt (1966) study described below. The Burt study (1996) is the basis of a population IQ differential used to establish a NOAEL dose from the Schull et al. (1998) study.

The study by Burt (1966) determined differences in intelligence in monozygotic twins reared together (n=95) and apart (n=53). All tests were conducted in school and consisted of (1) a group test of intelligence containing both non-verbal and verbal items, (2) an individual test (the London Revision of the Terman-Binet Scale) used primarily for standardization and for doubtful cases, and (3) a set of performance tests based on the Pitner-Paterson tests and standardization. The methods and standard remained much the same throughout the study. The children were brought up by parents or foster parents (occupation ranged from unskilled to professional). The standard deviation of the group of separated monozygotic twins was reported at 15.3 as compared to 15.0 of ordinary siblings. Twins brought up in different environments were compared with those brought up in similar circumstances. The average IQ scores of the twins measured on a conventional IQ scale (SD=15) was 97.8 for the separated monozygotes, 98.1 for monozygotes brought up together. The difference of 0.3 IQ point between the separated and unseparated identical twins (97.8–98.1) is considered a NOAEL for this study.

Husen (1959) reported a study involving 269 pairs of Swedish monozygotic (identical) twins where the intrapair IQ difference was 4 IQ points for a combination of twins raised together and apart. This is somewhat lower than the value of 7 IQ points for identical twins raised apart, and just larger than the range of IQ scores for Washington DC children repetitively tested (Jacobi and Glauberman 1995).

Supporting evidence for the acute MRL is provided by Jacobi and Glauberman (1995). Children in the 1st, 3rd, and 5th grades born in Washington DC were tested, and average IQ levels of 94.2, 97.6, and 94.6

were reported. The differences of up to 3.4 IQ points between the grades and over time were considered to be small and could not be tied to environmental deficiencies. This difference is a potential LOAEL for acute doses of ionizing radiation and would yield an MRL of 0.004 Sv (3.4 IQ points x 1 Sv/25 IQ points ÷ 30 [10 for use of a LOAEL and 3 for a sensitive human population]).

Additional supporting evidence for the acute MRL is provided by Berger et al. 1997, in a case study of accidental radiation injury to the hand. A Mexican engineer suffered an accidental injury to the hand while repairing an x ray spectrometer. The day after the accident, his symptoms included a tingling sensation and itching in the index and middle fingers. On days 4 and 7, a "pinching" sensation, swelling, and slight erythema were observed. By day 7, the tip of his index fingers was erythematous and a large blister developed with swelling on other fingers. On day 10, examination by a physician showed that the lesions had worsened and the fingers and palms were discolored. On day 10, he was admitted to the hospital where hyperbaric oxygen therapy was administered without success. One month after the accident, the patient entered the hospital again with pain, discoloration, and desquamation of his hand. Clinical examination showed decreased circulation in the entire hand, most notably in the index and middle finger. Total white blood count decreased to 3,000/µL (normal range 4,300–10,800/µL). Cytogenic studies of peripheral blood lymphocytes revealed four dicentrics, two rings, and eight chromosomal fragments in the 300 metaphases studied. The estimated whole body dose was reported to be 0.382 Gy (38.2 rad). This dose is a potential LOAEL for acute ionizing radiation and would yield an MRL of 0.004 Sv (0.38 Sv ÷100 [10 for use of LOAEL and 10 for human variability]).

The Nuclear Regulatory Commission set a radiation exposure limit of 5 mSv (500 mrem) for pregnant working women over the full gestational period (USNRC 1991). For the critical gestational period of 8 to 15 weeks ATSDR believes that the acute MRL of 4 mSv is consistent with the NRC limit and could be applied to either acute (0–14 day) or intermediate (15–365 day) exposure periods.

The acute MRL is based on the finding that a 1 Gy dose (1 Sv dose equivalent) results in a 25 IQ point reduction (range = 21–29 points; mean = 25) (Schull et al. 1988). This assumes that the relationship between radiation dose and IQ point reduction is linear (Schull et al 1988). After applying an uncertainty factor of 3 (human variability/sensitive population), this results in an MRL of 0.004 Sv (0.4 rem).

There are recognized uncertainties in the results from both the Schull et al. (1998) and the Burt (1966) studies. Although the linear relationship developed for data from the Japanese fetal-exposed population is strong, it has not been established that the linear relationship holds all the way to the lowest potential exposure levels. Another important uncertainty is the selection of an appropriate population IQ shift that

could be accepted as a non-adverse effect. A change in median population IQ test results is far different from natural fluctuations in individual test results or from the natural variation in a population (e.g., standard deviation in population IQ of 15 points). Selection of a population shift of 0.3 IQ points is an understandably conservative, yet appropriate, approach in setting a health guideline for acute exposures to ionizing radiation. Though the IQ reduction end point is based on a sensitive population (8–25 week-old fetuses), ATSDR has applied an additional uncertainty factor of 3 for human sensitivity.

Our understanding of the health hazard posed by ionizing radiation will continue to expand and, therefore, be subject to change. As additional new information concerning the potential public health impact of ionizing radiation becomes available, ATSDR will evaluate that information. ATSDR will continue to work with our Federal partners to ensure an up-to-date assessment of all relevant biomedical data to protect the public from exposure to harmful levels of ionizing radiation. The acute MRL value is supportive of the Nuclear Regulatory Commission fetal protection dose equivalent of 5 mSv (500 mrem) during the gestation period. EPA has derived neither an RfD nor an RfC for ionizing radiation (IRIS 1999).

- An MRL of 1.0 mSv/yr (100 mrem/yr) above background has been derived for chronic-duration external ionizing radiation exposure (365 days or more).

No individual studies were identified that could be used to base a chronic-duration external exposure MRL that did not result in a cancer-producing end point. However, BEIR V (1990) reports that the average annual effective dose to the U.S. population is 3.6 mSv/yr. A total annual effective dose equivalent of 3.6 mSv (360 mrem)/year to members of the U.S. population is obtained mainly by naturally occurring radiation from external sources, medical uses of radiation, and radiation from consumer products. Since this annual dose of 3.6 mSv/yr has not been associated with adverse health effects or increases in the incidences of any type of cancers in humans or other animals, the 3.6 mSv/yr is considered a NOAEL for purposes of MRL derivation. An uncertainty factor of 3 (for human variability) was applied to the NOAEL of 3.6 mSv/yr to derive the MRL of 1.0 mSv/yr.

The chronic MRL value is supportive of the 1 mSv/yr (100 mrem/yr) dose equivalent limit to the public that is recommended by the International Commission on Radiological Protection and required by the Nuclear Regulatory Commission. The EPA has derived neither an oral RfD nor an inhalation RfC for ionizing radiation (IRIS 1999). EPA has derived limits for concentrations of selected radioactive materials in drinking water under the Safe Drinking Water Act. The population is simultaneously

exposed to radiation through oral, inhalation, and external routes of exposure, and the chronic MRL is applicable to the cumulative exposure by all routes.

3.2.1 Acute (Immediate and Non-Carcinogenic) Effects from Ionizing Radiation Exposure

A considerable body of information is available in the literature on the acute exposure, high-dose health effects of ionizing radiation. Such health effects would not be possible from levels of residual radioactive material at NPL sites. There are three circumstances in which a person may conceivably be exposed to acute high-level doses of ionizing radiation that would initially result in one or many immediate non-carcinogenic effects. One instance would involve being in the immediate proximity of an atomic blast, as were the Japanese populations of Hiroshima and Nagasaki in August 1945 or the Marshall Islands fallout victims injured from fallout from an atomic weapons blast on Bikini Atoll in March 1954. The second instance would be a laboratory or industrial accident, where only those onsite and involved with high intensity radioactive sources or radiation generating equipment would be affected. The third and most likely opportunity for exposure to high levels (or repeated doses) of ionizing radiation would involve medical sources in the treatment of disease (protracted exposures to x rays, fluoroscopy, radioiodine therapy, etc.) or exposure to displaced medical or industrial radiography sources. People who volunteer to be exposed to ionizing radiation for the purpose of medical research also fall into the third category (see Table 3-2). People who have a large enough area of their body exposed to high doses ($\geq$100 rad) of radiation in any of these situations may exhibit immediate signs known as acute radiation syndrome. In addition to radiation sickness, overexposure to ionizing radiation can result in lens opacities (~0.2 Gy threshold and protracted exposure), and fetal and developmental anomalies.

The acute and delayed effects of exposure to ionizing radiation in humans and laboratory animals have been studied quite extensively. Laboratory animal data have provided a large volume of information related to the health effects of radiation; however, the most useful information related to human health effects comes from human exposure data. The data collected from the larger exposed populations, such as those from Hiroshima and Nagasaki, some medically-exposed populations, or the radium dial painters, have provided valuable information on both the acute and the delayed (long-term) health effects in humans exposed to radiation from certain radionuclides. A number of studies performed on smaller groups of people as early as the 1930s have been recently identified and made public (DOE 1995). These experiments will not be discussed in depth in this toxicological profile (for reasons listed below), but will be briefly summarized. Most of these exposures to sources of ionizing radiation were performed in small

groups of human volunteers at a few institutions sponsored or supported by the Department of Energy (DOE), U.S. Energy Research and Development Administration (ERDA), the U.S. Atomic Energy Commission (AEC), the Manhattan Engineer District (MED), and the Office of Scientific Research and Development (OSRD). Other studies took place at universities, private hospitals, and other institutions. The bulk of these human studies may be categorized as either tracer studies, metabolism studies, dose-response studies, or as experimental treatments for disease. Many of the studies listed in the DOE report were done before the 1970s, so the 1995 report represents the culmination of significant efforts to assemble the appropriate documentation to reconstruct and describe the purpose of each experiment, the experimental designs, the dates and locations of the exposures, the doses and routes of administration, the population size and how the populations were chosen, the use of informed consent among these individuals, and whether any of these individuals were followed through the remainder of their life in order to determine possible delayed effects from exposures to these radionuclides. In spite of the problems associated with interpreting these experiments, they yielded a useful database of information that describes the health effects of radiation exposure in humans. Some of these studies are summarized in Table 3-2.

All cells that comprise the body's tissues and organ systems are not equally sensitive to the biological effects of ionizing radiation; the sensitivity of cells is affected by age at the time of exposure, sex, health status, and other factors. Cells that are rapidly growing and dividing (such as those found in the gastrointestinal tract, bone marrow, reproductive and lymphoid tissues, and fetal nerve cells) are more sensitive to the cytotoxic effects of ionizing radiation. Higher doses showed more effects in the gastrointestinal tract than in the bone marrow. Tissues that undergo little cell growth and mitosis under normal conditions (such as those found in the central nervous system, the adrenal, adipose, and connective tissues, and the kidney) are more resistant to these effects, requiring a much larger acute absorbed dose before outward toxicological effects may be observed. Why are these growing and dividing cells the most sensitive to the effects of ionizing radiation? The answer relates to the effect on the genome of the cell. Ionizing radiation may damage the cell's DNA (which the cell relies on to manufacture proteins and enzymes, perform routine cell functions, and maintain cell integrity and homeostasis) to the point that normal cell functions are markedly decreased or stopped, resulting in cell damage and death. Once damaged, the cell can either repair the damage or die. Repair or misrepair may or may not result in cell lethality. When precursor cells in the hematopoietic system (which multiply quite frequently to replenish aging leukocytes) are damaged or die, leukopenia may occur in the peripheral blood, leaving the body susceptible to infections and disease. At ~0.5 Gy (50 rad), there may be transient changes in formed elements of the blood in some individuals. At 1 Gy (100 rad), most individuals express transient

Table 3-2. Summary of Some Studies of Humans Exposed to Radiation and Radionuclides

Location	Year(s)	Radionuclide	Purpose of experiment	Number of people dosed	Dose and route of exposure	Result
ANL	1931-1933	^{226}Ra	Determine the retention time of ^{226}Ra in humans	NA	70–50 µg; injected	Incomplete
ANL	1943-1946	x rays; ^{32}P	Determine effects of radiation, process chemicals and toxic metals in humans	4	x rays: 30 R ^{32}P: route not specified	White blood cell chemistry was important in assessing the radiation sensitivity of workers exposed to radiation
ANL	1944-1945	^{32}P	Study the metabolism of hemoglobin in cases of polycythemia rubra vera	7	15–40 µCi; route not specified	NA
ANL	1962	^{3}H	Study the uptake of ^{3}H thymidine in tumors and the effects of ^{3}H on tumors	4	10 µCi; injected	Similar growth was noted in both cancerous and non-cancerous cells treated with ^{3}H
ANL	1943-1944	x ray	Study hematological changes at varying doses of radiation in cancer therapy	14	27–500 R; external exposure	Reduction of white blood cells formed in lymphoid tissue; routine monitoring of blood components not a practical way of assessing the usual occupational radiation exposures
ANL	1948-1953	^{76}As	Determine effects of ^{76}As on hemato-poietic tissues in leukemia patients	24	17–90 mCi; intravenous	^{76}As as effective as more commonly used leukemia therapeutic agents.
BNL	1950	^{131}I	Determine the usefulness of ^{131}I to treat patients with Grave's Disease and metastatic carcinoma of the thyroid	12	4–360mCi or 6–20 mCi; route not specified	NA
BNL	1951	^{131}I	Study interaction of the thyroid and ^{131}I in children with nephrotic syndrome	8	NA	Maximum uptake of ^{131}I was 30-60% of administered dose (3–5 µCi); no impairment of I uptake in children with nephrotic syndrome.
BNL	1952-1953	^{42}K ^{38}Cl ^{131}I (1 patient)	Examine formation and cycling of cerebrospinal fluid (CSF)	2	NA; injected route not specified	The amount of CSF produced daily is small and fluid production is not solely produced by the choroid plexus

Table 3-2. Summary of Some Studies of Humans Exposed to Radiation and Radionuclides (continued)

Location	Year(s)	Radionuclide	Purpose of experiment	Number of people dosed	Dose and route of exposure	Result
BNL	1963	^{59}Fe	Study iron absorption in women with various menstrual histories	9	1–10 µCi; oral	Menstrual blood loss in women with excessive bleeding was 110–550 mL. Normal women lost 33–59 mL during menstruation. Heavy menstruating women had higher gastrointestinal tract (GIT) absorption of iron than normal women
BNL	1967	^{47}Ca	Study the role of dietary Ca in osteoporosis	7	25 µCi; intravenous	Diets high in Ca had a small but positive impact on osteoporosis
BNL	Early 1970s	^{82}Br	Study the kinetics of halothane	4	2.5 µCi; inhalation	Concentrations of halothane were initially high in upper parts of the body and low in lower parts of the body. Diffusion equilibrium throughout the body was achieved in about 24 minutes.
HS	1963	^{131}I	Determine uptake kinetics of ^{131}I in humans	8	NA. Dairy cows consumed 5 mg to 2 g/day of I. Volunteers consumed milk produced by the cows exposed to ^{131}I in the diet.	Uptake of ^{131}I in humans was characterized.
LBL	1942-1946	x ray	Determine if blood cell changes could be used to indicate exposure in workers on the Manhattan Project.	29	5–50 R, daily dose 100–300 R, total dose. Whole body external exposure.	Significant deviations in white blood cell counts, anemia formed in relation to dose.
LBL	1948-1949	x ray	Determine the effects of radiation on the pituitary gland during treatment of cancers of other tissues	> 1	8,000–10,000 rad; external exposure	Pituitary is extremely resistant to x rays.
LBL	1949-1950	x ray	Effect of radiation on the pituitary gland and its effect on advanced melanoma and breast cancer.	3	8,500–10,000 rad; external exposure	Pituitary is extremely resistant to x rays.

Table 3-2. Summary of Some Studies of Humans Exposed to Radiation and Radionuclides (continued)

Location	Year(s)	Radionuclide	Purpose of experiment	Number of people dosed	Dose and route of exposure	Result
LBL	Early 1950s	^{60}Co	Determine feasibility of treating bladder cancer using beads labeled with ^{60}Co	35	5,000–6,000 rad over 7 days. Beads were placed inside the bladder cavity.	Non-infiltrating cancers were more successfully treated than were the infiltrating bladder cancers.
LBL	1961	^{90}Y	Determine the effectiveness of ^{90}Y in the treatment of acute leukemia in a child	1	200 rad to lymphatic tissue; route not specified.	Therapy resulted in temporary remission of leukemia; little effect on peripheral blood cells and red blood cells.
LLNL	1980s	^{13}N ^{41}Ar	Determine the uptake and clearance of nitrogen gas in order to better understand “decompression sickness” in deep-sea divers.	11	NA. Inhalation route of exposure. Doses in the mCi range. Absorbed dose to the lungs estimated to be 0.3–0.5 rad.	NA
LANL	1955	NA	Obtain information needed to plan for the safe and effective use of military aircraft near “mushroom clouds” during combat operation	4	#15 R; Inhalation and external routes were the likely routes of exposure.	No significant internal deposition of fission products or unfissioned Pu were detected in urine or via whole-body counting.
LANL	1961-1962	^{85}Sr	Determine the cutaneous absorption kinetics of ^{85}Sr through human skin	2	70 µCi; dermal exposure	Absorption of ^{85}Sr across the skin was low, and ranged from 0.2% to 0.6% total absorption.
OR	1956-1973	^{60}Co ^{137}Cs	Study efficacy of total-body irradiation on the treatment of leukemia, polycythemia rubra vera, and lymphoma	194	50–300 R, one person received 500 R; external exposure	Higher frequency of remissions after 150 R compared to 250 R. Total body irradiation survived as long-but not longer-than patients treated with non-radiation treatments
OR	1953-1957	^{233}U ^{235}U	Study the distribution and excretion of uranium in humans	NS.	4–50 mg; intravenously	99% of injected uranium cleared the blood within 20 hrs and the remainder either deposited in the skeleton and kidneys or excreted via the urine

Table 3-2. Summary of Some Studies of Humans Exposed to Radiation and Radionuclides (continued)

Location	Year(s)	Radionuclide	Purpose of experiment	Number of people dosed	Dose and route of exposure	Result
OR	1945	^{32}P	Study effects of beta rays on skin	10	140–1,180 rad; external exposure.	Threshold dose of beta radiation that resulted in mild tanning was about 200 rad. Erythema resulted after a dose of 813 rad
UC	1937-1954	x rays	Study the effect of x rays for the treatment of gastric ulcers	116	1,100–2,930 rad; external exposure	Claimed that moderate irradiation of the stomach reduced acid secretion and was a valuable adjunct to conventional gastric ulcer therapy. Therapy was later discontinued due to risks outweighing benefits
UC	1959	^{51}Cr	Determine feasibility of using implanted radiation sources in the treatment of cancer	24	2–5 mCi; Implanted within cancerous tissues	16 had good or favorable results; the remainder of patients had questionable or unfavorable results. Implants were generally well tolerated.
UC	1960s	Various. Fallout contains many alpha, beta, and gamma emitting radionuclides. Simulated fallout contained ^{85}Sr, ^{133}Ba, or ^{134}Cs	Gain information in civil defense planning prior to nuclear fallout	10	0.2–0.7 µCi actual fallout; 0.4–14 µCi simulated fallout. Subjects ingested actual fallout from Nevada test site, as well as simulated fallout particles	No gastrointestinal symptoms were reported. Studies provided a basis for estimating the systemic uptake and internal radiation dose that could result from the ingestion of fallout after nuclear bomb detonation.
UR	1946-1947	^{234}U ^{235}U	Determine dose level at which renal injury is first detectable; measure U elimination and excretion rates	6	6.4–70.9 µCi/kg intravenously	U excretion occurred mainly via the urine and 70–85% was eliminated with 24 hrs. Acidosis decreased U excretion. Humans tolerated U at doses as high as 70 µg/kg
UR	1956	^{222}Rn	Determine radiation doses to different parts of the respiratory tract from inhaled ^{222}Rn	2	0.025 µCi; inhalation	Average retention of ^{222}Rn and daughter products in normal atmospheric dust was 25%; retention in filtered air was 75%. Radiation exposure to the lungs was due to radon daughter products rather than by ^{222}Rn itself.

Table 3-2. Summary of Some Studies of Humans Exposed to Radiation and Radionuclides (continued)

Location	Year(s)	Radionuclide	Purpose of experiment	Number of people dosed	Dose and route of exposure	Result
UR	1966-1967	^{212}Pb	Study absorption of lead from the gastrointestinal tract and determine the radiation hazard and chemical toxicity of ingested lead.	4	1 µCi intravenous and/or 5 µCi orally	Lead might be released from binding sites only when red blood cells die.
MISC	1950s	^{131}I	Study the transmission of ^{131}I in maternal breast milk to nursing infants	2	100 µCi; oral	^{131}I concentration in maternal milk was high enough to allow significant uptake in the thyroids of nursing infants. ^{131}I tracers should be used with caution when nursing infants.
MISC	1953	^{131}I	Study uptake of ^{131}I by the thyroids of human embryos	NA	100–200 µCi (maternal dose); route not specified	Pregnant women were scheduled for abortion prior to receiving ^{131}I. Results indicated that it would be unwise to administer ^{131}I for diagnostic or therapeutic purposes while pregnant.
MISC	1963-1973	x rays	Determine the effects of radiation on human testicular function	60	7.5–400 rad; external exposure	Doses of 7.5 rad yielded no adverse effect on testicular function. 27 rad inhibited generation of sperm, and 75 rad destroyed existing sperm cells. Doses of 100–400 rad produced temporary sterility. All persons eventually recovered to pre-exposure levels prior to vasectomy.

Source: Human Radiation Experiments Associated with the U.S. Department of Energy and its Predecessors. U.S. Department of Energy, Assistant Secretary for Environment, Safety, and Health, Washington, DC, July, 1995. Document #DOE/EH-0491

ANL = Argonne National Laboratory; BNL = Brookhaven National Laboratory; HS = Hanford Sites; LBL = Lawrence Berkeley Laboratory; LLNL = Lawrence Livermore National Laboratory; LANL = Los Alamos National Laboratory; ORS = Oak Ridge Sites; UCLA = University of California, Los Angeles; UCACRH = University of Chicago Argonne Cancer Research Hospital; UR = University of Rochester; MISC = Other miscellaneous studies performed at other institutions; NA = information not available.

hematopoietic manifestations. Similarly, the cells lining the gastrointestinal tract, which normally have high turnover rates, will fail to multiply and replace dying cells, making the body susceptible to malabsorption syndromes, secondary bacterial infections, fluid loss and electrolyte imbalance. Fetal nervous system cells go through a period of rapid development between weeks 8–15, during which time they are more sensitive to radiation damage. Mechanisms by which ionizing radiation affects cells are described in greater detail in Chapter 5 of this profile. The phases of acute toxicity of ionizing radiation are discussed in the following section.

Acute Radiation Syndrome (ARS). Doses of radiation below 0.15 Gy (15 rad) produce no observable symptoms or signs. Lifetime radiation exposure from radioactive NPL waste sites, nuclear power plant operations, consumer products, natural background radiation, and most hospital nuclear medical tests are in this range. As the radiation dose increases, subclinical responses begin to occur at 0.15–1 Gy (15–100 rad), and clinical responses occur from 0.5 to $30 Gy (50 to $3,000 rad). Acute radiation syndrome (ARS) is seen in individuals following acute whole body doses of 100 or more rad. The degree of ARS in humans may be classified by the absorbed dose and the time over which the energy from the radiation is deposited in tissue. The clinical phase can be divided into four overlapping phases: (1) a mild phase (0.5–1 Gy, 50–100 rad), (2) hematopoietic syndrome (1–8 Gy, 100–800 rad), (3) the gastrointestinal syndrome (8–30 Gy, 800–3,000 rad), and (4) central nervous system syndrome (>30 Gy, >3,000 rad). If the energy is deposited over more than a few days (i.e., at a lower dose rate), the severity of the effects may be greatly reduced and time of onset delayed. Each of these syndromes and the tissues they are most likely to affect are briefly discussed below.

Subclinical Response (0.15 to <0.5 Gy, 15 to <50 rad). This phase is characterized by very few, if any, clinical or hematological manifestations of illness. There are no visible symptoms from this level of radiation exposure. Chromosomal breaks may occur within this dose range. At around 50 rad, there may be transient changes in formed elements of the blood in sensitive individuals.

Clinical Response (0.5 to $30 Gy, 50 to $3,000 rad).

0.5–1 Gy, 50–100 Rad. This phase of ARS is characterized by mild, but non-specific signs of toxicity. At 100 rad, most individuals express transient hematopoietic manifestations. Acute clinical signs of toxicity appear within 4–8 hours of receiving the dose; these initially consist of nausea and vomiting. Within 7–15 days after exposure, a moderate leukopenia appears; however, blood cell counts eventually return to normal within 4–6 weeks after exposure. There is no perceptible decrease in mental capabilities. Rest, extra fluids, antibiotics, and self-care are generally all that is needed for these

individuals to fully recover. Any treatment which is offered could include antibiotics and supportive care, much the same as one may treat cold or flu symptoms.

Hematopoietic Syndrome (1–8 Gy, 100–800 rad). This form of ARS is characterized by four phases. The first phase, the prodromal phase, typically lasts up to 2–3 days, depending on the dose; it is characterized by fatigue, listlessness, and lethargy that progresses to headache, anorexia, nausea, and vomiting within approximately 8 hours after initial exposure, depending on the dose. Laboratory findings are limited to varying alterations in the peripheral blood, with the earliest changes demonstrated as a marked lymphopenia about 1 day after exposure. The second stage, the latent phase, begins on the third to fourth day and may last up to 3 weeks from the time of initial exposure. This phase is marked by a progressive decrease in total blood leukocyte counts and hair loss (epilation) toward the third week. The third phase, the symptomatic or bone marrow depression phase, is present 18–21 days after exposure. Chills, fever, malaise, a swollen oropharynx (throat), gingivitis, bleeding gums, petechiae (small blood blisters), ecchymoses (bruises), anemia, and acute infectious diseases are characteristic of persons in this phase. The leukopenia and thrombocytopenia due to destruction of stem cells in the red marrow undermine the body's natural defenses against disease and hemorrhage, leaving the body susceptible to acute infections and illnesses. Depending on the dose and the aggressiveness of the treatment protocols, the clinical picture can vary from serious to fatal. The fourth phase, the recovery phase, is marked by a general improvement of the patient over a 3–6 month period. For doses from 1 to 6 Gy (100 to 600 rad), the prognosis for recovery is good; for doses of 6–8 Gy (600–800 rad) the prognosis is poor, but some victims are expected to survive if they receive aggressive medical treatment. The $LD_{50/30}$ for whole body irradiation is estimated to be between 350 and 450 rad (3.5–4.5 Gy) for those who receive minimal or no medical treatment.

Gastrointestinal Syndrome (8–30 Gy, 800–3,000 rad). The prodromal phase of this syndrome is very abrupt in onset, characterized by nausea and diarrhea, which typically subsides after several days, followed by a short latent period. Symptoms then return, which include white blood cell depression as seen in the hematopoietic form of ARS, nausea, vomiting, diarrhea (sometimes bloody), fever, and massive electrolyte imbalances, which ultimately will result in death. Treatments are palliative. Persons exposed to absorbed doses of $10 Gy (1,000 rad) are expected to die, although aggressive medical intervention may improve survival rates. There is one exception. If the dose is fractionated, as with bone marrow transplant patients who receive a standard whole body dose of 15.75 Gy (1,575 rad) and are well-managed, with fluids, antibiotics, and a sterile environment, the individual has a reasonable chance of survival.

Central Nervous System Syndrome (≥30 Gy, 3,000 rad). Symptoms in this syndrome classically have an immediate onset, and include violent nausea and vomiting, diarrhea, irrational behavior, circulatory system collapse, and neuromuscular incoordination occurring within a few minutes after irradiation. Convulsions, coma, and death ensue within 48 hours after irradiation.

The phases of acute radiation effects discussed above are summarized in Table 3-3.

Studies of Acute Effects. Most studies which showed acute radiation effects were from external radiation, indicating that internally-deposited radionuclides typically do not produce sufficient dose and dose rate to induce acute effects. As Table 3-3 shows, the overt signs of radiation toxicity follow a dose-effect relationship as long as the radiation dose rate is high. Individuals exposed to single acute doses of radiation that are less than 1 Gy (100 rad) experience few if any significant clinical signs of toxicity; however, as the dose is doubled (2 Gy, 200 rad), some systems begin to show signs of overt toxicity. At this dose, the cells that multiply the most rapidly (gastrointestinal cells, blood-forming cells) are only being mildly affected (nausea/vomiting, leukopenia). Red blood cell precursors are also likely to be affected at this dose; however, because of the lifespan of a peripheral red blood cell (90–120 days), anemia may not become clinically evident for several days or weeks after exposure. Cells that proliferate more slowly (e.g., the cells of the central nervous system, connective tissues, etc.) are largely unaffected. As the absorbed dose increases to 6 Gy (600 rad), more severe changes in the hematopoietic and gastrointestinal systems present as more intense, quicker onset vomiting for longer durations and severe white blood cell depression (leukopenia). Infections are of a greater concern, since the white blood cell's main defenses against infectious microorganisms (gastrointestinal cell barriers, neutrophils, lymphocytes) are severely compromised or non-functional. Coagulapathies begin to appear due to platelet anomalies (pupura, hemorrhage) as well as hair follicle death (hair epilation). Also at this dose, the first signs of central nervous system disruption begin to appear, with short periods of decreased cognitive abilities. As the dose of ionizing radiation increases beyond 8 Gy (800 rad), a dose-dependent increase in the severity of the hematological, gastrointestinal, and central nervous system toxicity occurs, and death will likely ensue due to catastrophic multi-organ failure, including complete destruction of the blood forming cells in the red marrow and destruction of the basement cells in the lining of the intestinal walls.

Table 3-3. Summary of the Dose Response Effects of Ionizing Radiation in Humans

Phase	Feature	Subclinical range	100–800 rad (sublethal ranges)			Over 800 rad (lethal range)	
		0–100 rad	100–200 rad	200–600 rad	600–800 rad	800–3000 rad	>3000 rad
Initial phase	Incidence of nausea and vomiting	None	5–50%	50–100%	75–100%	90-100%	100%
	Time of onset		3–6 hours	2–4 hours	1–2 hours	<1 hr	< 1 hr
	Duration		<24 hours	<24 hours	<48 hours	<48 hours	48 hours
	Mental and physical capabilities	100%	100%	Able to perform routine tasks. Cognitive abilities impaired for 6–20 hours.	Able to perform simple and routine tasks. Significant incapacitation in upper part of dose range. Lasts more than 24 hours.	Progressive incapacitation	
Latent phase	Duration	> 2 weeks	7–15 days	0–7 days	0–2 days	None	
Secondary phase	Signs and symptoms	None	Moderate leukopenia	Severe leukopenia; pneumonia; purpura, hemorrhage; infection; hair loss (epilation) at about 300 rads		Diarrhea; fever; disturbance of electolyte balance	Convulsions; tremor; ataxia; lethargy
	Time of onset after exposure		>2 weeks	Several days to 2 weeks		2–3 days	
	Critical period after exposure		None	4–6 weeks		5–14 days	1–48 hours
	Organ system affected	None		Hematopoietic and respiratory tissues	Hematopoietic and respiratory tissues	Gastrointestinal tract;respiratory tissues	Central nervous system
Hospitalization	Percentage	None	<5%	90%	100%	100%	100%
	Duration		45–60 days	60–90 days	90–120 days	2 weeks	2 days
Incidence of death		None	None	0–80%	90–100%	90–100%	
Average time to death				3 weeks to 2 months		1–2 weeks	2 days
Medical therapy		None	Hematologic surveillance	Blood transfusions and antibiotics		Maintenance of electrolytebalance	Sedatives

Source: adapted from Academy of Health and Science 1995

Death has been reported soon after an individual has received a very high single or multiple external radiation dose. Most of these studies have in common very high doses (several hundred to several thousands of rad) being administered over a relatively short period of time (acute exposure), usually over the course of minutes or hours. This was seen in the human case report by Stavem et al. (1985) in which a worker was exposed to 2,250 rad (22.5 Gy) within a few minutes time, resulting in death due to acute radiation sickness (depressed leukocyte counts, vomiting, diarrhea, etc).

There are many reports of studies in which animals inhaled large activities of soluble and insoluble particles. The inhalation studies pointed to a number of immediate or near-immediate causes of death, including bone marrow hypoplasia (Gillette et al. 1987a); radiation pneumonitis and fibrosis (Brooks et al. 1992; Hahn et al. 1981, 1987; Lundgren et al. 1991); and blood abnormalities, such as thrombocytopenia, neutropenia, lymphopenia, and anemia (McClellan et al. 1973). Death is most likely a result of these systems being adversely affected by the deleterious effects that radiation has on the cell functionality within these organ systems. The overwhelming damage that radiation induces in rapidly dividing (or undifferentiated) cells at these high doses (i.e., cell functional loss, necrosis, apoptosis, and death of precursor cells) leads to decreased numbers of functional cells for an extended period of time, leaving the body highly susceptible to systemic infections that can lead to organ failure and death. It has been suggested that the damage to lung tissue from radiation is principally vascular, with the sloughing of dead and dying endothelial cells causing capillary leakage, both interstitially and onto the alveolar surface. Another theory suggests that the damage to type II pneumocytes causes serious alterations in the amount of surfactant phospholipids, ultimately altering the normal functioning of the lung and leading to lung inflammation. A third theory suggests that type I pneumocytes necrose and slough, leaving denuded basement membranes and alveolar debris. Finally, a few researchers believe that the role of lymphocytes, the immune system, and the interaction of bacteria plays a major part in the induction of radiation pneumonitis (Coggle et al. 1986). In the case of experimental animals given acute doses, causes of later in life are primarily related to the cancerous effects (Boecker et al. 1988; Lloyd et al. 1994).

The clinical signs of toxicity from high radiation doses follow the classic dose-effect curve, with some organs more severely affected at each dose than others. A number of studies have been summarized that describe the no-observed-adverse-effect level (NOAEL) and the lowest-observed-adverse-effect level (LOAEL) of ionizing radiation on multiple body systems. These data are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile. More specific information on some organ systems affected after receiving high doses of ionizing radiation is discussed in more detail below.

3.2.1.1 Gastrointestinal Effects

Prominent gastrointestinal effects due to high acute doses of radiation can occur, usually after oral intakes of radionuclides or after whole-body exposures. Localized doses of external radiation of about 1,000 rad (10 Gy), have been reported to cause inflammation and swelling of the oral cavity, including the cheeks, soft and hard palate, tongue, and throat. The large doses necessary to cause these effects and the absence of effects following dental x rays demonstrate that salivary glands are not very sensitive to radiation. The structures near the stomach, which have stratified squamous epithelial coverings, seem to be much less severely affected than the stomach, small and large intestines, and colon, largely due to the lower cell turnover rates associated with this type of epithelium. The gastrointestinal epithelium, which includes the epithelium covering the stomach and intestines, is the most sensitive to the effects of radiation due to the high cell turnover rates. Very large doses (>1,000 rad, 10 Gy) to the germinal epithelium of the stomach and intestines damage these cells, rendering them unable to divide and replace older, more senescent cells lining these structures. As a result, ulceration, sloughing of cells, diarrhea, and hemorrhage may occur, leading to the gastrointestinal syndrome described in Table 3-3 (Adams and Wilson 1993).

Numerous laboratory animal studies identified gastrointestinal effects after exposure to high-level radiation. For example, male Swiss albino mice were injected with tritiated water with a specific activity of 10 mCi/mL, followed by maintenance on tritiated drinking water at 2.5 μCi/mL for 12 days. Mice were estimated to have cumulative doses of 116, 440, 1,320, 2,200, and 5,280 mrad (1.2, 4.4, 13.22, and 5.3 mGy) for the 0.25, 1, 3, 5, and 12 days of treatment, respectively. A significant decrease in the total cell population and mitotic figure per crypt section was observed 6 hours after exposure; the decrease continued through day 1. After that, the total cell population stayed at a constant value for 3–5 days), after which it showed a significant increase on day 12. The number of mitotic figures increased slightly on day 3 followed by a decrease on day 5, but these changes were not significant. On day 12, the mitosis also increased slightly. The number of pycnotic nuclei and necrotic cells increased significantly 6 and 24 hours after exposure, and then decreased on day 3. After that, the number of cells increased again on day 5. The number of cells per villus column showed a significant decrease 6 hours after exposure; this decline continued up to day 5, when the cell count was 67.5% of normal (control). After this, the count showed a significant increase on day 12. The villus height was slightly reduced 6 hours after exposure, and significantly reduced from day 1 to 5. The height was 81% of normal at day 5, and 91.5% of normal at day 12. In summary, all of the parameters studied showed partial recovery towards normal on day 12 at the doses tested (Kumar et al. 1983).

Gastrointestinal effects have also been described after inhalation exposure to radionuclides. Gastrointestinal effects are most likely due to inhaled particles lodging in the nasopharyngeal mucus and in the tracheobronchial mucus layers of the conducting airways of the lungs and then being carried up the airways, where they enter the pharynx and are swallowed. Several reports describe such gastrointestinal effects after inhalation exposure. Gillett et al. (1987a) exposed young adult Beagle dogs (12–14 months old) once to soluble aerosols containing $^{90}SrCl_2$. Different airborne concentrations (2.16–418.5 μCi ^{90}Sr/L) and exposure durations (2–22 minutes) were used to produce graded levels of initial lung burdens; 72 Beagle dogs were exposed, and another 25 unexposed dogs served as controls. The long-term retained burden ranged from 1.0 to 118.8 μCi ^{90}Sr/kg body weight. Clinical signs of radiation-induced illness appeared about 2 weeks after exposure. The first signs, fever and anorexia, including bloody diarrhea, developed during the last 48 hours before death. In another study, Hahn et al. (1975) studied the effects of ^{90}Y laden particles clearing to the gastrointestinal tract after an acute-duration inhalation exposure. Ten Beagle dogs were exposed by nose-only inhalation to aerosols of ^{90}Y in fused-clay particles; three control dogs were exposed to fused clay only. Gastrointestinal burdens ranged from 8 to 34 mCi. A rapid initial decrease in body burden occurred (typical of an insoluble material deposited by inhalation), which was largely due to the clearance of particles from the upper respiratory tract through the gastrointestinal tract by way of mucociliary clearance mechanisms in the respiratory tract; 4 of 6 dogs with 18–34 mCi gastrointestinal burden developed a mucoid diarrhea. The dog with the highest exposure developed hemorrhagic diarrhea; 2 of 7 dogs exposed to 18–32 mCi gastrointestinal tract burden (32–50 mCi whole-body burden) developed colitis. At necropsy, lesions were found to be confined to the colon, except for one dog with ulcerative esophagitis. No gross lesions were seen in the stomachs or small intestines of any of the dogs; no histologic lesions were found. In the dogs with colitis, ulcerative and atrophic foci were scattered in the terminal third of the colon. Loss of mucosal epithelial cells and collapse of the lamina propria were the most severe pathologic alterations in the colon. The colon received the highest radiation dose in the two exposed dogs, although the stomach and small intestines also received significant doses. Of the two dogs sacrificed at 8 days postexposure, the only lesions that were seen at necropsy were in the colon of the dog that received an estimated 3,200–5,700 rad (32–57 Gy). No lesions were seen in the intestines of the dog that received 2,800 rad or less. Lesions were most likely in response to a high dose of ionizing radiation due to the long transit time of the radiolabeled material through the colon (increased exposure time).

Similar effects from external gamma radiation have been reported. In one human case report, Stavem et al. (1985) described a 64-year-old male worker who accidentally received a large dose of gamma radiation in a plant for sterilizing medical equipment. He was exposed for only a few minutes and was

most likely exposed to a mean whole-body dose of 2,250 rad. The worker developed ARS. Histologically, the mucosa of the gastrointestinal tract (and respiratory tract) showed only a few mononuclear cells, and no granulocytes. There was slight atrophy of glands in the stomach, marked atrophy in the small intestine, and total atrophy of the glands in the large intestine. As in humans, laboratory animals exposed to extreme doses of external radiation exhibit effects on the exposed organ systems. A group of 12 male BALB/c mice was exposed to a single whole-body dose of 1,500 rad gamma rays from a ^{60}Co source. The degree of gastrointestinal motility and the condition of the abdominal blood vessels, spleen, and the contents of the stomach and intestine were examined 1 hour, 3 hours, 18 hours, and 3 days after irradiation. Gastrointestinal mobility was present at all times after the exposure. Vascular dilatation was absent at all times. Lumial contents were present 1–3 hours after the exposure and slightly present 18 hours to 3 days after the exposure. The mucosal surface displayed changes in the shape of the villi, with rudimentary villi being the most advanced type of collapse seen. Villus shape changes were seen at all times post-exposure. Changes in tissue structure were seen at the 18-hour time point including less distinct crypts with disintegrating cells present (Indran et al. 1991). Ijiri (1989), studying the influence of circadian rhythm on apoptosis, found that gamma irradiation (from ^{137}Cs) between 0900 and 1500 hours caused a higher incidence of apoptotic cells in the small intestine of male C57BL/6crSlc mice than irradiation between 2100 and 0300 hours, irrespective of dose rate; similar differences, but with lower incidences of apoptotic cells, were also noted in the descending colon. The mean lethal dose values for continuous irradiation with gamma rays were 21 rad (0.21 Gy) for the cells of the small intestine and 38 rad (0.38 Gy) for the cells of the descending colon, and the respective values for HTO (beta radiation) were 13 and 28 rad (0.13 and 0.28 Gy), indicating the high radiosensitivity of these cells.

In summary, higher doses, starting in the range of 200–300 rad (2–3 Gy), are required to produce effects in the gastrointestinal tract than in bone marrow. The severity of effects follows a typical dose-effect relationship. The cells responsible for lining the tract frequently undergo mitosis, leaving them particularly susceptible to DNA damage, cell death, and altered cell kinetics that affect the cell's ability to proliferate. These effects include karyorrhexis (fragmentation of a nucleus with scattering of pieces in the cytoplasm), pyknotic nuclei (having polymerized and contracted chromosomal components), necrosis, decreased number of cells/villi, and changes in shapes of the villi and mucosal surfaces. The damage to the epithelial lining cells results in the loss of the natural barrier between intestinal microbes and the body, making it susceptible to systemic infections, fluid imbalances and losses, bloody diarrhea, colitis, and a host of other clinical signs, depending on the radiation dose (Gillett et al. 1987a; Hahn et al. 1975; Kumar et al. 1983).

Data for acute gastrointestinal effects in humans and laboratory animals from large doses of radiation are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

3.2.1.2 Hematological and Lymphoreticular Effects

Hematological effects are one of the syndromes seen after acute doses to bone marrow (see Table 3-3) of about 50 rad (0.5 Gy). The magnitude of effect on hematopoiesis is dependent on the total dose absorbed, regardless of the route of exposure. As Table 3-3 shows, hematological symptoms begin to occur at doses of 100–200 rad (1–2 Gy). Like the gastrointestinal system, the hematopoietic system contains a large population of cells that requires the frequent replacement of senescent cells. To meet this need, a pool of undifferentiated precursor cells called stem cells in the red marrow of many bones (e.g., ribs, pelvis, vertebrae, skull, and ends of long bones) undergo high rates of mitotic activity and differentiate into the various cell types to replace those that die off naturally. This pool of cells is critical for the production of replacement cell populations for erythrocytes, granulocytes, lymphocytes, and thrombocytes. The dose of radiation received by stem cells damages or kills these cells, thereby depressing the marrow activity, resulting in anemia, leukopenia, thrombocytopenia, septicemia, infections, and death. The severity of these lesions depends on the depression of bone marrow activity due to the total dose absorbed, with irreversible total destruction resulting from doses to the red marrow on the order of 800 or more rad ($8 Gy).

As an example of hematological lesions in humans obtained after exposure to ionizing radiation, Klener et al. (1986) reports one case in which a man was accidentally irradiated by a sealed ^{60}Co source. His health status was followed for 11 years after the accident. A film dosimeter worn during the accident indicated an exposure of 159 rad (1.59 Gy). Twelve to 24 hours after the accident, the worker felt general malaise without vomiting; however, a blood count showed no marked deviations from normal. Eight days after the accident, he developed minor deviations in peripheral blood counts. Leukocyte values were lowest 31–49 days after exposure. The lymphocyte count was normal the first day after the accident, but decreased on days 19–23 and day 49. Neutrophils with coarse granulations and hypersegmentation of nuclei were observed. In another acute exposure case, Stavem et al. (1985) reported on a 64-year-old male worker who was accidentally exposed to gamma radiation in a plant that used ionizing radiation for sterilization purposes. He was exposed for only a few minutes and received an estimated 2,250 rad (22.5 Gy). The worker developed ARS, with the leukocyte count rapidly diminished to low values. Extensive chromosome injuries were seen in cultured blood lymphocytes, and virtually no undamaged

cells were found. The worker died 13 days after exposure. An autopsy found the bone marrow to be markedly hypocellular with a few scattered plasma cells.

Hematological effects have been reported after inhalation exposures in laboratory animals. The effects depend on the dose absorbed. Brooks et al. (1992) exposed male monkeys, divided into mature (5.0±0.5 kg) and immature (2.1±0.3 kg) groups, to an aerosol of $^{239}Pu(NO_3)_4$ by nose-only inhalation to produce projected initial lung burdens of either 1.08, 0.27, or 0.1 µCi (40, 10, or 3.7 kBq). No significant changes in blood lymphocyte numbers were observed. Gillett et al. (1987a) exposed young adult Beagle dogs (12–14 months old) to soluble aerosols containing $^{90}SrCl_2$. A review of the hematological parameters of all dogs showed a similar, consistent, and dose-related pancytopenia in those animals having a long-term retained burden greater than 10 µCi (370 kBq) ^{90}Sr/kg. A profound dose-related depression of platelet counts was also found. Decreases in platelet numbers were manifested by 7 days and were maximal by 28 days. Platelet counts were depressed in all exposed groups, compared to controls, when evaluation was extended to 1,000 days after exposure. Platelet counts among animals having a long-term retained burden greater than 40.5 µCi (1,500 kBq) ^{90}Sr/kg frequently fell to less than 10% of pre-exposure values. Animals having slightly lower long-term retained burden also exhibited depressed but less severe thrombocytopenia. The degree of platelet depression was related to the degree of long-term retained ^{90}Sr. The decline in platelet counts seen in dogs with a long-term retained burden of 27.0–118.8 µCi ^{90}Sr/kg at 1,000 days was also associated with the presence of hemangiosarcomas. Thrombocytopenia and neutropenia persisted in all exposed dogs through 1,000 days after exposure. Lymphocyte numbers were also depressed in a dose-related manner at activity concentrations greater than 10 µCi (370 kBq) ^{90}Sr/kg. Reduced erythrocyte mass occurred in dogs having a long-term retained burden greater than 10 µCi (370 kBq) ^{90}Sr/kg between 14 and 21 days after exposure. Red blood cell counts fell to 70–80% of pre-exposure values, with maximal depression at 32 days.

Hobbs et al. (1972) also observed dose-related clinical, hematological, serum chemical, and pathological alterations more than 1 year after intake. Thirty-three Beagle dogs were given lung burdens of 3,600, 1,800, 1,200, 780, 400, 210, 110 and 0 µCi (133, 67, 44, 29, 15.8, and 4 MBq) ^{90}Y/kg body weight. Cumulative doses between 990 and 55,000 rad (9.9–550 Gy) to the lungs through the end of the study or the death of the animals were reported. Dogs that had initial lung burdens of 670–760 µCi/kg (25–28 MBq) and radiation doses to lung of 8,400 to 9,400 rad (8.4–9.4 Gy) and died within 31 days after intake had a dose-related depression of circulating lymphocytes (lymphopenia), as well as a marked

marrow suppression and deletion of hemic elements. Rib marrow was depopulated in dogs that died after 31 days.

Exposure to primarily β and γ radiation from external sources yielded similar results. Seed et al. (1989) exposed male and female Beagle dogs to 7.5 rad/day (0.075 Gy/day) gamma radiation for 150–300 days from a ^{60}Co source. The irradiated dogs showed a significant suppression/recovery pattern for the five circulating types of cells studied (granulocytes, monocytes, platelets, erythrocytes, and lymphocytes), compared with levels from the control animals. These daily doses were high and would have likely been fatal if the entire dose had been received within a period of a few days.

A large number of reports are available in the literature regarding immunological effects associated with radionuclides that have been inhaled by laboratory animals. Lymphopenia is a common sequela of exposure to ionizing radiation affecting the immune system of both humans and animals. Gillett et al. (1987a) exposed young adult Beagle dogs (12–14 months old) to soluble aerosols containing $^{90}SrCl_2$ and found that lymphocyte numbers were depressed in a dose-related manner at exposures greater than 10 μCi ^{90}Sr/kg. Benjamin et al. (1976) exposed 6 Beagle dogs, (3 males and 3 females, 17–20 months old) by nose-only inhalation to ^{90}Y, ^{144}Ce, or ^{90}Sr in fused-clay particles. Initial lung burdens were 560, 46, and 28 μCi/kg (21, 1.7, and 1.0 MBq/kg) for ^{90}Y, ^{144}Ce, and ^{90}Sr, respectively. Cumulative absorbed dose at death or at sacrifice after 44 weeks were 8,700, 42,000, and 39,000 rad (87, 420, and 390 Gy) for ^{90}Y, ^{144}Ce, and ^{90}Sr exposures, respectively. Lymphopenia was observed in dogs exposed to ^{90}Y within several days after intake and was statistically significantly depressed though 8 weeks but returned to control levels by 16–20 weeks. No change in peripheral lymphocytes was observed. Lymphocyte counts in dogs exposed to ^{144}Ce were significantly lower (lymphopenia) than controls from 4 to 28 weeks after exposure. In a study conducted by Lundgren et al. (1976), the effect of ^{90}Y inhaled in fused-clay particles on the pulmonary clearance of inhaled *Staphyloccus aureus* in mice was investigated. Groups of male CFW mice were exposed to ^{90}Y for 10–20 minutes. Aerosol concentrations ranged from 14.5 to 428 μCi/L (0.5–16 MBq/L) air and the activity median aerodynamic diameter (AMAD) ranged from 0.7 to 1.4 μm. The initial lung burden ranges of the groups were 2.5–4, 7–12, 20–47, and 50–76 μCi in experiment I and 5–7 and 8–12 μCi in experiment II. Pulmonary clearance of inhaled *S. aureus* was suppressed in mice with an initial lung burdens of 20 μCi ^{90}Y or greater at 2, 3, and 4 weeks after exposure. Lymphocyte counts were suppressed in the 20–47 μCi and 50–76 μCi groups at 2 weeks postexposure and in the 50–76 μCi group at 3 weeks after intake. Clearance of bacteria at a reduced rate was observed in 20–47 μCi mice at 2, 3, and 4 weeks and in 50–76 μCi mice at 2 and 3 weeks after intake.

Similarly, Hobbs et al. (1972) observed dose-related pathological alterations more than 1 year post-exposure in 33 Beagle dogs exposed to ^{90}Y. Of the 33 dogs exposed, 21 with initial lung burdens from 670 to 5,200 μCi/kg (25–192 MBq/kg) and radiation doses to the lungs ranging from 8,400 to 55,000 rad (84–550 Gy) died between 7.5 and 163 days after intake. Tracheobronchial lymph nodes (TBLNs) in the early deaths showed marked lymphoid depletion, some sinus hemorrhage, and, later, phagocytosis of hemosiderin pigment. In the dogs that died 38 days or more postexposure, the nodes were enlarged and exhibited hyperplastic repopulation of lymphocytes. Hahn et al. (1976) also studied the effects of exposure on TBLNs in 16 male and 14 female Beagle dogs exposed by nose-only inhalation to aerosols of ^{144}Ce in fused-clay particles. Between 2 and 730 days postinhalation, the ^{144}Ce dose to TBLNs ranged from 240 to 230,000 rad (2.4–2,300 Gy). The concentration of ^{144}Ce in the TBLNs increased during the first year after exposure as a result of the translocation of ^{144}Ce from the lungs via the lymphatics. Histologically, the changes were atrophic in nature. The cortex showed progressive reduction in size with increasing time after intake; by 730 days after intake, there was little cortex remaining. Fibrosis was first noted 128 days after intake and was more severe at each succeeding time period up to 730 days. There was also a loss in numbers of lymphocytes in the paracortical area 56 days after intake, although this loss was not as severe as the depletion of lymphocytes from the cortex. At later times the cortical and paracortical areas were nearly devoid of lymphocytes and were populated mainly by macrophages. Particles could be seen in macrophages 2 days after inhalation exposure. The authors note that since lymph nodes play a key role in immunologic responses associated with humoral antibody production and cell-mediated immunity and, in view of the severe atrophy and fibrosis in the TBLNs in the dogs in this study, the immunologic function in the TBLNs would seem to have been severely impaired.

Lymphocytes are responsible for providing cell-mediated and humoral-mediated (antibodies) resistance to infection. Galvin et al. (1989) evaluated the cell-mediated and humoral immune responses to $^{239}PuO_2$ in the blood and lung lavage fluid. Four Beagle dogs per group (8 total) were exposed to monodisperse aerosols (0.72–1.4 μm AMAD) of $^{239}PuO_2$, with initial lung burdens ranging from 0.51 to 0.95 μCi (0.02–0.04 MBq). Cumulative dose ranges were 1,400–2,400 rad (14–24 Gy) to the lungs; 620,000–930,000 rad (6,200–9,300 Gy) to the TBLNs; 290,000–440,000 rad (2,900–4,400 Gy) to the mediastinal lymph nodes; 200–300 rad to (2–3 Gy) the sternal lymph nodes; and 2–3 rad (0.02–0.03 Gy) to the spleen. The dog with the highest cumulative dose to the TBLNs (930,000 rad, 9,300 Gy) was the only dog noted to have had chronic lymphopenia; blood cell counts of the other 3 dogs showed normal lymphocyte counts. TBLNs of all dogs displayed severe diffuse fibrosis and atrophy with elimination of all lymphatic cells and follicles. Lymphatic vessels were moderately to markedly distended. The spleen

and other peripheral lymph nodes were histologically normal. Systemic humoral response induced by lung immunization was not different in the age-matched and exposed groups. Peak humoral immune response (lung lavage, immunoglobulin G [IgG]) measured in immunized lung lobes of exposed and control dogs was significantly greater than saline-lavaged control lung lobes.

Leukopenia (severe lymphopenia and granulocytopenia) and splenic congestion were found in one male worker who accidentally received an external gamma dose of 2,250 rad (22.5 Gy) (Stavem et al. 1985). Mazur et al. (1991) exposed male Swiss mice to a single dose of 1,000 rad (10 Gy) whole-body irradiation from a ^{60}Co source. Spleen weights were significantly lower in the irradiated group during the 24-hour period. No statistically significant differences in acid phosphatase activity were seen in the spleens and livers of radiation-exposed mice; however, the acid phosphatase activity in the spleen and liver was statistically significantly higher in the irradiated rats as compared to controls. An increased activity of beta-glucuronidase was seen in the spleen, but the enzyme activity did not differ from controls in the liver.

In summary, the hematological and lymphoreticular systems are target systems susceptible to the effects of ionizing radiation, the severity of which occurs in a dose-dependent manner. As with the gastrointestinal tract, the hemopoietic system is largely composed of undifferentiated rapidly dividing cells, making it more susceptible to the toxic effects of ionizing radiation than are the tissues composed of highly differentiated more slowly dividing cells (central nervous system). In many of the studies, pancytopenia was one of the first major peripheral blood changes to occur. Neutrophils have a naturally short lifespan in the peripheral blood (12–48 hours) and depend upon constant replenishment by the bone marrow to adequately defend the body against infection. Acute high (sublethal) radiation doses from an external source or from inhaled or ingested radionuclides that distribute to bone and irradiate the sensitive cells in the bone marrow will first noticeably affect the progenitor cells that produce leucocytes, since their turnover rates for this cell type are very high. The immediate peripheral blood counts of red blood cells with longer lifespans in the peripheral blood and lower turnover rates will not be affected because of their long lifetime (3–4 months). Radionuclides that preferentially distribute to the bone for long periods of time will, if the dose is high, cause prolonged depression of most red and white blood cell types, due to constant irradiation of the bone marrow components. Anemias, thrombocytopenia, and leukopenias (all cell types) are also frequent findings in such situations (Benjamin et al. 1976, 1979; Davila et al. 1992; Gillette et al. 1987a; Hahn et al. 1976; Hobbs et al. 1972). Animals administered sublethal doses of ionizing radiation have the ability to recover from these effects once the radiation source is removed (Gidali et al. 1985; Hobbs et al. 1972; Seed et al. 1989, 1993) or its dose rate is sufficiently reduced.

The data for hematological and lymphoreticular effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile. Because of the high threshold dose for changes in peripheral blood counts, blood counts are not used to routinely monitor the health of radiation workers.

3.2.1.3 Reproductive Effects

Cells that reproduce frequently, such as those found in intestinal crypts, bone marrow, and the reproductive systems of animals, are more radiosensitive than cells that are highly differentiated and reproduce slowly. This radiosensitivity is dependent on of the type of ionizing radiation or the source. Specific cells in the reproductive tract of both males and females replicate at accelerated rates, making them more at risk to the effects of ionizing radiation. In males, the spermatogonia are the cells most sensitive to the effects of ionizing radiation. These are the germ cells responsible for producing spermatocytes and later, spermatids and mature sperm. Spermatids and sperm are very radioresistant to cytotoxic effects of radiation. Decreases in sperm numbers in semen do not occur immediately; in humans, decreased sperm counts are not seen until 30–45 days after significant exposures. Azospermia can occur 10 weeks after exposure to absorbed doses >100 rad (1 Gy); a dose of 250 rad (2.5 Gy) may cause sterility for 1–2 years. An absorbed dose of 600 rad (6 Gy) can cause permanent sterility (Adams and Wilson 1993). In females, the mature oocyte is less sensitive than male spermatogonia cells, but it is the most radiosensitive reproductive cell. Absorbed doses of 65–150 rad (0.65–1.5 Gy) have been reported to produce temporary sterility (Adams and Wilson 1993); however, a fractionated dose of 600–2,000 rad (6–20 Gy) can be tolerated (BEIR V 1990).

Several studies were found in the literature that support these findings. In one human study, Birioukov et al. (1993) investigated the reproductive effects of ionizing radiation in 12 men (29–78 years old) with chronic radiation dermatitis caused by accidental exposure to beta and gamma radiation during and after the Chernobyl nuclear reactor accident. These men were examined for changes in sexual behavior, hormonal status, and spermatogenesis. All were diagnosed with ARS, which was categorized as first degree (100–200 rad, 1–2 Gy), second degree (200–350 rad, 2–3.5 Gy, Group A), and third degree (350–550 rad, 3.5–5.5 Gy, Group B) based on their location at the time of the incident. Of the 12 men evaluated, 9 reported decreased sexual potency, and 3 refused to answer the question. Two patients reported impotence, and seven patients had decreased libido. The sperm of 7 patients were examined (5 refused to give a semen sample). All patients tested had normal semen pH values. Other sperm

anomalies reported in both groups A and B included azoospermia, asthenospermia, and teratospermia. Others had slightly increased numbers of abnormal cells (morphological changes in the sperm head). Abnormal motility was present in all but one patient (in group B). Follicle-stimulating hormone was increased in 6 of 9 patients in group A and was normal in group B patients. Testosterone was decreased in 2 patients in each group. A decrease of luteinizing hormone and an increase of prolactin were measured only in 1 patient.

Similar reproductive effects have been noted in laboratory animals. Ramaiya et al. (1994) performed a comparative estimation of the frequencies of genetic disorders induced in germ cells of male mice by a single or long-term exposure to incorporated ^{137}Cs. Groups of 10 male mice received a single oral administration of 0.1, 0.5, 1.0, 2.0, and 3.0 µCi/g (3.7, 18, 37, 74, and 111 kBq/g) as ^{137}Cs. Groups of 10–30 males were also given daily injections of ^{137}Cs nitrate in phosphate buffer solution for 2 weeks at activities of 0.5, 2.0, and 5.0 µCi/g (18, 74, and 190 kBq/g) as ^{137}Cs. The total absorbed dose to the testes during the 5 weeks after the single oral exposure was 10, 50, 100, 200, and 300 rad (0.1, 0.5, 1.2, and 3 Gy), respectively, while the total absorbed doses during the 5 weeks of multiple injections was 38, 154, and 385 rad (0.38, 1.54, and 3.85 Gy), respectively. A decrease in the fertility of males was observed in the 2.0 and 3.0 µCi/g (74 and 111 kBq) exposure groups, beginning from the 4th week for radiation doses of 190–197 rad and 285–295 rad (1.90–1.97 Gy and 2.85–2.95 Gy), respectively. Complete, but temporary, sterility observed in animals exposed to 300 rad (3 Gy) after 6 weeks was attributed to the death of spermatogonial cells. There was a significant increase in post-implantation embryo mortality and, correspondingly, in the dominant lethal mutation frequency, at a total dose of $180 rad (1.8 Gy).

Pinon-Lataillade et al. (1991) irradiated male Sprague-Dawley rats so that only the testes and surrounding organs were exposed to a gamma-ray beam of 900 rad (9 Gy). Groups of 6 irradiated rats and age-matched controls were sacrificed at 7, 15, 23, 34, 50, 71, 118, and 180 days after irradiation. Testis weight dropped to 85% of the control by day 7, 58% of the control by day 23, and 41% by day 34. Epididymal weight decreased to 88% of control by day 15, 63% by day 50, and plateaued out at 55% of the control value. Spermatocytes were damaged, and by day 34, only elongated spermatids remained in a few tubules and very little regeneration of the seminiferous tubule had occurred. From day 15 after the irradiation, the epididymal content of androgen-binding protein (ABP) value dropped to 26% of the control and by day 34 it was back to only 14% of this value. From day 50 to the end, the ABP value remained below 10% of the control levels. No significant changes were observed in the weights of the seminal vesicles or in the concentrations of seminal vesicles.

Another study of acute duration estimated comparative frequencies of genetic disorders induced in germ cells of male mice by a single or long-term exposure to incorporated ^{137}Cs or to external gamma radiation. Groups of 10 male mice were exposed to a ^{137}Cs apparatus for a whole-body dose of gamma radiation of 300 rad (3 Gy) at a rate of 0.675 rad/hour. Subsequent data on effective matings and embryo mortality were collected. Animals that mated and that were exposed to external gamma radiation had a significant decrease in male fertility, and at 3 weeks the animals became sterile. During weeks 1 and 2, there was a significant increase in total and post-implantation embryo mortality (Ramaiya et al. 1994).

Studies of longer exposure duration have demonstrated similar results. Searle et al. (1976) exposed 13 adult C3Hx101 hybrid male mice continuously to 1,128 rad (11.28 Gy) ^{60}Co gamma radiation over 28 weeks at the rate of 5.8 rad/day (0.058 Gy/day). There were significant reductions in testis mass (35% of controls) and epididymal sperm count (15% of controls). An increased percentage of abnormal sperm was observed in gamma-irradiated animals (17.1% versus 3.9% controls). The frequency of chromosomal translocations was significantly higher than in controls. There was also good evidence for the induction of dominant lethal mutations, with an increase in pre-implantation loss from 16% (controls) to 28% (radiation exposed) and in post-implantation loss from 10% (control) to 22% (radiation exposed). In addition, Grahn and Carnes (1988) exposed groups of 4–13 male B6CF$_1$ mice to ^{60}Co gamma-rays or fission neutrons at once-weekly doses for periods up to 60 weeks (10, 25, 40, 50, or 60 weeks of exposure and observations at 75, 90, and 99 weeks). Doses rates were 0, 5, 7.5, and 10 rad (0, 50, 75, and 100 mSv) per week. An increased frequency of abnormal sperm was observed at all doses and all exposure durations. After exposure ended, frequencies of sperm abnormalities returned to near-normal levels.

In summary, male reproductive organs are at risk for non-carcinogenic effects when exposed to high doses of ionizing radiation due to the relative high rates of cell divisions that occur in these organs. Sperm anomalies, temporary impotence, decreased libido, and hormonal imbalances have been reported in men exposed to 100–550 rad (1–5.5 Gy) (Birioukov et al. 1993). Similar effects in laboratory animals, such as decreased testes weights, decreased fertility, sterility, decreased sperm counts, chromosomal reciprocal transformations, sperm anomalies, and embryo mortality, have been reported at similar dose levels (Grahn and Carnes 1988; Pinon-Lataillade et al. 1991; Ramaiya et al. 1994; Searle et al. 1976; Shevchenko et al. 1992).

The data for reproductive effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

3.2.1.4 Teratogenic/Embryotoxic Effects

The rapidly dividing cells in the developing fetus, like those in the reproductive system, are also at a much higher risk of radiation damage, independent of the type of ionizing radiation, or the source or route of exposure, than slowly dividing, differentiated cells. The vast majority of the available literature reported numerous toxicological end points on the developing fetus associated with external radiation exposure. External exposure to the fetal animal by alpha and beta radiation is of no concern because α and β radiation cannot penetrate the mother's body tissues and the placental sac. Gamma radiation is very penetrating and can expose the fetus. The embryo/fetus is always uniformly exposed to external gamma rays from background radiation. There may also be partial body exposure from medical x rays or from internal exposure to a radionuclide such as ^{90}Sr, which results in preferential uptake during fetal bone development. Of most concern in cases of human exposure are the effects of embryo organogenesis and how these changes will affect the individual as a child and an adult.

During the early days of development, the human embryo largely consists of a mass of undifferentiated cells, which are the cells most sensitive to the effects of ionizing radiation. These cells transform into more specialized (differentiated) cells at specific times during gestation and develop into the more organized tissues seen later at maturity. For the purposes of describing teratogenic and other effects of *in utero* exposure, gestation is divided into three major periods: preimplantation, 0-2 weeks, major organogenesis, 2–8 weeks, and the fetal period, 8–40 weeks (Brent et al. 1980). Central nervous system (CNS) injury of radiological importance results from exposure in the early fetal period. CNS development in humans can be subdivided into four basic periods of development after conception: weeks 1–7, weeks 8–15, weeks 16–25, and $25 weeks. During weeks 1–7, the cells that will later differentiate into neurons are steadily multiplying. During weeks 8–15, the population of neurons rapidly increases, and neurons migrate to their functional sites, and lose their ability to further divide. Between weeks 16 and 25, these neurons continue to develop, but more importantly, they undergo synaptogenesis in order to communicate. From week 25 on, the neurons continue to differentiate into more mature neurons, with continued growth of the cerebrum (cognitive thought and motor skills) and cerebellum (motor coordination) (BEIR V 1990; ICRP 1986).

Fetal Central Nervous System Developmental Defects (Mental Retardation and Impaired Intelligence). Analysis of human data from fetuses exposed to very high doses of radiation during the bombing of Hiroshima and Nagasaki suggests that the cells of the developing central nervous system are among the cells most sensitive to the effects of ionizing radiation in the developing human fetus. The major clinical effects on these susceptible cells were mental retardation and IQ reduction; these effects were observed after birth during childhood development. Human fetuses exposed to doses of ionizing radiation from 1 to 7 weeks after conception suffered no discernable ill effects after birth. A dose-dependent increase in mental retardation occurred in individuals who were irradiated *in utero* during weeks 8–15 after conception. Severe mental retardation in all 30 cases in the clinical sample was diagnosed before age 17, based on clinical impressions and not on IQ scores. A "no effect" threshold was seen for doses in the range of 20–40 rad (0.2–0.4 Gy); at a dose of 100 rad (1 Gy), the frequency of observed mental retardation was 43% (BEIR V 1988; ICRP 1986; Schull et al. 1988). Similar results were seen in fetuses exposed from weeks 16 to 25; however, the relative risk of mental retardation was significantly lower. No discernable adverse effects occurred in children exposed during the period from week 26 to birth. Although the mothers of the retarded children had suffered very large radiation doses, some groups have suggested that these CNS effects on their unborn children may not have been caused by radiation but by genetic variation, nutritional variation, bacterial and viral infections during pregnancy, and embryonic or fetal hypoxia (BEIR V 1990; ICRP 1986).

Intelligence quotient (IQ) test scores of children fetally exposed to high radiation doses during each of these time frames support the supposition that exposure to ionizing radiation during fetal development may cause adverse effects. The MRL is based on a combination of two studies, one by Schull et al. (1988) and one by Burt (1966). Schull et al. (1988) evaluated the quantitative effect of exposure to ionizing radiation on the developing fetal and embryonic human brain. The end point measured was change in intelligence test scores. The effects on individuals exposed *in utero* during the atomic bombing of Hiroshima and Nagasaki were based on the original PE86 samples (n=1,759; data on available intelligence testing) and the clinical sample (n=1,598). The original PE86 sample included virtually all prenatally exposed individuals who received tissue-absorbed doses of 0.50 Gy or more, and many more individuals in the dose range 0–0.49 Gy than in the clinical sample. The clinical sample does not include children prenatally exposed at distances between 2,000–2,999 m in Hiroshima and Nagasaki. Children exposed at greater distances or not present in the city were selected as controls. In 1955–1956, Tanaka-B (emphasis on word-sense, arithmetic abilities, and the like, which were associated with the more subtle processing of visual clues than their simple recognition and depended more on connectedness) and the

Koga (emphasis on perception of spatial relationships) intelligence tests were conducted in Nagasaki and the Koga test in Hiroshima. No evidence of radiation-related effect on intelligence was observed among individuals exposed within 0–7 weeks after fertilization or in the 26th or subsequent weeks. The highest risk of radiation damage to the embryonic and fetal brain occurred 8–15 weeks after fertilization under both T65DR and DS86 dosimetric systems. These systems represent the best estimates of radiation doses to individual Japanese survivors using the best data available through 1965 and 1986, respectively. The T65DR dosimetry used site-specific data along with information obtained during later atomic bomb testing under arid conditions, whereas the DS86 dosimetry incorporated effects of high atmospheric humidity that existed when the weapons were exploded over Japan. The regression of intelligence score on estimated DS86 uterine absorbed dose is more linear than with T65DR fetal dose, and the diminution in intelligence score under the linear model is 21–29 points at 1 Gy. The regression of intelligence score on estimated fetal absorbed dose was linear for the exposed 8–15 weeks after fertilization and possibly linear for the 16–25 week group. The cumulative distribution of test scores suggested a progressive shift downwards in individual scores with increasing exposure; the mean IQ scores decrease significantly and systematically with uterine or fetal tissue dose within the groups exposed at 8–15 and 16–25 weeks.

In summary, analysis of intelligence test scores at 10–11 years of age of individuals exposed prenatally showed that:

- There is no evidence of a radiation-related effect on intelligence scores among those individuals exposed within 0–7 weeks of fertilization or in the 26th week of gestation and beyond;
- The cumulative distribution of test scores suggests a progressive shift downwards in intelligence scores with increasing exposure to ionizing radiation (dose-response relationship);
- The most sensitive group was the 8–15 week exposure group. The regression in intelligence scores was found to be linear, with a 1-Gy dose resulting in a 21–29 point decrease in intelligence scores.

Using the Schull et al. (1988) data in conjunction with the observations of Burt (1966), an MRL of 0.004 Sv (400 mrem) was derived for acute-duration external radiation exposures.

Embryo Organogenesis Defects and Body Weight Alterations. Beta and gamma radiation have been demonstrated to induce embryo/organogenic defects in laboratory animals. As in the human fetus, the developing central nervous system of laboratory animals during specific stages of development is at varying degrees of risk from exposure to ionizing radiation. In laboratory animals, effects such as hydrocephaly, anencephaly, encephalocele, spina bifida, functional and behavioral effects, motor defects,

hyperactivity, and defects in learning, as well as a host of other defects have been reported (BEIR V 1990). For example, Bruni et al. (1994) studied the effects of low levels of ionizing radiation on embryogenesis. Pregnant Sprague-Dawley rats were exposed for 14–17 seconds on gestational days 9.5, 15, and 18 to 50 rad (0.5 Gy) of ^{60}Co radiation. Irradiated rats and controls were sacrificed at prenatal intervals of 4 hours, 48 hours, and 10 days (term) after exposure. No statistically significant difference was seen in the number of embryos recovered per litter for control and irradiated embryos sacrificed 4 hours after exposure. With the exception of the neuroepithelium, no histopathological changes were observed in embryos in this group. In irradiated embryos, mitoses were reduced within the neuroepithelium; pyknosis and some necrosis of cells were apparent at this gestational interval. No significant difference was seen in the number of embryos recovered per litter, the crown-rump length, or the head length of irradiated embryos sacrificed 48 hours after irradiation compared to controls. Among the gross developmental abnormalities observed in embryos 48 hours after irradiation, excessive flexion of the embryo (seen in 3.7%) and abnormal flexion of the head (seen in 1.2%) were the only effects that appeared to possibly be radiation-induced. At term, no significant differences in litter size or resorption rates were observed in irradiated animals compared to the controls. Mean fetal body and placental weights were not significantly different. There was a higher incidence of developmental abnormalities in irradiated fetuses (9.7%) than in controls (4%), but this observation was not statistically significant. The most common anomalies were defects in ocular development; microphthalmia (small eyes) and anophthalmia (absence of eyes) were seen in 3% and 1.5% of irradiated fetuses, respectively. Scoliosis was also significant with a prevalence of 1%. Viscerally, abnormally positioned kidneys were found in 5.8% of irradiated fetuses and 7.1% of controls. Ureteric anomalies and hemorrhagic liver lesions were encountered in 2% and 11.5% of irradiated fetuses, respectively. No significant developmental differences were observed in the nervous system of irradiated versus control fetuses at term. The authors concluded that *in utero* doses of 50 rad (0.5 Gy) of gamma radiation during the period of early organogenesis can produce some irreversible defects that are discernable at term.

External Malformations, Growth Retardation, and Death. Many other types of birth defects in animals have been reported. Kusama and Hasegawa (1993) designed a study to precisely determine the radiosensitive period in the development of mouse embryos during which external malformations and growth retardation tended to occur. Pregnant mice were treated at various times during the gestation period with a single whole-body gamma radiation dose of 150 rad (1.5 Gy) delivered at a dose rate of 20 rad/minute (0.2 Gy/min) from a ^{137}Cs source. Death of the embryo/fetus, especially during the early period of organogenesis, was most frequent in mice irradiated between days 6.75 and 8.25 of gestation.

There was no difference in radiosensitivity between male and female fetuses. Reduction of fetal body weight was found to be a good indicator of radiation effects. Body weights of all irradiated fetuses were significantly less than controls. The reduction in fetal body weights was marked in mice irradiated during the intermediate stage of organogenesis (between days 9.75 and 12.75 of gestation). The body weights of abnormal fetuses with external malformations other than exencephalia (exposed brain) and eventration were not significantly different from those of fetuses without external malformations. Exencephalia appeared most often in mice irradiated between 6.5 and 8.75 days of gestation (0.6–21.7%) and at a low frequency between days 10.25 and 10.75 of gestation (0.5–1.5%). Cleft palate appeared in mice irradiated between days 8.25 and 12.75 of gestation (1.1–20.5%). Micromelia, ectrodactyly, and polydactyly were observed in fore- and hindpaws. The forepaw malformations appeared in fetuses exposed on days 10.25–12 of gestation (0.8–46.2%). Hindpaw malformations showed two periods of high sensitivity, from days 7.5 to 8.75 (0.6–3.8%) and from days 10.25 to 12 (0.6–28.9%) of gestation. Shortened and/or bent tails were observed in groups irradiated from days 7 to 11.5 of gestation (0.7–32.5%), with the peak frequency among those irradiated on day 9.25 of gestation.

Other animal studies support the observation of increased incidences of birth defects after exposure to ionizing radiation. Devi et al. (1994) exposed the whole abdominal region of pregnant Swiss mice (n=25) to 5–50 rad (0.05–0.5 Gy) of ^{60}Co gamma radiation (at a dose rate of 83 rad/min, 0.83 Gy/min) on postcoitus day 11.5. Increased fetal mortality and retarded growth was seen among the 50 rad (0.5 Gy) group. At this level, retarded growth was observed in 12% of fetuses, with body weight and body length decreased (7% and 3%, respectively). A significant reduction in head length, width, and brain weight was seen at 25 rad (0.25 Gy) and above. A significant increase in the incidence of microphthalmia was also observed at 25 rad (0.25 Gy) and above in 14% of fetuses. Zaman et al. (1992) also studied the effects of acute-duration prenatal radiation on myelination of the developing brain, as well as some physical parameters. Rats were treated with a single dose of gamma radiation (6.8, 15, or 150 rad, 0.068, 0.15, or 1.5 Gy) on the 20th day of pregnancy. At day 30, absolute brain, kidney, heart, and spleen weights of the 150 rad (1.5 Gy) treated group were significantly lower than that of any other treatment group. Relative brain, ovary, adrenal, kidney, liver, heart, spleen, and lung weights showed no significant differences among the lower treatment groups. At postnatal day 52, brain weight of the 150 rad (1.5 Gy) treated group was significantly lower than the other treatment groups and controls. No significant differences were seen in other organ weights at day 52. The relative weight of the cerebral cortex was significantly less than controls in the 150 and 15 rad (1.5 and 0.15 Gy) groups at day 30 and in the 150 rad (1.5 Gy) group on day 52 (9–11%). In addition, Reyners et al. (1992) evaluated the effects of radiation on fetal

brain development in pregnant Wistar rats exposed on gestation day (Gd) 15. Protracted gamma irradiation to total doses up to 80 rad (0.8 Gy) was performed with a ^{60}Co source. The dose rate varied from 1 rad/day to 13.3 rad/day (0.01–0.133 Gy/day). Exposure was carried out either from Gd 12 to 16 (4 days) or from Gd 14 to 20 (6 days). ^{60}Co gamma irradiation protracted over 4 days from Gd 12 to 16 significantly reduced the brain weight in 3-month-old rats by 3%, 4%, and 13% after 160, 350, and 560 rad (16, 35, and 56 Gy) exposures. Animals irradiated for 6 days from Gd 14 to 20 also showed a significant reduction in the 3-month-old brain weight of 5%, 4%, and 7% after exposures to 17, 34, and 80 rad (0.17, 0.34, and 0.8 Gy), respectively. The cingulum volume was also significantly decreased in the 80 rad group by 19%.

Dental and Oral Cavity Development. Ionizing radiation can also affect dental and oral cavity development. Lee et al. (1989) irradiated Beagle dogs *in utero* at 8, 28, or 55 days postcoitus or postnatally at 2, 70, or 365 days postpartum. Whole-body ^{60}Co gamma radiation doses ranged from 0 to 380 rad (3.8 rad). After a threshold effect dose of 83 rad (0.83 Gy), there was an age-dependent dose-related increase in premolar hypodontia for dogs irradiated at 55 days postcoitus or 2 days postpartum. Dogs irradiated at 55 days postcoitus were the most sensitive, with fewer than 20% having normal teeth at doses above 83 rad (0.83 Gy). After irradiation at 28 days postcoitus, no effect was seen below doses of 120 rad (1.2 Gy). Similarly, Saad et al. (1991) exposed pregnant CD-1 Swiss albino mice on the 12th gestational day to an external gamma radiation dose of 400 rad (4 Gy). All irradiated fetuses presented clefts of the secondary palate but usually not cleft lip. The development of the maxillary and mandibular incisors was retarded in irradiated fetuses and was in early bell stage, whereas controls had elaborated their matrices.

Fetal Blood Forming Organs. Significant doses of ionizing radiation can also affect the fetal blood-forming organs. Koshimoto et al. (1994) mated female Wistar rats, and on the 13th, 14th, or 15th day of gestation, and then externally irradiated them with 50–800 rad (0.5–8 Gy) of ^{137}Cs gamma radiation. Forty-eight hours later, the pregnant animals were sacrificed and the numbers of ovulations, implantations, and surviving fetuses were determined. Blood cell volume was measured, and fetal blood was collected. The numbers of erythrocytes and hepatocytes in the livers in the fetuses were counted. The number of blood cells in circulating blood after the fetuses were irradiated to 800 rad (8 Gy) on day 15 was significantly lower than the controls, and the formation of micronuclei was significantly increased at 50 rad (0.5 Gy) and above. The erythrocyte counts in the fetal liver were significantly lower than controls at 400 and 800 rad (4 and 8 Gy), and the ratio of the large hematocyte count to the small hematocyte count was significantly higher than controls at doses of 100 rad (1 Gy) and above.

Reproductive Tract. The *in utero* exposure to large doses of ionizing radiation can affect the forming reproductive tracts of male and female embryos. As an example, Inano et al. (1989) exposed pregnant rats to whole-body irradiation at Gd 20, with 260 rad (2.6 Gy) gamma rays from a ^{60}Co source. It was found that the seminiferous tubules of the irradiated male offspring were remarkably atrophied with free germinal epithelium and contained only Sertoli cells. Female offspring also had atrophied ovaries. The testicular and ovarian weight in irradiated offspring were 18% and 34%, respectively, of controls. No oocytes or Graafian follicles were found in ovaries of the irradiated rats. Testicular tissue obtained from control and ^{60}Co-irradiated rats was incubated with ^{14}C-labeled pregnenolone, progesterone, 17-alpha-hydroxyprogesterone, and androstenedione as a substrate. Intermediates for androgen production and catabolic metabolites were isolated after the incubation. The amounts of these metabolites produced by the irradiated testes were low in comparison with the control. The activities of delta[5]-3-beta-hydroxysteroid dehydrogenase, 17-alpha-hydroxylase, C(17, 20)-lyase, and delta[4]-5-alpha-reductase in the irradiated testes were 30–40% of those in nonirradiated testes. The activities of 17-beta- and 20-alpha-hydroxysteroid dehydrogenases were 72% and 52% of controls, respectively. The activity of delta[5]-3-beta-hydroxysteroid dehydrogenase of the irradiated ovary was only 19% of the control. The authors note that these results suggest that high-dose ^{60}Co irradiation of the fetus *in utero* markedly affects the production of steroid hormones in the testes, ovaries, and adrenal glands after birth.

Behavioral Alterations. Behavioral changes have also been noted in laboratory animals after birth when exposed to certain doses of ionizing radiation during the embryo stages of development. Minamisawa et al. (1992) investigated social behavior, in particular aggressive behavior (AB), in mice exposed prenatally to ionizing radiation. Pregnant C57BL/6 mice (n=3) were exposed to whole-body gamma radiation from a ^{137}Cs source on Gd 14. The dose rate to the midline of the mouse was 25 rad per minute (0.25 Gy/min) and doses of 0, 100, and 200 rad (0, 1, and 2 Gy) were given. AB in first-generation (F1) hybrid male offspring was studied. The number of instances of AB was significantly higher in the 100-rad (1 Gy) group than in controls during the first 45 minutes of observation. The AB of the 200-rad (2 Gy) group was significantly more intensive than that of the control group. There is little information in the literature with which to compare these findings.

In a similar study, Zaman et al. (1993) treated adult female Fischer 344 rats with a single dose of total-body gamma radiation (6.8, 15, or 150 rad [0.0068, 0.15, or 1.5 Gy]) on the 20th day of gestation (thus, the offspring received the radiation doses on the 20th day of prenatal life). During the 3 weeks of the offspring's postnatal life, changes in pivoting, crawling, negative geotaxis, cliff avoidance, hindlimb

support, eye opening, and tooth eruption were studied. Pups irradiated with 150 rad (1.5 Gy) exhibited significantly lower pivoting than any other group on days 15–16 of the observation period. No significant differences were observed between treatment groups for crawling, geotaxis, or hindlimb support when suspended. Cliff avoidance was recorded from days 3 to 10 postnatally. Cliff avoidance was significantly different in the 15 and 150 rad (0.15 and 1.5 Gy) groups compared to the 6.8 rad (0.068 Gy) group and controls on day 8 only; however, the mean score was not significantly different in the 15 rad (0.15 Gy) group. Data from this study suggest that radiation affects several of the tested locomotion parameters. Based on the data presented in this study, it appears that areas of cerebral cortex including the somatosensory and sensory cortex, the primary cortex, and the premotor cortex were adversely affected by doses of 150 rad (1.5 Gy) when delivered around gestation day 20.

Sensorimotor Effects. Norton and Kimler (1987) also investigated the early postnatal behaviors involving sensorimotor integration and the thickness of the sensorimotor cortex in prenatally irradiated rats which received a dose of 100 rad (1 Gy) from a ^{137}Cs source. Performance in the negative geotaxis test was poorer in irradiated rats than in controls. Rats irradiated on Gd 17 were unable to equal the performance of either controls or rats irradiated on Gd 11 in the reflex suspension test. No gait alterations were seen in the irradiated rats. In a later study, Norton and Kimler (1990) exposed pregnant Sprague-Dawley rats to whole-body gamma radiation from a ^{137}Cs source on Gd 15 to doses of 25, 50, 75, or 100 rad (0.25, 0.5, 0.75, 1.0 Gy). The fetuses of irradiated dams were examined 24 hours after irradiation for changes in the cells of the cerebral mantle of the developing brain. Changes were seen in those rats treated with 50 or more rad ($0.5 Gy). Cortical thickness of the cerebral mantle was not significantly altered. The number of pyknotic cells, the number of macrophages, the nuclear area, and the number of mitotic cells were altered in a dose-related way. The number of mitotic figures in the ventricular zone was significantly reduced and the number of macrophages was significantly increased in fetuses from the 50-, 75- and 100 rad (0.5, 0.75, and 1 Gy) treatment groups. The nuclear area in fetuses prenatally exposed to 100 rad (1 Gy) was significantly increased. In fetuses prenatally exposed to 50 rad (0.5 Gy), the nuclear area of subventricular zone cells was significantly increased compared to controls 12 hours postirradiation but returned to almost the control value at 24 hours postirradiation. The number of macrophages in the ventricle and in the cortical mantle was significantly increased at 12 and 24 hours in fetuses prenatally exposed to 50 rad (0.5 Gy). Several vesicles containing nuclear fragments were present in each macrophage at these times. The number of mitotic figures in the ventricular zones was significantly increased at 3 and 6 hours postexposure and significantly decreased at 12 and 24 hours postexposure in fetuses prenatally exposed to 50 rad (0.5 Gy) compared to controls. Pyknotic cells

developed rapidly after irradiation with 50 rad (0.5 Gy). At 3 hours postirradiation, the total number of pyknotic cells in the cortical mantle had increased from nearly 0 to 166. This number increased slightly from 3 to 6 hours and then declined from 12 to 24 hours. The number of pyknotic cells in the ventricular and subventricular zones decreased while the proportion in the intermediate and cortical plate zones increased. Both the percentage and number of pyknotic cells increased with time in the two latter zones. A positive correlation between the number of pyknotic cells and the number of macrophages developed with time. At 3 hours after irradiation, about 60% of pyknotic cells were found in the subventricular zone and about 25% in the intermediate zone and cortical plate. The number of such cells in the upper layers of the cortex steadily increased up to 24 hours, at which time about 70% of pyknotic cells were in these two layers.

In summary, the developing fetus, with its rapidly dividing cell characteristics, has been an area of intense study relating to the effects of radiation, particularly for large gamma radiation doses. Laboratory animal models have been used to delineate many of these effects. Radiation, above a threshold dose of about 25 rad (0.25 Gy) can impair development of embryonic structures, in particular the structures of the central nervous system when delivered during a sensitive period. Radiation affects specific cells of the developing nervous system at specific times during its developmental process, although the exact mechanisms behind these alterations are not known. Many of these reports include descriptions of decreased fetal body weights (Devi et al. 1994; Minamisawa et al. 1990; Norton and Kimler 1987; Zaman et al. 1992) and developmental anomalies, such as necrosis of neuroepithelial cells, microphthalmia, anophthalmia, scoliosis, decreased myelination of the brain, hypodontia, cleft palate, micromelia, ectrodactyly, polydactyly, as well as many more defects (Bruni et al. 1994; Kusama and Hasegawa 1993; Lee et al. 1989; Reyners et al. 1992; Saad et al. 1991; Zaman et al. 1992) at doses of <300 rad (3 Gy). Social behavior changes have also been reported in male mice at doses of 100 rad (1 Gy) and higher (Minamisawa et al. 1992). Locomotor difficulties have also been reported (Norton and Kimler 1987, 1988; Zaman et al. 1993) as well as reproductive organ anomalies (Inano et al. 1989). From these animal studies, it is clear that the developing embryo and fetus are subject to damage from radiation at doses greater than 25–50 rad (0.25– 0.5 Gy).

Data for developmental effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

3.2.1.5 Central Nervous System (CNS) Effects

As a whole, the central nervous system of the adult human and laboratory animal is extremely resistant to the effects of radiation (see Table 3-2). In contrast to the rapidly dividing cells of the gastrointestinal and hematopoietic systems, the central nervous system has a relatively static population of cells, with cell mitosis occurring between long intervals of latency, if at all. This allows cells to be exposed to much larger doses of radiation because the cells have much more time to repair themselves before they multiply. The brain appears to be sensitive to ionizing radiation only at extremely large doses; a dose of approximately 1,500 rad (1.5 Gy) was necessary to produce discernable deterministic effects. Necrosis of the brain (associated with demyelination and cerebral vascular damage) may occur within 3 years after a 5,500 rad (55 Gy) dose received over a 6-week time frame. Demyelination and necrosis of neurons in the white matter of the spinal cord can also develop within 6 months after exposure to high doses (>6,000 rad or 60 Gy) of radiation. These are very large doses of radiation.

Birioukov et al. (1993) reported that one man exposed to 200–350 rad (2–3.5 Gy) had clinical symptoms such as permanent headache and vision impairment after accidental exposure to gamma radiation during and after the Chernobyl atomic power plant accident. Reports are available that describe the effects that radiation has on the nervous system of the developing embryo in laboratory animals (Minamisawa et al. 1992; Norton and Kimler 1987, 1990). Harmful effects have been found from extremely high doses of radiation to adult animals. Cockerham et al. (1986) explored the effects of radiation on early transient incapacitation (ETI) and performance decrement (PD) in support of nuclear warfare research efforts. Rhesus monkeys (n=6) were exposed to a lethal whole-body total dose of 10,000 rad (1,000 Gy) from a ^{60}Co source. Autopsy findings included destroyed nerve cells (neurons), supporting tissue in the brain (glial cells), and lining cells (endothelium) of the capillaries in the brain.

Bassant and Court (1978) exposed rabbits to a ^{60}Co gamma ray source, with a mean absorbed dose of 450 rad (4.5 Gy). According to the authors, the $LD_{50/30}$ for rabbits ranges from 600 to 650 rad (6–6.5 Gy). Following irradiation, the hippocampal cellular activity was highly disturbed, as described by the EEG activity.

Data for neurological effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

3.2.1.6 Respiratory and Cardiovascular Effects

The respiratory tract has long been known to be a target organ of both internal and external radiation. Respiratory effects have been reported in humans (Stavem et al. 1985) who had received radiotherapy for breast cancer and those who had been accidentally overexposed, as well as in laboratory animals (Rezvani et al. 1989; Salovsky and Shopova 1992). No harmful effects have been seen in the millions of people who receive occasional diagnostic x rays of the chest. Local injury is tolerated much more than diffuse injuries. Irradiation of large portions of one or both lungs initially results in alterations in blood flow, initially manifested as edema, and later as pneumonitis and pulmonary fibrosis, depending on the total dose received. Radiation pneumonitis, followed by pulmonary fibrosis (i.e., fibrosis of alveolar structures involving changes in the ratios of some pulmonary collagens), are two of the most commonly reported aberrations in laboratory animals following an inhalation of large activities of radioactive material (Benjamin et al. 1978, 1979; Brooks et al. 1992; Hahn et al. 1975, 1981; Lundgren et al. 1980a, 1991).

The mechanism behind the induction of radiation pneumonitis is not completely understood; however, a vascular component (comprised of sloughing and of dead and dying endothelial cells that may lead to capillary leakage) has been suggested. Damage to type II pneumocytes, which can lead to serious alterations in the amount of surfactant phospholipids and to lung inflammation, has also been considered. The role of type I pneumocytes, which by necrosing and sloughing leave denuded basement membranes and alveolar debris, may also be significant. Any one or all of these mechanisms may be involved in the development of pneumonitis. Fibrosis, a serious sequela of pulmonary inflammation due to large populations of cells dying and not being replaced, is seen in the lungs after exposure to ionizing radiation at moderate to high doses or to fibrogenic dusts, such as quartz and asbestos or even aluminum (ATSDR 1999a). A more in-depth discussion of radiation pneumonitis and subsequent fibrosis after exposure to ionizing radiation is available in a report by Coggle et al. (1986).

Most respiratory studies have focused on the effects of ionizing radiation on the lungs when associated with inhaled insoluble (and, to a lesser degree, soluble) particles. Most of these studies looked at acute inhalations of large quantities of radioactive material resulting in high initial lung burdens and cumulative radiation doses on the order of hundreds of rad (several Gy). After the radioactive material was inhaled, clinical signs were related to the organ system which received the major radiation dose during and after redistribution of these particles had occurred. Important aspects of this redistribution related to whether these radionuclides were in a soluble or insoluble form and to the size of the inhaled particle. Soluble

particles tended to dissolve in the lung matrix and redistribute based on chemical mechanisms; then they had the potential to affect other organ systems. These soluble particles tended to deliver a higher dose rate to the lungs shortly after inhalation; the rate tended to decrease rapidly as the material was dissolved and the radionuclide redistributed to other organs via the normal lung clearance mechanisms. Soluble particles deposited in the respiratory tract tended to result in lower overall lung dose and higher overall distal organ dose over time when compared to insoluble particles because they exposed the lung tissue for a shorter period of time.

Unlike the soluble particles, the bulk of the inhaled insoluble particles tended to remain for long periods of time in the lungs (several days to several years), irradiating the tissues and depositing large radiation doses to the tissue immediately around the particles. Some fraction of these particles would initially be coughed up or removed by the ciliary clearance mechanism and then swallowed during the first few days after exposure, thereby exposing the gastrointestinal tract as the particles passed through and cleared the body. In addition, smaller particles (1–3 μm) tended to penetrate to the deeper regions of the lungs (terminal bronchioles and alveoli); larger (>6 μm) particles were deposited in the upper respiratory tract (trachea, conducting airways). The effect of inhaled radioactive particles, therefore, varied with the size distribution and solubility of the inhaled particles, as well as the type and quantity of the inhaled radioactivity.

Respiratory insufficiency was a common finding in many studies following high radiation doses to the lungs. This was manifested clinically as increased respiratory rates, increased abnormal lung sounds and cyanosis, decreased lung volumes, and total lung capacity, and compliance (common but not pathoneumonic symptoms of pneumonia). These clinical symptoms were most likely related to inflammatory and fibrotic changes occurring within the lungs. This observation is supported by radiographic, gross, and histopathological evidence, such as increased radiographic focal or diffuse lung-field densities, and by interstitial, perivascular, peribronchial, and pleural fibrosis; emphysema; inflammation; vascular damage; fibrin exudation; congestion; and hemorrhage (Benjamin et al. 1976; Hahn et al. 1976; Lundgren et al. 1991).

Numerous assessments of human exposure to inhaled radionuclides (with no dermal or oral component) have been identified in the open literature. A group of 26 workers inhaled quantities of ^{239}Pu dust that were many times larger than acceptable occupational standards. These workers have been followed medically since the inhalation in 1944. To date, one person has died from heart disease and one from bone cancer. Another report involved a U.S. military airplane crash near Palomares, Spain, in January

1966. The aircraft was carrying four thermonuclear weapons containing ^{239}Pu. Two of the devices were recovered, and the other two devices detonated their conventional explosives and released fissile material upon ground impact. Partial ignition (chemical burning) of the fissile material resulted in a cloud formation that contaminated approximately 2.25 km^2 of farmland. The deposition density of alpha emitters was 32.4 μCi/m^2 (1.2 MBq/m^2); estimates of the inhaled and ingested dose from ^{239}Pu and ^{240}Pu were derived. Of the 714 people examined through 1988, 124 had urine concentrations of Pu greater than the minimum detection limits. An estimate from Iranzo et al. (1987) states that the 70-year committed effective dose for 55 of those 124 people, due to inhalation of radioactive particles, was 2–20 rem (0.02–0.2 Sv); however, no acute respiratory effects were reported and there has apparently been no long-term follow-up of these individuals.

There is a considerable database available on the effects seen from inhaled radionuclides in laboratory animals. For example, Hobbs et al. (1972) exposed Beagle dogs to initial lung burdens of 3,600, 1,800, 1,200, 780, 400, 210, and 110 μCi (133, 67, 44, 29, 15.8, and 4 MBq) ^{90}Y/kg body weight. The AMADs of the aerosols used ranged from 0.8 to 1.2 μm. Death was reported in 21 of 33 dogs exposed within 7.5 and 163 days postexposure, with their initial lung burdens ranging from 670 to 5,200 μCi/kg causing cumulative radiation doses through time of death of 8,400 to 55,000 rad (84–550 Gy). Clinical signs in the dogs that died included progressive increase of respiratory rates, abnormal lung sounds on auscultation, anorexia, progressive weight loss, and eventual cyanosis of the mucous membrane. Additionally, thoracic radiographs showed marked, generally diffuse nodular increases in density of lung fields. The authors note that clinical signs did not differ from high to low doses; however, the time to the onset and the duration of the illness varied considerably. A dose response could be demonstrated with these exposures: “acute symptoms” occurring 7–10 days after inhalation, with initial lung burdens of 1,700–5,200 μCi/kg (62–190 MBq/kg) and doses to the lungs of 21,000–55,000 rad (210–550 Gy); “subacute symptoms” with signs of respiratory insufficiency 3–4 weeks postexposure, initial lung burdens of 1,000–2,400 μCi/kg (37–89 MBq/kg) and doses to the lungs of 13,000–29,000 rad (130–290 Gy); “subacute to chronic symptoms” appearing at 6–8 weeks, which included a gradual deterioration in the animals' condition. Animals in this group had initial lung burdens of 670–760 μCi/kg (25–28 MBq/kg) and cumulative radiation doses to the lungs of 8,400–9,400 rad (84–94 Gy). Pathological findings at necropsy included pulmonary and pleural fibrosis, occlusive pulmonary vascular lesions, metaplasia and/or hyperplasia of terminal bronchiole and alveolar epithelium, right heart dilation, and hypertrophy. Small indurated hemorrhagic areas near the ventricular junction were present in the right atria of the hearts of 7 of the 12 dogs that died 64–92 days postexposure. Infarctions of the right atria were found in some animals.

Similarly, Muggenburg et al. (1988) exposed 216 Beagle dogs by inhalation to initial lung burdens of 3–54 μCi (0.1–2 MBq) ^{239}Pu/kg monodisperse $^{239}PuO_2$ aerosols with AMADs of 0.75, 1.5, or 3.0 μm, which produced a protracted alpha irradiation dose to the lungs. From the group of 78 dogs which survived to 7.1 years post-inhalation, 20 were selected for cardiorespiratory function tests and further clinical evaluation. Of these 20 dogs, 10 were selected because they had persistent respiratory frequencies of 40 breaths/min for more than 1 year (group I). The second 10 dogs were selected because they had similar or slightly lower plutonium lung burdens at the time of inhalation as the dogs in group I, but had normal respiratory frequencies (group II). Ten controls were used (group III). The average dose to the lungs through 2,600 days after inhalation for the dogs in group I ranged from 230 to 3,200 rad (2.3 to 32 Gy) and for the dogs in group II, from 80 to 1,570 rad (0.8 to 15.7 Gy). Respiratory tract injury was again first observed as an increased respiratory frequency on average 3.4 years after inhalation; this change in breathing pattern persisted for at least 1 year. Only the dogs in group I with signs of lung injury had a mild respiratory function disorder consisting of smaller lung volumes, decreased total lung capacity, vital capacity, functional residual capacity, reduced dynamic and quasistatic compliance, and increased respiratory frequency and minute volume. Carbon monoxide diffusing capacity was significantly reduced in both groups I and II. These findings indicate that alpha irradiation of the lungs of humans could produce restrictive lung disease at long times after initial inhalation.

In addition to alterations in respiratory rates and respiratory function, pneumonitis and pulmonary fibrosis are two of the most commonly reported respiratory effects in animals (and humans) after lung exposure to large activities of inhaled radionuclides (Coggle et al. 1986). Hahn et al. (1975) studied the radiation dose of ^{90}Y to the upper respiratory tract in Beagles exposed by nose-only inhalation to aerosols of ^{90}Y in fused clay. Initial whole-body burdens ranged from 23 to 65 mCi (850–2,400 MBq), with initial lung burdens ranging from 9 to 35 mCi (520–1,300 MBq). A rapid initial decrease in body burden, typical of an insoluble material deposited by inhalation, was due to the clearance of particles from the upper respiratory tract entering the gastrointestinal tract. Of the 7 dogs surviving 27–29 days, 6 dogs exposed to 14–35 mCi initial lung burden developed radiation pneumonitis. Radiation pneumonitis was characterized by accumulations of alveolar macrophages, bizarre alveolar lining cells, and alveolar hemorrhage; vasculitis was the most consistent histopathologic finding. Benjamin et al. (1976) exposed 6 Beagle dogs to a nose-only inhalation of ^{90}Y, ^{144}Ce, or ^{90}Sr in fused aluminosilicate particles (FAP). The initial lung burdens were 560, 46, and 28 μCi/kg (21, 1.7, and 1 MBq/kg) for ^{90}Y, ^{144}Ce, and ^{90}Sr, respectively. Deterioration in the health of the dogs exposed to ^{90}Sr included an increased respiratory rate, dyspnea, cyanosis, and dry and moist rales. Increased radiographic focal or diffuse lung-field

densities, with clear evidence of ventricular enlargement, was apparent. The lungs of dogs exposed to ^{90}Y and ^{144}Ce showed radiation pneumonitis characterized by interstitial, perivascular, peribronchial, and pleural fibrosis, focal emphysema, and acute and chronic inflammation with increased numbers of alveolar macrophages. Vascular damage included congestion, hemorrhage, fibrin exudation, and occasional vessels with fibrinoid necrosis or proliferation. Epithelial changes included denudation of terminal bronchioles and alveolar ducts, with regeneration of bizarre lining cells and proliferation of bizarre, hypertrophied alveolar lining cells. Adenomatous epithelial proliferation and squamous metaplasia were common findings in the ^{90}Y dogs.

Later, Benjamin et al. (1978) again exposed Beagles to ^{144}Ce in FAP by nose-only inhalation using particle sizes 1.4–2.7 μm. Initial lung burden ranges were around 25–35 μCi/kg body weight in dogs sacrificed or those that died between 1.4 and 4.1 years postexposure. The cumulative absorbed lung doses to death for these groups of dogs ranged from 27,000 to 47,000 rad (270–470 Gy). Dogs were sacrificed at half- to full-year intervals from 1.5 to 4 years. By 2 years after exposure, more than 90% of the radiation dose had been delivered. Beyond that time, radiation pneumonitis and pulmonary fibrosis were evident in approximately 80% of the dogs. Other reports of radiation pneumonitis and/or pulmonary fibrosis have been described in dogs (Benjamin et al. 1979; Hahn et al. 1976), monkeys (Brooks et al. 1992; Hahn et al. 1987; LaBauve et al. 1980), mice (Lundgren et al. 1980a, 1981, 1991), and hamsters (Lundgren et al. 1983).

Some laboratory animal studies were found that dealt with the effects of external radiation on the respiratory tract. In one study, Rezvani et al. (1989) determined the effects of external radiation on the diaphragmatic lobe of the left lung in female large white pigs irradiated with single doses of 900–1,470 rad (9–14.7 Gy) of ^{60}Co gamma rays at a dose rate of 80 rad/min (0.8 Gy/min). Standard lung function tests were performed prior to irradiation and at 4 and 13 weeks after irradiation, then at 13 week intervals up to 104 weeks. At 104 weeks after irradiation, the animals were sacrificed and the lungs were excised and examined for gross changes. A marked impairment in the ventilation capacity of the lungs 4 weeks after irradiation was seen, but was not considered to be dose-dependent. After a dose of 900 rad (9 Gy), the initial impairment in lung function was resolved within 13 weeks, while at 1,470 rad (14.7 Gy) damage persisted. There was an elevation in the breathing rate at 4 weeks after irradiation, which was most marked in animals irradiated with the highest doses; however, the breathing rate returned to normal within 13 weeks at all dose levels. At 104 weeks after irradiation, postmortem examination revealed only one case of adhesion between the lung and chest wall. In animals irradiated with $1,090 rad (10.9 Gy), atrophy of the irradiated left lobe of the left lung was seen. This was particularly

characteristic in all lungs irradiated with 1,470 rad (14.7 Gy) in which the lungs showed severe atrophy. At 1,280 rad (12.8 Gy), a general and severe thickening of the interlobular septa was seen in some animals. The authors calculated a 50% effective dose (ED_{50}) value for pathological changes (fibrosis and focal scarring) in the lungs of 1,112 rad (11 Gy).

With regard to external exposure to radiation, Salovsky and Shopova (1992) exposed male Wistar rats to 0, 400, 800, or 1,500 rad in a single whole-body dose in order to study the changes present in broncheo-alveolar tissue after exposure to ionizing radiation. Eight animals of each group were sacrificed on days 1, 5, and 15. Prior to sacrifice, a broncheoalveolar lavage was performed. The lavage fluid was analyzed for lactase dehydrogenase (LDH), alkaline phosphatase (APH), acid phosphatase (AcPH), angiotensin converting enzyme (ACE), and protein content. LDH activity was decreased on day 1 in the 1,500 rad (15 Gy) group. At day 5, the 400 and 800 rad (4 and 8 Gy) groups LDH levels were significantly decreased by 30% and 49%, respectively. No significant difference was observed at day 15. Both APH (31–41%) and AcPH (40–67%) were significantly decreased on day 1 in all irradiated groups. In the 800 rad (8 Gy) group, APH was significantly increased on day 15 (203%). ACE activity was examined only on day 1, with a significant increase in ACE in the 800 rad (8 Gy) (190%) and 1,500 rad (15 Gy) (187%) groups. Protein content decreased significantly only in the 1,500 rad (15 Gy) group, measured only on day 1. ACE is normally bound to lung endothelial cell surfaces, with increased concentrations suggesting endothelial cell injury. Increased protein content in the broncheoalveolar lavage fluid (BALF) indicates vascular permeability changes due to adverse events in the endothelial cells lining the capillaries. LDH, APH, and AcPH are normally intracellular enzymes, and their release into the extracellular domain indicates lung cellular membrane damage. From these data, it appears that LDH decrease may provide a non-specific biomarker of exposure to ionizing radiation at 1 week after exposure has occurred, whereas APH increase would be a non-specific biomarker of exposure at 2 weeks after exposure, to higher doses of ionizing radiation.

No harmful radiation effects on the heart have been seen at dose levels below hundreds of rad (tens of Gy). However, cardiovascular effects have been reported after exposure to inhaled radioactive material that led to very high radiation doses to the heart. The study described earlier by Muggenburg et al. (1988) noted no abnormal cardiac function parameters in any of the dogs studied; however, Hobbs et al. (1972) reported cardiac lesions in 33 Beagle dogs exposed in groups to mean initial lung burdens of 3,600, 1,800, 1,200, 780, 400, 210, and 110, μCi (133, 67, 44, 29, 15, 8, and 4 MBq) of ^{90}Y/kg body weight. Electrocardiogram changes, consistent with the right heart enlargement and/or conduction defect, were

observed in 5 of the animals that died 64–92 days postexposure after receiving a dose of 8,400 rad (84 Gy). Pathological cardiac findings included right heart dilation and hypertrophy. Small indurated hemorrhagic areas near the ventricular junction were present in the right atria of the hearts of 7 of the 12 dogs that died 64–92 days postexposure. Infarcts of the right atria were also found in some animals. ECG changes occurred in 5 of 12 and hemorrhagic areas were found near the ventricular junction in the right atria of 7 of 12 dogs that died 64–92 days after exposure.

Durakovic (1986a) studied cardiac function in male Beagle dogs that received 3,000, 6,000, or 10,000 rad (30, 60, or 100 Gy) of gamma radiation applied bilaterally to the precordium. The electrocardiograms remained normal after irradiation at all dose levels. The atrium, right and left ventricle, and papillary muscle of every dog all showed focal areas of perivasculitis. No evidence of focal necrosis was observed. The left ventricular ejection fraction (LVEF) did not show statistically significant decreases until 58–70 days after the irradiation, when a marked impairment of heart function was finally observed.

With regard to cardiovascular effects and external exposure to ionizing radiation, Stavem et al. (1985) reported a case of a 64-year-old male worker who accidentally received a large dose of gamma radiation in a facility that used ionizing radiation for sterilization. He was exposed for only a few minutes. From spectroscopic analyses of electron-spin resonance in irradiated material, the following mean doses were estimated: whole body, 2,250 rad (22.5 Gy); bone marrow, 2,100 rad (21 Gy); and brain, 1,400 rad (14 Gy). The dose to nitroglycerin tablets that were in the worker's pocket at the time was 4,000 rad (40 Gy). The worker developed an ARS and an autopsy was performed after death. The left ventricle of the heart was hypertrophic and the anterior descending ramus of the coronary artery was markedly stenotic; however, it was not clear whether this was an age-related effect or directly related to the effects of the radiation since much larger doses to animals are needed to produce such effects.

In summary, respiratory effects have been reported in humans (Stavem et al. 1985) as well as in laboratory animals (Rezvani et al. 1989; Salovsky and Shopova 1992) exposed to very high doses from internal and external sources of radiation because the respiratory system appears to be resistant to high doses of radiation. Most research has focused on radiation effects on the lungs when associated with inhaled insoluble (and, to a lesser degree, soluble) particles. These studies were acute, high-dose exposures resulting in high initial lung burdens on the order of several millicuries (tens of thousands of Bq), which resulted in cumulative doses in the thousands of rad (tens of Gy). After the radioactive material was inhaled, clinical signs were related to the organ system that received the major radiation

dose. Soluble particles dissolved in the lung and redistributed, depending on the radionuclide, to the liver or bone to induce toxic effects in those organ systems. After an initial clearance phase from the lungs, from which a portion of the initial lung burden was transferred to the gastrointestinal tract, the balance of the insoluble particles remained for long periods of time in the lung (days to years), irradiating the tissues closest to their immediate lung location and leaving the lungs very slowly. The effect of ionizing radiation on the lungs varied with the dose and length of exposure of the lung tissue. Respiratory insufficiency, manifested clinically as increased respiratory rates, increased abnormal lung sounds, and cyanosis, was a common finding in these studies (Hobbs et al. 1972; Muggenburg et al. 1988), in association with decreased lung volumes, total lung capacity, and compliance (common but not pathognomonic of pneumonia) (Muggenburg et al. 1988). These clinical signs are most likely related to inflammatory and fibrotic changes occurring within the lungs. This observation is supported by radiographic, gross, and histopathological evidence, such as increased focal or diffuse radiographic lung-field densities, and by interstitial, perivascular, peribronchial, and pleural fibrosis; emphysema; inflammation; vascular damage; fibrin exudation; congestion; and hemorrhage (Benjamin et al. 1976; Hahn et al. 1976; Lundgren et al. 1991). Radiation pneumonitis, followed by pulmonary fibrosis (fibrosis of alveolar structures involving changes in the ratios of some pulmonary collagens), are two of the most commonly reported aberrations in laboratory animals following the inhalation of radioactive substances (Benjamin et al. 1978, 1979; Brooks et al. 1992; Hahn et al. 1975, 1981; Lundgren et al. 1980a, 1991). Radiation pneumonitis is characterized by sloughing of dead and dying endothelial cells that may lead to capillary leakage. Damage to type II pneumocytes, which can lead to serious alterations in the amount of surfactant phospholipids and lung inflammation, has also been considered. The role of type I pneumocytes, that by necrosing and sloughing leave denuded basement membranes and alveolar debris, may also be significant. Alterations in cardiovascular functions could not be definitively linked to ionizing radiation after inhalation or external ionizing radiation exposures in laboratory animals (Durakovic 1986a; Hobbs et al. 1972; Muggenburg et al. 1988) or in one man exposed to external ionizing radiation (Stavem et al. 1985); however, some changes in regional cerebral blood flow were noted in one study (Cockerham et al. 1986) that used Rhesus monkeys as a model and these were probably linked to histamine release. However, all of these effects are due to very high radiation doses, which are extremely unlikely at radioactive waste sites.

Data for respiratory and cardiovascular effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

3.2.1.7 Ocular Effects

The lens of the eye is not among the most radiosensitive tissues in the body, but it has less efficient repair capabilities than many other tissues. This allows radiation damage to build up with less repair, even when doses are fractionated or delivered at low dose rates. Exposure of the lens to sufficient doses of ionizing radiation results in cataract formation, which can range from minimally detectable opacities that do not impair vision to blindness. The target cells in the lens are the epithelial cells on the interior surface of the anterior capsule of the lens. These cells differentiate into lens fibers, which are normally transparent. The function of the lens is to focus the light entering the pupil onto the retina. After exposure to ionizing radiation, these cells fail to divide to produce lens fibers of the appropriate length or transparency. These defective fibers then tend to migrate to the posterior pole of the lens, where they can be seen ophthalmologically as a small, opaque dot. The appearance of the opacities can appear anytime between 0.5 and 35 years postexposure. Occurrence is affected by the dose, dose rate, and the type and energy of the radiation. Cataracts can be induced with as little as 2 Gy (200 Gy) of x ray irradiation (Adams and Wilson 1993). Data from those victims exposed to large doses of ionizing radiation after the bombings of Hiroshima and Nagasaki show a threshold of 0.6–1.5 Gy (60-150 rad) of low LET radiation. However, typical human exposures over a long period of time are thought to have a vision impairing threshold greater than 8 Gy (800 rad) (BEIR V 1990).

The effects of ionizing radiation on the eye have been reported in some human exposure cases. Ham (1953) described the radiogenic cataracts in cyclotron physicists from mixed gamma-neutron doses of 700–1,000 rad (70–100 Gy) to the lens. Klener et al. (1986) reported on a human case study in which a male technician was accidentally irradiated by a sealed ^{60}Co source he had been installing. His health status was followed for 11 years after the accident. A film dosimeter worn during the accident indicated it received an exposure of 159 rad (1.59 Gy), but the dose to his eye was not reported. Changes in the lens of the left eye began to appear gradually, leading to the deterioration of visual acuity. Later, opacities of the lens of the right eye were also found.

Schweitzer et al. (1987) exposed Beagle dogs to single, bilateral, whole-body exposures to ^{60}Co gamma radiation at various stages during fetal ocular development. Dogs were irradiated during middle or late pregnancy at 28 or 55 days postcoitus (dpc) or as neonates on the second postpartum day (ppd), with mean whole-body doses ranging from 100 to 386 rad (1–3.86 Gy). The dose to the eyes was essentially equivalent to the whole-body dose. For dogs exposed on ppd 2, the most prominent fundic alteration on

or before 70 days of age was a reduction in arterioles and a narrowing of the venules. The venules were dull, the tapetal fundus mottled in appearance, the nontapetal fundus lighter in color than controls, the optic disc paler, and the eyes characterized by a generalized slight haziness of the ocular media. Dogs sacrificed at 2–4 years of age had more marked reductions in arterioles and attenuation of the venules. Hyperreflectivity from the eye was found, and homogeneity was often lost in affected eyes. General and focal degenerative lesions were evident as were color changes. Partial tapetal atrophy with increased pigmentation in the area previously occupied by tapetum was noted in some eyes. Loss of color and hyperreflectivity were related to focal loss of pigment and thinning of atrophic retinal foci. With severe retinal atrophy or degeneration, choroidal circulation was seen in the nontapetal fundus. Retinal lesions were progressive in severity and extent, and the degree of injury was similar for both eyes. A correlation was seen between lesions (mostly in the retina and lens) and radiation treatment, with respect to both age at exposure and radiation dose. Due to fixation and sectioning artifacts, most lenses couldn't be adequately evaluated histopathologically. Retinal dysplasias and atrophy were the most striking lesions seen. The stage of development at exposure had a marked effect on the distribution of retinal lesions. The most severe changes were seen in the portion of the retina undergoing differentiation at the time of the insult. In dogs sacrificed at 70 days of age, the lesions were primarily dysplasias, consisting of ectopic nuclear aggregates in the photoreceptor layer, retinal folds, and retinal rosettes. With increasing age, there appeared to be progression of the extent of the clinically evident lesions, and there was a change in the nature of the lesions from dysplasia to atrophy. This was accompanied by marked attenuation of the retinal vasculature. In dogs exposed on ppd 2, retinal degeneration was evident in all dogs sacrificed at 70 days, 2 years, or 4 years of age. Retinal dysplasias were evident in all dogs sacrificed at 70 days of age and in 4 of the 13 dogs sacrificed at 2 years. Retinal dysplasia was not evident in dogs sacrificed at 4 years. Atrophy in dogs exposed on ppd 2 was evident in 19 of the 20 dogs sacrificed at 70 days of age and in all dogs sacrificed at 2 and 4 years of age. Dysplasias included focal aggregates of nuclei in the rod and cone layer, retinal folds, and retinal rosettes. Atrophic changes included altered rosettes, as well as the rest of the retina, loss of rods and cones, and/or thinning of inner and outer nuclear layers. These lesions were bilateral and focal-to-diffuse in nature. They increased in severity with increasing radiation dose. In dogs exposed on ppd 2, central retinal lesions only were seen in 1 of the 20 dogs sacrificed at 70 days of age. No lesions were seen in dogs sacrificed at 2 or 4 years. Central and peripheral retinal lesions were seen in 19 of the 20 dogs and in all dogs sacrificed at 70 days and at 2 or 4 years, respectively.

In summary, ocular effects have been reported in both humans and laboratory animals after radiation doses exceeding 0.6 Gy (60 rad). These effects range from mild opacities of the lens to cataract formation

and alterations in both the posterior chamber of the eye and of the retinal structures. The effects are not immediate, and in people may occur several years after the initial exposure.

3.2.1.8 Dermal Effects

Clinically observable dermal radiation effects ranging from erythema (skin reddening) to necrosis have been observed following external beta, gamma and x ray exposure above threshold doses at high dose rates. A transient erythema, the earliest sign of overexposure of the skin, occurs after a dose of about 300 rad (3 Gy), and was once used by physicians to calibrate x ray machines. The erythema appears several hours after exposure, and disappears within a day. Much greater radiation doses lead to a second erythema several weeks later, which lasts for about a month. Greater doses lead to loss of hair, peeling of the skin (dry desquamation), blistering (wet desquamation), ulceration, and necrosis (Potten 1985). The USNRC limit for occupational exposure of the skin is 50 rem (0.5 Sv) per year is protective for such effects. The skin has a susceptible cell population sensitive to the effects of ionizing radiation. The target cells are those comprising the germinal cells of the skin (stratum germinativum), also known as the basal cell layer, which is itself affected by the thickness of the various skin layers of the epidermis. Normally, the basal cells give rise to the outer layers of the skin (stratum granulosum, stratum lucidum, etc.) and finally form the outmost protective dead layer of the skin, the stratum corneum.

Radiation effects on the skin are proportional to the dose received by this germinal cell layer and to the type of radiation received. Alpha particles with energies greater than 7.5 MeV (8.8 MeV ^{212}Po in the ^{232}Th series, 8.8 MeV ^{213}Po in the ^{241}Pu series, 7.7 MeV ^{214}Po in the ^{238}U series and possibly 7.4 MeV ^{215}Po in the ^{235}U series) can penetrate the stratum corneum; therefore, there could be an alpha skin dose in these situations, but much of their energy will be expended in the epidermis, leaving only a small portion for dermal exposure. In general, alpha particles with energies less than 7.5 MeV that deposit on the skin surface (stratum corneum) have little effect, given the short penetration range of this type of radiation. The bulk of the dose is absorbed by the stratum corneum, comprised of dead cells, phospholipids, waxes, and other large complex molecules (Riviere and Spoo 1995). Beta and gamma radiation, which can penetrate deeper to live cell layers, can produce erythema, indicating a vascular component manifested by vasodilation and probably mediated by histamine or other inflammatory mediators. As the dose increases, epilation, dry and/or moist desquamation, and necrosis can occur. The threshold dose of gamma radiation in humans required to produce skin erythema over an area of 10 cm^2 is 600–800 rad (6–8 Gy) for single doses and 3,000 rad (30 Gy) for multiple (fractionated) doses (Adams and Wilson 1993). The threshold

dose increases with decreasing area of the irradiated skin. The dermis is less severely affected, given its population of less active cells, connective tissue, sebaceous glands, and nerve fibers. However, the endothelial cells associated with the dermal blood vessels are somewhat more susceptible and may play a role in the production of erythema after receiving doses of ionizing radiation. The long-term effects on the skin after receiving over 1,000 rad (10 Gy) of ionizing radiation include pigmentation, epidermal atrophy, dermal fibrosis, and atrophy of several dermal and epidermal structures, such as sweat and sebaceous glands and hair follicles.

Hahn et al. (1975) reported the effects of ionizing radiation on the skin of Beagle dogs after inhalation exposure to ^{90}Y in FAP. Four of the 7 dogs exposed to 14–22 mCi (520–814 MBq) initial lung burden (32–40 mCi [1,200–1,500 MBq] whole-body burden) developed a nasal dermatitis. Hobbs et al. (1972) exposed 33 Beagle dogs to initial lung burdens of 3,600, 1,800, 1,200, 780, 400, 210, 110, and 0 μCi (133, 67, 44, 29, 15, 8, 4, and 0 MBq) ^{90}Y/kg body weight. Patches of radiation alopecia were found on the dorsum of the nose of four animals that died 70–91 days postexposure. These patches were characterized by a thinning of the outer epidermal layer of the skin, atrophy, and loss of hair follicles and hair shafts. Dermal collagen seemed unaffected. Nasal dermatitis, however, is unlikely to occur in humans for two reasons: (1) these animals were exposed to very high activities of ^{90}Y that are essentially out of the realm of possibility for humans, and (2) these effects are likely to occur in animals with long snouts or muzzles.

Syrian golden (23) and white (24) hamsters (8 weeks of age) were exposed to a ^{85}Kr source that was in direct contact with the skin. Skin-absorbed doses ranged from 2,000 to 10,000 rad (20–100 Gy) and were delivered at the rate of 495 rad/min (4.95 Gy/min). Within 24 hours after radiation, erythematous reactions developed and persisted for several days postexposure. At sites where larger doses were applied, severe radiation dermatitis developed and sometimes resulted in ulcerative changes in the epidermis. Permanent epilation resulted at doses of 10,000 rad (100 Gy), and doses of 4,000 rad (40 Gy) induced temporary epilation up to the 17th week in all males and most of the females. Growth of grey hair was subsequently observed in the exposed areas of all animals in the 4,000 rad (40 Gy) dose group. Females receiving 2,000 rad (20 Gy) showed about 12 weeks of epilation followed by growth of grey hair in most of them. Some males showed epilation for a short period of time, and the rest of the males showed initial and transient periods of epilation followed by growth of normal hair. Complete epilation occurred in white hamsters receiving 4,000 and 10,000 rad (40 and 100 Gy) and recuperation of hair growth in these animals was not observed. A short period of epilation was observed, followed by growth

of normal hair in animals exposed at the 2,000-rad (20 Gy) level. Few animals showed complete epilation preceded or interrupted by periods of growth of normal hair. No spreading of the hair-greying effect of beta particles was observed in this experiment (Garcia and Shubik 1971).

Similar results were found in pigs, whose skin is considered to be most like that of humans. Hopewell et al. (1986) studied the dose-effect relationship as a function of an irradiated area of the skin by irradiating an area of skin in 3–4 month old large white pigs with ^{90}Sr, ^{170}Tm, or ^{147}Pm disk sources of different diameters. These radionuclides emit beta particles with energies of 0.55, 0.97, and 0.22 MeV that can penetrate 2, 4, and 0.5 mm of tissue, respectively, compared with 0.007 mm for the stratum corneum. The diameter of the sources varied from 1 to 40 mm for ^{90}Sr, from 0.1 to 19 mm for ^{170}Tm, and from 2 to 15 mm for ^{147}Pm. In the porcine model, the ED_{50} values for moist desquamation for ^{90}Sr varied from 2,750 rad (27.5 Gy) for the 22.5-mm diameter source to 7,500 rad (75 Gy) for the 5-mm source. An increase in source diameter to 40 mm did not significantly change the ED_{50} value from that obtained with a 22.5-mm source. ^{170}Tm irradiation in the pig produced no distinct area effect for sources 5–19 mm in diameter (ED_{50} for moist desquamation ~8,000 rad [~80 Gy]). Acute tissue necrosis was only achieved in pig skin by very high doses (ED_{50} $14,000 rad [$140 Gy]) from sources #2 mm in diameter. Irradiation of pig skin with ^{147}Pm produced acute epithelial breakdown but only after high skin-surface doses (ED_{50} 55,000–72,500 rad [550–725 Gy] for 15–2 mm sources). In a similar experiment, Hopewell et al. (1986) exposed SAS/4 randomly-bred male mice, 11–12 weeks old to ^{90}Sr, ^{170}Tm, and ^{147}Pm, again with the sources varying in diameter. ^{90}Sr and ^{170}Tm exposure in the mouse resulted in a distinct field-size effect for sources 5–22.5 mm in diameter; the ED_{50} values for moist desquamation were 2,200–2,750 rad (22–27.5 Gy) for the 22.5-mm source and 7,500–9,000 rad for the 5-mm source. There was a distinct source area effect; the ED_{50} values decreased as the source diameter increased. Acute tissue breakdown was only achieved in mouse skin by very high doses (ED_{50} $14,000 rad) from sources of #2 mm in diameter from both types of beta emitters. The large differences in doses required to produce the same effect, with higher energy beta particles producing a greater effect from the same size source by these three radionuclides, may be due to differences in penetrating power. The lower energy beta particles deposit a larger portion of their energy in the dead layers of the stratum corneum, compared with live tissue, so the actual live tissue doses may be larger for the higher energy beta emitters.

A study by Song et al. (1968) examined the efficacy of several anti-inflammatory agents on the suppression of the early increase in radiation-induced vascular permeability to plasma protein in guinea

pigs (radiodermatitis is one limiting factor in radiation therapy because the skin is the first in line for exposure to absorb the energy). Albino male guinea pigs were exposed to 3,000 rep (1 rep . 1 rad) of β particles (750 rad/min [7.5 Gy/min]) from a ^{90}Sr /^{90}Y source. Immediately after irradiation, ^{125}I-labeled guinea pig serum albumin (15 μCi [0.56 MBq] in 0.15–0.20 mL of saline) was injected into the blood. The peak increase in accumulation of vascular permeability as measured by plasma protein between the control and the 3,000-rad (30 Gy) beta-irradiated skin was determined to occur at 18 hours. A significant increase in vascular permeability occurred in the control group receiving no anti-inflammatory drug, as demonstrated by an approximately 3- and 1.6-fold increase in the 18-hour accumulation of plasma protein in the irradiated epidermis and dermis, respectively.

External radiation exposure shows similar results in humans. Birioukov et al. (1993) reported on a case study in which 12 men developed different forms and stages of chronic radiation dermatitis caused by accidental exposure to beta and gamma radiation during and after the Chernobyl nuclear power plant accident. Nine of the men were close enough to the accident to receive doses ranging from 350–550 rad (3.5–5.5 Gy). Three men received doses ranging from 200–350 rad (2–3.5 Gy): two had worked in the contaminated zone for 2 months to 3 years and one was inside the power plant during the accident. All the men were diagnosed with ARS of varying severity after the accident. All the men except one had chronic radiation dermatitis on the upper and lower extremities. The other patient had slight radiation dermatitis on the neck.

Klener et al. (1986) reported another human case study in which a male technician was accidentally irradiated by a sealed 3,000 Ci (110 TBq) ^{60}Co telotherapy source that he had been installing. A film dosimeter worn during the accident indicated a dose of 159 rad (1.59 Gy); however, his whole body was highly non-uniformly irradiated. His health status was followed for 11 years after the accident.
Eight days after the accident, he developed severe skin changes on the left hand (reddening and painful inflammation) that would result from doses much greater than 159 rad (1.59 Gy). Clearly, his left hand suffered a very much greater dose than that shown on his film badge. Since he was left-handed, it seems likely that his left hand was closer to the radioactive source and received a much larger dose than his film badge. Apparently, he severely overexposed his left hand during his several unsuccessful attempts and his final successful attempt to place the source back into the container using improvised tools. He also suffered epilation in a small area of the left temporal region, with minor deviations in peripheral blood counts. In the following year, repeated surgery due to secondary skin defects of the left hand resulted in

the loss of the second through fifth fingers; effects included serious trophic changes characterized by a smoothed discolored skin, hard swelling of deep skin layers, and disturbed local blood flow.

In laboratory animal studies, Hulse (1966) exposed albino hairless mice to 750–1,500 rad (7.5–15 Gy) of ^{204}Tl radiation (0.77 MeV beta particles) to determine if a nonepilating dose produced skin erythema. No visible changes in the skin of albino hairless mice were observed with a 750-rad (7.5 Gy) exposure. Only slight erythema was noted in the 1,500-rad (15 Gy) animal groups. Using slightly higher doses, Etoh et al. (1977) irradiated male albino guinea pigs at a total of 6 sites per animal. Maximum cell loss of recognizable basal cells of 20% on day 8, 60% on day 12, and 75% on day 15 occurred after irradiation with 1,000, 2,200, and 3,000 rad (10, 22, and 30 Gy), respectively. The data for the 5,000-rad (50 Gy) exposure were similar to data for 3,000 rad (30 Gy). Regeneration occurred from survivors within the irradiated area after 1,000 and 2,200 rad (10 and 22 Gy), and was completed in 5 days. No hyperplasia was seen at 1,000 rad (10 Gy), but a long-lived hyperplastic epidermis resulted after the higher doses. Lefaix et al. (1993) exposed large white pigs to a single dose of 12,000, 16,000, or 25,600 rad (120, 160, or 256 Gy) applied to the outer side of the right thigh; in another group, some animals were given single doses of 1,600, 3,200, 4,800, 6,400, 8,000, and 9,600 rad (16, 32, 48, 64, 80, and 96 Gy) applied to the back skin. Data were collected 30 weeks after exposure. No change in the skin surface was observed following a dose of 1,600 rad (16 Gy). After a 3,200-rad (32 Gy) dose, erythema was observed. After 4,800 rad (48 Gy), desquamation of the epidermis developed at the 12th week post-irradiation. At 6,400, 8,000, and 9,600 rad (64, 80, and 96 Gy) all showed a moderate erythema in the first 3–4 days, a distinct erythema after 3–5 weeks, and moist desquamation after 7–12 weeks. Skin necrosis was observed during the 5th week following doses to 12,000 and 16,000 rad (120 and 160 Gy), and cutaneous and muscular ulceration during the 6th week. The highest dose of 25,600 rad (256 Gy) caused skin necrosis at the end of the second week and well-delimited ulceration by the third week. After doses of 12,000, 16,000, and 25,600 rad (120, 160, and 256 Gy), which all induced skin and skeletal muscle ulceration, and 6,400, 8,000, and 9,600 rad doses, which induced dried exudate crusts, damaged skeletal muscles healed by replacement fibrosis and scar formation. It should be noted that the 0.77 MeV ^{204}Tl beta particles can penetrate 300 mg/cm^2 of material, or approximately 0.3 cm of tissue, which is enough to penetrate all layers of the skin and continue to penetrate into the skeletal muscle.

In summary, the skin is resistant to the deterministic effects of radiation until a threshold of 200–300 rad (2–3 Gy) is reached, after which the effects appear to follow a dose-effect relationship (Etoh et al. 1977;

Hulse 1966; Lefaix et al. 1993). Ionizing radiation affects the deep, rapidly multiplying cells of the epidermis (basal cells), which are at a mean depth of 0.007 cm below the outer surface layer of dead cells and which are responsible for the production of the more superficial layers of the epidermis. Other cells within the epidermis that multiply rapidly, such as cells that surround the hair follicle, can also be affected by ionizing radiation, resulting in epilation. Dermal radiation effects seem to be most common after either a direct dermal exposure to a beta or gamma emitter or after external exposure scenarios; alpha emitters, due to their short penetration range, do not penetrate the upper, dead layers of the epidermis (stratum corneum). A clear dose-effect relationship between radiation and skin damage as a whole was demonstrated in humans and in animals. In humans, the earliest response is a mild, transitory erythema that appears several hours after a dose of about 300 rad (3 Gy). Responses ranged from mild epilation that led to the return of normal hair growth at a dose of 2,000 rad (20 Gy), to ulcerative dermatitis and permanent epilation at doses up to 10,000 rad (100 Gy) (Garcia and Shubik 1971). Moist desquamation occurred in pigs at 2,250–7,500 rad (22.5-5.75 Gy) and acute tissue necrosis occurred at doses of 14,000 rad (140 Gy) and above (Hopewell et al. 1986). Erythema and epilation, followed by serious trophic changes and altered skin blood flow, have also been reported in a man whose film badge showed a dose of 159 rad (1.59 Gy); however, the affected areas on the hand received a much higher dose than that reported on the film dosimeter (Klener et al. 1986). Men exposed to external radiation (200–550 rad [2–5.5 Gy]) from the Chernobyl reactor accident also developed chronic dermatitis as a result of the exposures.

Data for dermal and ocular effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

3.2.1.9 Genotoxic Effects

The scientific literature contains abundant information on the genotoxic effects of all forms of ionizing radiation from multiple routes of exposure. Tables 3-4 and 3-5 summarize several representative studies that demonstrate the genotoxic end points that can be caused by radiation using *in vivo* and *in vitro* testing systems. However, genetic effects of radiation have never been seen in any human population exposed to any level of radiation.

The data presented in Tables 3-4 and 3-5 show that genotoxicity is a major toxicological end point for exposure to ionizing radiation; specific end points consist of chromosomal aberrations and breaks,

reciprocal translocations, deletions, sister chromatid exchanges, dominant lethal mutations, sperm anomalies, and mutations. DNA is a major target molecule during exposure to radiation (see Chapter 5). 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 described so far in this chapter. Cells depend on their DNA for coding information to make specific enzymes, proteins, hormones, vasoactive substances, and a host of other essential chemicals. When the genetic information containing the "blueprint" for these substances is disturbed, cellular homeostasis is disrupted, resulting in a wide-range of immediate and/or delayed toxicological effects in a number of organ systems, as described earlier in this chapter. Disruptions and changes of the cellular genome are also thought to be responsible for the formation of cancer in both humans and laboratory animals.

Radiation can interact either directly or indirectly with the cellular DNA to produce the effects seen in Tables 3-4 and 3-5. These interactions can be classified as direct and indirect interactions. In direct interactions with DNA (as well as other macromolecules), an alpha particle, beta particle, or gamma ray knocks an electron out of the DNA molecule through an ionizing collision. This can break the intramolecular chemical bond that contains the vital information that must be transmitted to the daughter cells. Complete repair is normally expected, but if the damage goes unrepaired, the information encoded in the DNA structure is distorted, and faulty information is transmitted to the daughter cells during mitosis, or else the cell dies and terminates the genetic defect. These effects can result in the genetic effects listed in Tables 3-4 and 3-5. In indirect interactions of with DNA, radiation has no direct contact with the DNA; instead it interacts with smaller molecules, especially water, surrounding the DNA to produce highly reactive radicals and ions like those produced in normal metabolic processes, and the end-products of this reaction diffuse away from the site of interaction with the radiation and interact with the DNA, breaking its molecular bonds just as with direct radiation. Misrepair and replication can then produce the adverse effects listed in Tables 3-4 and 3-5. More specific information about how radiation produces its effects on DNA and other macromolecules is presented in Chapter 5 of this profile.

Table 3-4. Genotoxicity of Ionizing Radiation *In Vivo*

Species (test system)	End point	Results	Reference	Radionuclide
ALPHA PARTICLES				
Mammalian cells:				
Human peripheral blood lymphocytes	Chromosomal aberrations	+	Pohl-Ruling and Fischer 1979	[222]Rn (E)
Human peripheral blood lymphocytes	Chromosome aberrations	+	Sasaki et al. 1987	[232]Th (I)
Human peripheral blood lymphocytes	Chromosome aberrations	+	Steinstrasser 1981	[232]Th (I)
Monkey peripheral blood lymphocytes	Chromosome aberrations	+	Brooks et al. 1992	[239]Pu (I)
Monkey peripheral blood lymphocytes	Chromosome aberrations	+	LaBauve et al. 1980	[239]Pu (I)
Mouse germ cells (male)	Chromosomal aberrations	+	Beechey et al. 1975	[239]Pu (I)
Mouse germ cells (male)	Chromosome fragmentation	+	Pomerantseva et al. 1989	[238]Pu (I)
Mouse germ cells (male)	Heritable reciprocal translocations	+	Generoso et al. 1985	[239]Pu (I)
Mouse germ cells (male)	Reciprocal translocations	+	Grahn et al. 1983	[239]Pu (I)
Mouse germ cells (male)	Reciprocal translocations	+	Pomerantseva et al. 1989	[238]Pu (I)
Mouse germ cells (male)	Reciprocal translocations	+	Searle et al. 1976	[238]Pu (I)
Mouse germ cells (male)	Dominant lethal mutations	+	Pomerantseva et al. 1989	[238]Pu (I)
Mouse germ cells (male)	Dominant lethal mutations	+	Searle et al. 1976	[238]Pu (I)
Mouse	Sperm abnormalities	+	Beechey et al. 1975	[239]Pu (I)
Mouse	Sperm abnormalities	+	Pomerantseva et al. 1989	[238]Pu (I)
Mouse	Sperm abnormalities	+	Searle et al. 1976	[238]Pu (I)
BETA PARTICLES				
Invertebrate animal cells:				
Drosophila melanogaster (male)	Large deletions	+	Fossett et al. 1994	HTO: [3]H (I)
Plants:				
Brassica campestris T10 and T151	Chromosome aberrations	+	Dasgupta 1970	[32]P, [35]S (E)
Vicia faba	Chromosome breakage	+	Lazanyi 1965	[90]Sr-[90]Y (E)
V. faba	Sister chromatid exchange	–	Kuglik and Slotova 1991	[3]H (I)
V. faba	Micronuclei	+	Kuglik and Slotova 1991	[3]H (I)

Table 3-4. Genotoxicity of Ionizing Radiation *In Vivo* (continued)

Species (test system)	End point	Results	Reference	Radionuclide
Mammalian cells:				
Mouse liver cells	Chromosome aberrations	+	Brooks et al. 1976	HTO: [3]H (I)
Mouse skin cells	Unscheduled DNA synthesis	+	Ootsuyama and Tanooka 1986	[90]Sr-[90]Y (E)
Mouse germ cells (male)	Reciprocal translocations	+	Ramaiya et al. 1994	[137]Cs (I)
Mouse germ cells (male)	Reciprocal translocations	+	Shevchenko et al. 1989	[131]I (I)
Mouse germ cells (male)	Dominant lethal mutations	+	Ramaiya et al. 1994	[137]Cs (I)
Mouse germ cells (male)	Dominant lethal mutations	+	Shevchenko et al. 1989	[131]I (I)
Mouse germ cells (female)	Dominant lethal mutations	+	Zhou et al. 1986	HTO: [3]H (I)
Mouse	Sperm abnormalities	+	Shevchenko et al. 1989	[131]I (I)
GAMMA RAYS:				
Plants:				
Vicia faba	Chromosome breakage	+	Lazanyi 1965	[60]Co (E)
V. faba	Sister chromatid exchange	+	Kuglik and Slotova 1991	[60]Co (E)
V. faba	Micronuclei	+	Kuglik and Slotova 1991	[60]Co (E)
Mammalian cells:				
Human peripheral blood lymphocytes	Chromosome aberrations	+	Bigatti et al. 1988	NS (E)
Human peripheral blood lymphocytes	Chromosome aberrations	+	Klener et al. 1986	[60]Co (E)
Human peripheral blood lymphocytes	Chromosome aberrations	+	Lloyd et al. 1994	[192]Ir (E)
Human peripheral blood lymphocytes	Chromosome aberrations	+	Milkovic-Kraus et al. 1992	[60]Co (E)
Human peripheral blood lymphocytes	Chromosome aberrations	+	Natarajan et al. 1991	[137]Cs (E)
Human peripheral blood lymphocytes	Chromosome aberrations	+	Padovani et al. 1993	[137]Cs (E&I)
Human peripheral blood lymphocytes	Chromosome aberrations	+	Pohl-Ruling and Fischer 1979	NS (E)
Human peripheral blood lymphocytes	Chromosome aberrations	+	Stavem et al. 1985	NS (E)

Table 3-4. Genotoxicity of Ionizing Radiation *In Vivo* (continued)

Species (test system)	End point	Results	Reference	Radionuclide
Human peripheral blood lymphocytes	Chromosome aberrations	+	Stram et al. 1993	NS (E)
Human bone marrow	Chromosome aberrations	+	Stavem et al. 1985	NS (E)
Chinese hamster liver cells	Metaphase chromosomal aberrations	+	Brooks et al. 1971a, 1971b	[60]Co (E)
Mouse bone marrow (maternal)	Chromosome breaks	+	Ricoul and Dutrillaux 1991	[60]Co (E)
Mouse fetal liver cells	Chromosome breaks	+	Ricoul and Dutrillaux 1991	[60]Co (E)
Human peripheral blood lymphocytes	Reciprocal translocations	+	Maes et al. 1993	NS (E)
Monkey germ cells (male)	Reciprocal translocations	+	Tobari et al. 1988	[137]Cs (E)
Mouse germ cells (male)	Reciprocal translocations	+	Bayrakova et al. 1987	[60]Co (E)
Mouse germ cells (male)	Reciprocal translocations	+	DeLuca et al. 1988	[60]Co (E)
Mouse germ cells (male)	Reciprocal translocations	+	Gilot-Delhalle et al. 1988	[60]Co (E)
Mouse germ cells (male)	Reciprocal translocations	+	Grahn and Carnes 1988	[60]Co (E)
Mouse germ cells (male)	Reciprocal translocations	+	Grahn et al. 1983	[60]Co (E)
Mouse germ cells (male)	Reciprocal translocations	+	Ramaiya et al. 1994	[137]Cs (E)
Mouse germ cells (male)	Reciprocal translocations	+	Searle et al. 1976	[60]Co (E)
Mouse germ cells (male)	Reciprocal translocations	+	Shevchenko et al. 1992	NS (E)
Mouse germ cells (male)	Dominant lethal mutations	+	Ramaiya et al. 1994	[137]Cs (E)
Mouse germ cells (male)	Dominant lethal mutations	+	Searle et al. 1976	[60]Co (E)
Mouse germ cells (female)	Dominant lethal mutations	+	Zhou et al. 1986	[60]Co (E)
Mouse	Sperm abnormalities	+	Grahn and Carnes 1988	[60]Co (E)
Mouse	Sperm abnormalities	+	Searle et al. 1976	[60]Co (E)
Mouse	Sperm abnormalities	+	Shevchenko et al. 1992	NS (E)
Mouse bone marrow	Micronuclei	+	Abraham et al. 1993	[60]Co (E)
Mouse thymocytes	DNA fragmentation	+	Sellins and Cohen 1987	[60]Co (E)
Mouse liver cells	DNA fragmentation	–	Sellins and Cohen 1987	[60]Co (E)
Pig skin fibroblasts	Abnormal karyotypes	+	Sabatier et al. 1992	[192]Ir (E)

+ = Positive result; – = Negative result; (E) = External dose, (I) = Internal dose; HTO = tritiated water.

Table 3-5. Genotoxicity of Ionizing Radiation *In Vitro*

Species (test system)	End point	Result		Reference	Radionuclide
		With activation	Without activation		
ALPHA PARTICLES					
Prokaryotic organisms:					
Escherichia coli	DNA double-strand breaks	ND	+	Wilkins 1971	[241]Am
E. coli	DNA single-strand breaks	ND	+	Wilkins 1971	[241]Am
Mammalian cells:					
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	DuFrain et al. 1979	[241]Am
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Fajgelj et al. 1991	[235]U
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Purrott et al. 1980	[238]Pu
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Takatsuji and Sasaki 1984	NS
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Takatsuji et al. 1989	NS
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Wolff et al. 1991	[226]Ra
Mouse bone marrow	Chromosome aberrations	ND	+	Kadhim et al. 1992	[238]Pu
Mouse 10T1/2, 3T3 cells	Chromosome aberrations	ND	+	Nagasaswa et al. 1990a	[238]Pu
Chinese hamster ovary cells, K-1	Chromosome aberrations	ND	+	Nagasawa et al. 1990b	[238]Pu
Human fibroblasts	Chromosome breaks	ND	+	Loucas and Geard 1994	NS
Chinese hamster M3-1 cells	Chromosome damage	ND	+	Welleweerd et al. 1984	[238]Pu
Human AT2BE cells and normal fibroblasts	DNA double-strand breaks	ND	+	Coquerelle et al. 1987	[241]Am
Ehrlich ascites tumor cells	DNA double-strand breaks	ND	+	Blocher 1988	NS
Chinese hamster cells, V79-4	DNA double-strand breaks	ND	+	Jenner et al. 1993	[238]Pu
Human peripheral blood lymphocytes	Sister chromatid exchange	ND	+	Aghamohammadi et al. 1988	[238]Pu
Mouse 10T1/2, 3T3 cells	Sister chromatid exchange	ND	+	Nagasawa et al. 1990a	[238]Pu
Chinese hamster ovary cells, K-1	Sister chromatid exchange	ND	+	Nagasawa et al. 1990b	[238]Pu
Chinese hamster V79 cells	Mutations	ND	+	Thacker 1986	NS

Table 3-5. Genotoxicity of Ionizing Radiation *In Vitro* (continued)

Species (test system)	End point	Result: With activation	Result: Without activation	Reference	Radionuclide
BETA PARTICLES					
Eukaryotic organisms:					
Fungi:					
Saccharomyces cerevisiae PG-60	Mitotic recombination	ND	+	Gracheva and Korolev 1974	[32]P
Mammalian cells:					
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Bocian et al. 1977	HTO: [3]H
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Ribas et al. 1994	HTO: [3]H
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Tanaka et al. 1994	HTO: [3]H
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Vulpis 1984	HTO: [3]H
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Vulpis and Scarpa 1986	[90]Sr
Human bone marrow cells	Chromosome aberrations	ND	+	Tanaka et al. 1994	HTO: [3]H
Human spermatozoa and zona-free hamster oocytes fertilization system	Chromosome aberrations	ND	+	Kamiguchi et al. 1990	HTO: [3]H
Human spermatozoa	Chromosome aberrations	ND	+	Mikamo et al. 1990, 1991	HTO: [3]H
Human bone marrow cells	Chromatid aberrations	ND	+	Tanaka et al. 1994	HTO: [3]H
Chinese hamster ovary cells	DNA single-strand breaks	ND	+	Cleaver 1977	[3]H
Chinese hamster ovary cells	DNA strand breaks	ND	+	Dikomey and Franzke 1986	[3]H
Human peripheral blood lymphocytes	Sister chromatid exchange	ND	+	Crossen and Morgan 1979	[3]H
Human peripheral blood lymphocytes	Sister chromatid exchange	ND	–	Ribas et al. 1994	HTO: [3]H
Chinese hamster ovary cells	Sister chromatid exchange	ND	+	Roberts et al. 1987	[3]H
GAMMA RAYS					
Prokaryotic organisms:					
Escherichia coli K12	DNA double-strand breaks	ND	+	Krisch et al. 1976	[125]I

Table 3-5. Genotoxicity of Ionizing Radiation *In Vitro* (continued)

Species (test system)	End point	Result		Reference	Radionuclide
		With activation	Without activation		
Mammalian cells:					
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Doggett and McKenzie 1983	[137]Cs
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Fajgelj et al. 1991	[235]U
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Hintenlang 1993	[137]Cs
Human peripheral blood lymphocytes	Chromosome aberrations	ND	+	Iijima and Morimoto 1991	[137]Cs
Human blood peripheral lymphocytes	Chromosome aberrations	ND	+	Tanaka et al. 1994	[60]Co
Human blood peripheral lymphocytes	Chromosome aberrations	ND	+	Tanaka et al. 1994	[137]Cs
Human blood peripheral lymphocytes	Chromosome aberrations	ND	+	Rueff et al. 1993	[60]Co
Human blood peripheral lymphocytes	Chromosome aberrations	ND	+	Xiao et al. 1989	NS
Human bone marrow cells	Chromosome aberrations	ND	+	Tanaka et al. 1994	[60]Co
Human spermatozoa	Chromosome aberrations	ND	+	Mikamo et al. 1990, 1991	[137]Cs
Human bone marrow cells	Chromatid aberrations	ND	+	Tanaka et al. 1994	[60]Co
Human blood peripheral lymphocytes	DNA strand breaks	ND	+	Rueff et al. 1993	[60]Co
Human lung carcinoma lines (HC12, HX149, HX147A7, HX148G7)	DNA double-strand breaks	ND	+	Cassoni et al. 1992	[60]Co
Human AT2BE cells and normal fibroblasts	DNA double-strand breaks	ND	+	Coquerelle et al. 1987	[60]Co
Mouse (BALB/c, SC3T3/W, Scid/St cells)	DNA double-strand breaks	ND	+	Biedermann et al. 1991	[137]Cs
Chinese hamster cells, V79-4	DNA double-strand breaks	ND	+	Jenner et al. 1993	[60]Co
Mouse thymocytes	DNA fragmentation	ND	+	Sellins and Cohen 1987	[60]Co
Human peripheral blood lymphocytes	Sister chromatid exchange	ND	–	Iijima and Morimoto 1991	[137]Cs
Human spermatozoa and zona-free hamster oocytes fertilization system	Micronuclei	ND	+	Kamiguchi et al. 1991	[137]Cs
Chinese V79 hamster cells	Mutations	ND	+	Thacker 1986	[60]Co

NA = not applicable; ND = no data; – = negative results; + = positive results

The structure of the DNA molecule is damaged after direct or indirect interactions by radiation. Significant amounts of damage to the DNA lead to errors for gene coding of essential enzymes, proteins, and other essential molecules. DNA base-pair damage is the predominant type of DNA damage, followed (in decreasing order of incidence) by single strand breaks (which are four times less prevalent than base-pair lesions), DNA-protein cross-linkages, and double-strand breaks. At the molecular level, an important type of change to DNA that is frequently produced by radiation is the removal of a base, forming an apurinic or apyrimidinic site. The deletion or total destruction of DNA bases, destruction of deoxyribose residues, and deamination of cytosine or adenine are only a few of the many ways radiation can alter the DNA at a molecular level. Minor damage left unrepaired or damage that was not completely or correctly repaired can result in mutations. A more in-depth discussion of the alterations at the DNA level by radiation, including some DNA repair mechanisms, is presented in BEIR V (1990) and in Chapter 5.

Damage to genetic material in an organism may have one of several outcomes. First, enough damage can cause cell death. Second, the genetic material may be repaired by the cell's native DNA repair mechanisms. If the damage is small and the DNA can be repaired correctly prior to cell division, no adverse effects are likely to come from the genetic damage. Chromosomal repair mechanisms have likely existed since life began and our knowledge of these mechanisms has existed for many years. Without these repair mechanisms, the normal damage that occurs to the entire organisms's DNA every day spontaneously, and from other sources such as normal metabolic products, mutagenic chemicals and background radiation, could be lethal. Chromosomal repair mechanisms are a method of minimizing damage, including radiation damage to DNA, providing that the dose of radiation is not so large as to overwhelm them. If the damage is reparable and the cell divides prior to repair, or if the damage is so extensive it cannot be repaired by the normal mechanisms, the cell may die. The results range from no apparent effect on the organs if few or scattered cells die to damaged tissues at higher doses. Another alternative is that the DNA damage is not repaired, the cell lives and carries out its normal functions, and then divides to produce progeny cells. If the progeny cells die, then the mutational event is considered a lethal mutation with no consequences. If the progeny cells live, then the cells will likely carry these genetic mutations forward into all future daughter cells. In-depth reviews of these mutation processes and their impact on the induction of cancer in animals and humans are available (Hoffman 1996; Pitot III and Dragan 1996; Sanders 1983; Sanders and Kathren 1983).

If the cell survives the radiation-induced genetic damage and carries the mutations into future cell populations, two events can take place. First, the cell may carry the DNA defect and express an adverse event, such as altered protein and enzyme synthesis and defects in cellular metabolism. These defects can be numerous, depending largely on where on the genome the mutation takes place and how critical the normal gene is to normal cell function. The second event is multi-stage carcinogenesis, which is discussed in more detail later in Chapter 5.

Both somatic and reproductive cell chromosomes can sustain damage after exposure to radiation. Damage to the human genome in exposed populations of humans has potentially serious implications. If genetic damage occurs in the reproductive cells (sperm and ova), this may result in decreased fertility, malformed fetuses, and certain hereditary diseases. These effects have been observed in animal studies, but long-term follow-up of radiation-exposed human populations has not identified any genetic effects.

Estimates of spontaneous genetic diseases vary. Table 3-6 shows that genetic diseases occur spontaneously (naturally) in approximately 5% of the population (excluding genetic contributions to heart, cancer, and other selected human diseases). UNSCEAR (1993) reported that about 8% of liveborn humans will have a hereditary disease that leads to a serious handicap manifested before 25 years of age. This 8% figure includes all serious congenital anomalies, some of which may be only slightly influenced by transmitted mutations. Before one begins to determine whether human genetic damage can be caused by exposure to increasing doses of radiation, it is necessary to know what the normal, spontaneous, or "background" rates of genetic diseases are in the human population exposed to ambient levels. Several investigators have performed work to measure the spontaneous frequencies of genetic anomalies and spontaneous mutation rates of many genetic traits in humans throughout the world (Childs 1981; Czeizel and Sankaranarayanan 1984; Stevenson 1959, 1961; Stevenson and Kerr 1967). Difficulties are clearly inherent in such comprehensive studies. As an example, as our knowledge of human and animal genetics increases, discrepancies in the data may arise from changes in the classification of some genetic disorders. For example, Stevenson (1959) estimated that 30.7/1000 live births were due to autosomal dominant genetic disorders, while in a study 15 years later by Trimble and Doughty (1974) estimated that only 0.8/1000 live births for the same class of genetic disorders. The data from the Stevenson (1959) data

Table 3-6. Estimated Genetic Effects of 1 Rem (0.01 Sv) of Radiation per Generation[a]

	Spontaneous/ not irradiated	Irradiated Additional cases/10^6 liveborn offspring/rem (0.01 Sv)/generation	
Type of disorder	Current incidence per million liveborn offspring	First generation	Equilibrium
Autosomal dominant [b]			
Clinically severe	2,500[c]	5–20[d]	25[e]
Clinically mild	7,500[g]	1–15[d]	75[e]
X-linked	400	<1	<5
Recessive	2,500	<1	Very slow increase
Chromosomal			
Unbalanced translocation	600[h]	<5	Very little increase
Trisomies	3,800[i]	<1	<1
Congenital abnormalities	20,000–30,000	10[j]	10–100[k]
Other disorders of organs [l]			
Heart [m]	600,000		
Cancer	300,000	Not estimated	Not estimated
Selected others	300,000		

[a]Risks pertain to average population exposure of 1 rem per generation to a population with the spontaneous genetic burden of humans and a doubling dose for chronic exposure of 100 rem (1 Sv)

[b]Assumes that survival and reproduction are reduced by 20-80% relative to normal (s=0.2-0.8), which is consistent with the range of values in Table 2.2 in BEIR (1990).

[C]Approximates incidence of severe dominant traits in Table 2-2 in BEIR (1990).

[D]Calculated using Equations (2-7) in BEIR (1990) with s=0.2-0.8 for clinically severe and s = 0.01-0.2 for clinically mild.

[e]Calculated using Equations (2-1) in BEIR (1990), with the mutational component = 1.

[f]Assumes that survival and reproduction are reduced by 1-20 percent relative to normal (s=0.01-0.02).

[g]Obtained by subtracting an estimated 2,500 clinically severe dominant traits from an estimated total incidence of dominant traits of 10,000.

[h]Estimated frequency from UNSCEAR (1982, 1986).

[i]Most frequent result of chromosomal nondisjunction among liveborn children. Estimated frequency from UNSCEAR (1982, 1986).

[j]Based on worse-case assumption that mutational component results from dominant genes with an average s of 0.1: hence, using Equation 2.3 in BEIR (1990), excess cases <30,000 x 0.35 x 100^{-1} x 0.1 = 10.

[k]Calculated using Equation 2-1 in BEIR (1990), with the mutational component 5-35%.

[l]Lifetime prevalence estimates may vary according to diagnostic criteria and other factors. The values given for heart disease and cancer are round-number approximations for all varieties of the diseases, and the value for other selected traits approximates that for the tabulation in Table 2-4 of BEIR (1990).

[m]No implication is made that any form of heart disease is caused by radiation among exposed individuals. The effect, if any, results from mutations that may be induced by radiation and expressed in later generations, which contribute, along with other genes, to the genetic component of susceptibility. This is analogous to environmental risk factors that contribute to the environmental component of susceptibility. The magnitude of the genetic component in susceptibility to heart disease and other disorders with complex etiologies is unknown.

Source: adapted from BEIR V 1990

set included disorders now known to not be of an autosomal dominant mechanism, resulting in an artificially high estimate in the 1959 report. Definitions of serious and mild genetic disease, size of the population sampled and the specific world location sampled, in addition to the frequencies of some genetic diseases tending to wax and wane over a number of years, will all significantly contribute to the problem of obtaining stable and accurate estimates of background genetic disease burdens in humans.

Table 3-6 summarizes the current incidence of some generalized genetic anomalies (background levels of genetic disease) and the estimated genetic effects of 1 rem (0.01 Sv)/year/generation of radiation on the genome of humans based on an assumed doubling dose of 100 rem (1 Sv) (BEIR V 1990).

Determining the genotoxic effects of ionizing radiation in a population of humans is difficult. Several factors complicate making such predictions of genotoxic effects in humans. First, the genotoxic effects of radiation in humans must be detected in the offspring from the parent(s) that were irradiated.

Given the normally long life cycle of humans compared to laboratory animal models, it may be a few weeks to many years before any genetic effects induced by radiation express themselves in the offspring of an exposed human population. The epidemiologic studies that are needed to accumulate a sufficient database of information after such an exposure would be both time consuming and expensive, with the final results most likely not being available for years after exposure. In addition, radiation effects in an exposed population may vary significantly by exposure location: all of the population may not have received a uniform whole body dose, and different individuals would have received different radiation doses, thus complicating the data collection process. Distance-from-exposure source and total organ dose received are only estimates and not a precise measurement. Age and sex distribution of the exposed population and their normal probabilities of producing children must also be accounted for and determined using relevant control populations.

A major problem with the genetic studies on humans relates to the many remaining uncertainties about dosimetry. Many of the difficulties described above were encountered with the data collected from the exposures to radiation resulting from the atomic bombing at Hiroshima and Nagasaki, Japan; these exposures consisted primarily of external gamma radiation. The original dosimetry measurements from that exposure (T65D) have been revised (DS86) and are still undergoing revision to more accurately]

determine the actual doses of radiation received by individuals who survived the atomic bomb explosions in August 1945. Although no increased incidence of hereditary effects among the children and grandchildren of the atomic bombing survivors has been seen, certain authors and committees made certain assumptions about the induction of radiation-induced hereditary effects and have calculated the chances of the occurrence of these effects; the results and assumptions are presented and discussed in other texts (BEIR IV 1988; BEIR V 1990; UNSCEAR 1993). Another major problem in quantifying genetic effects is the wide spectrum of possible health outcomes that may be attributable to genotoxic events. The total genetic detriment includes health effects that may have minor or insignificant impact, major genetic diseases, and death. Some of these outcomes may be very difficult to measure.

Today, two basic models are used to estimate the risk for radiation-induced hereditary disease for low doses of radiation. These models are the Direct Method and the Doubling Dose Method. Both models are linear, no-threshold models for dose response.

In the Direct Method, the dose-related rate of hereditary effects in mice is extrapolated to humans. However, because of the many uncertainties in this extrapolation, this method is not favored for estimating the chances of a radiation-based hereditary effect in humans.

The Doubling Dose Method requires fewer assumptions and estimates than the direct method. The "doubling dose" of radiation is defined as the dose that induces a mutation frequency equal to the total spontaneous mutation frequency per generation. Hence, the doubling dose of radiation doubles the total mutation frequency per generation. In other words, the dose of radiation to the gonads (testes or ovaries) that, if delivered per generation to all members of a population would, at equilibrium after many generations, doubles the spontaneous burden that existed before exposure began (BEIR V 1990; Faw and Shultis 1993). This method uses the natural frequency of human hereditary disease in determining an estimate of the increased frequency of genetic alterations as a result of a sudden increase in radiation exposure to the general public. Compared to the direct method, the doubling dose method directly takes into account the effect of a genetic anomaly on all generations beyond the first generation. The problem of species extrapolation from animal to human is also somewhat circumvented; in theory, this method

relies entirely on a known estimate of a specific genetic mutation frequency in the human, although some of the doubling-dose estimates originate from data collected in the mouse animal model. Risk estimates of genetic disease using the doubling dose method have been adopted by the latest BEIR committee; however, UNSCEAR still relies on the direct method of risk estimation.

Risk estimates have been reported for humans exposed to radiation, despite the difficulties with the availability of data. Using the epidemiological data gathered after the atomic bombing of Hiroshima and Nagasaki in August 1945, which encompasses nearly 50 years of data, together with data from studies with mice, some estimates of genetic disease risk using the doubling dose method can be derived for human exposures to radiation. These estimates are presented in Table 3-7.

Table 3-7. Estimated Lower 95% Confidence Limits of Doubling Dose (in rem) from Chronic Radiation Exposure for Malformations, Stillbirths, Neonatal Deaths, and All Untoward Pregnancy Outcomes (Based on the Hiroshima and Nagasaki Atomic Bombing Data)

Group	Malformations	Stillbirths	Neonatal death	All untoward outcomes
All groups	96	124	90	60
Only mother exposed	277	32	23	29
Only father exposed	65	344	56	41
Combined	119	64	35	36
Both mother and father exposed	41	73	75	37

Source: adapted from BEIR V 1990 and Schull et al. 1981

NOTE: Data are the lower 95% confident limits of the doubling dose adjusted for concomitant sources of variation. For acute doubling doses, divide by 3. For all estimates adjusted for concomitant sources of variation, the range of the doubling dose is 23–344 rem (0.23–3.44 Sv), the median is 62 rem (0.62 Sv), and the mean is 86 rem (0.86 Sv).

Table 3-7 provides the lower 95% confidence limits of the minimum doubling dose estimates (in rem) on adjusted data from those individuals that survived the atomic blasts of 1945, and are for chronic radiation exposures only. The human data set closely approximates the median values obtained in mice (data not shown), and overall may suggest that humans are somewhat more radioresistant than mice, implying lower risk. Due to the data restrictions in this human population (discussed previously in this section), the human data may be biased in such a way as to yield an artificially lower number than that obtained using

the mouse data. The numbers in Table 3-6 are based on the application of actual doses to models derived from animal experiments. In the case of the survivors of the atomic bombing, Dr. J.V. Neel, who had been studying the genetic effects of these bombings since 1946, concluded that "the children of the most highly irradiated population in the world's history provide no statistically significant evidence that mutations were produced in their parents. . . . In particular, the studies should prove reassurance to that considerable group of exposed Japanese and their children, without whose magnificent cooperation these studies would have been impossible and who over the years have been subject to a barrage of exaggerations concerning the genetic risks involved" (Neel et al. 1990). In short, Neel and others believe that humans may be less sensitive to induction of mutations than mice. The data of Neel and colleagues indicated that mice may be much less sensitive than has been thought, however, to reach this conclusion they had to disregard the genes that have been studied the most (the specific-locus data), based on the argument that those genes might be atypically mutable.

In summary, the intracellular genetic materials in humans and in animals may be damaged by radiation. The severity of these lesions depends on the dose and type of ionizing radiation received and the extent to which these lesions can be repaired by the resident cellular repair systems. These lesions range from point mutations, which cause serious hereditary diseases, and chromosomal aberrations and breaks to lethal mutations of the genetic material, which lead to cellular death.

The amount of radiation needed to cause hereditary effects is not known, because hereditary effects have not been detected in humans. As stated in the UNSCEAR (1993) report, "Epidemiology has not detected hereditary effects of radiation in humans with a statistically significant degree of confidence. The risk estimate based on animals is so small that it would have been surprising to find a statistically significant effect in the end-points studied in Hiroshima and Nagasaki. . . . Risk estimation therefore rests on genetic experimentation with a wide range of organisms and on cellular studies, with limited support from the negative human findings." The two models that currently exist for making these determinations have both strengths and weaknesses. One of the weaknesses is the high rate of spontaneous chromosomal breaks; about 200,000 broken chromosomes are repaired per hour. The main difficultly with estimating genetic effects of radiation is that the frequency of the postulated effects, even for high radiation doses, is less than the annual statistical variability in the number of these that occur spontaneously.

3.2.2 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 due to 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.

With respect to chemical toxicity, 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 from environmental insults, 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 pre-natal and post-natal 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 and 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 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996).

According to the Law of Bergonie and Tribondeau, rapidly dividing and undifferentiated cells are more sensitive to radiation damage than slowly dividing and highly differentiated cells. This applies to fetal cells as their sensitivity changes with level of activity during the different stages of development, and to all types of radiation whether the dose is delivered internally or externally. Gamma and x rays from sources such as ^{60}Co and x ray machines are the radiation types with enough penetrating power to externally expose the fetus while *in utero*; alpha and beta emitters, such as ^{239}Pu and ^{90}Sr which preferentially distribute to fetal bone, must be internalized by the fetus to cause a radiation dose. The specific organ systems are expected to be the most sensitive to radiation damage during that system's primary period(s) of organogenesis. Prenatally injured cells that replicate while damaged may affect the individual as a child and as an adult. Exposure to radiation after birth results in similar effects in children and adults.

Radiation damage to the fetus thus depends on the dose and type of radiation that delivered it, and the sensitivities of the various organ systems during exposure. The expression of that damage will depend on the efficiency of the fetal repair system that all humans use for protection against low-level radiation to which all life is exposed. External radiation dose depends on the radiation dose rate which would exist if the mother and fetus were not present, the time of exposure, and the shielding which the mother's body and fluids provide the fetus. Natural terrestrial, cosmic, and internal radiation will normally represent the largest radiation dose to the fetus. This can be supplemented by external radiation doses from x ray and nuclear medicine procedures to the mother and any gamma radiation field from sources around the mother, such as radioactive fallout and any nearby radioactive sources. Terrestrial and cosmic radiation doses are affected by the concentrations of various radioactive materials in the surrounding environment, such as soil and construction material, and the altitude, which affects cosmic ray intensity. Internal radiation dose depends on the combination of gamma dose rate to the fetus from radionuclides inside the mother, plus the dose equivalent rate from alpha, beta, and gamma emitting radioactive materials which have entered and distributed within the fetus. Potassium-40, which is the inseparable radioactive component of natural, biologically important potassium, will probably cause the largest portion of the internal dose, but the dose from radon transformation products which cause the largest adult dose will be

minimally important in the fetus because it doesn't breathe. Absorption, distribution, metabolism (if any), and excretion of radionuclides depend largely on the pharmaco/toxicokinetics for both mother and fetus. If the mother can metabolize and excrete the radioactive compound prior to distribution to the fetal compartment, the dose to the fetus is minimized. Those compounds that are easily absorbed and freely distributed to the fetal and/or placental compartments may give a larger dose than those that have low absorption coefficients or those that never leave the maternal blood supply to penetrate peripheral tissues. Compounds that distribute to the fetal compartment and undergo little metabolism and excretion (i.e., extended fetal compartment residence times) are also more likely to cause damage to fetal tissues. The overall dose equivalent, which considers all radiation doses and the quality factors of the radiation, and the dose rate are the major players in predicting fetal toxicity.

Some of the fetal effects which have been observed in humans include mental retardation, IQ reduction, and microencephaly. The pivotal study that links the effects of external radiation to defects in child development is the study conducted by Schull et al. (1988) that describes decreases in IQ scores with increasing maternal doses of ionizing radiation. That study evaluated the quantitative effect of exposure to ionizing radiation on the developing fetal and embryonic human brain after the Hiroshima/Nagasaki atomic bombings of 1945. The sample included virtually all prenatally exposed individuals who received tissue-absorbed doses of 0.50 Gy (50 rad) or more, and many more individuals in the dose range 0–0.49 Gy (0–49 rad) than in the clinical sample. The clinical sample does not include children prenatally exposed at distances between 2,000–2,999 m in Hiroshima and Nagasaki. No evidence of radiation-related effect on intelligence was observed among individuals exposed within 0–7 weeks after fertilization or in the 26th or subsequent weeks. The highest risk of radiation damage to the embryonic and fetal brain occurs 8–15 weeks after fertilization under both the T65D individual specific dosimetric system, developed using data accumulated through 1965 and atomic bomb radiation data from tests in arid climates, and the DS86 system, which accounts for neutron dose reduction from the high ambient relative humidity in Japan during the 1945 blasts. The regression of intelligence score on estimated fetal absorbed dose was linear or linear-quadratic for the group exposed 8–15 weeks after fertilization and possibly linear for the 16–25 week group. The cumulative distribution of test scores suggested a progressive shift downwards in individual scores with increasing dose. The mean IQ scores decreased

significantly and systematically with uterine or fetal tissue dose within the groups exposed during 8–15 and 16–25 weeks postgestation. This effect was not reversible and was the basis for the acute duration MRL.

3.2.3 Carcinogenic Effects from Ionizing Radiation Exposure

3.2.3.1 Introduction

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. There is also a large database that exists for people exposed to radiation for diagnostic purposes, those treated for disease with radiation, occupational exposure populations, people that live in high background regions, survivors of radiation accidents, and nuclear bombing survivors. It is presently not clear whether humans are more or less sensitive to the adverse effects of low-levels of radiation than are the laboratory animal models.

The development of cancer is not an immediate effect. It may take several years to develop (referred to as the latent period or latency), if it develops at all. Radiation-induced cancers are the same types that are normally found in an unexposed individual. However, after exposure to radiation, these cancer types may occur with some increasing frequency and therefore can be detected only by epidemiological means. Most of these cancers occur only when those individuals reach an age when these cancers would normally be expected to develop (except for leukemia). For example, a female #10 years of age who was exposed to external radiation from the atomic blast, who survived the acute effects of the initial radiation exposure, would have an increased probability of developing breast cancer as a result of that exposure, but not before the end of the latent period for this specific cancer. The same would be true for the other types of cancers. Radiation-induced leukemia has the shortest latent period at 2 years, while other radiation induced cancers have latent periods >20 years. Radiation carcinogenesis has not been demonstrated in several types of human cells, possibly because the latent period exceeds the human lifespan. Raabe (1994) has developed two- and three-dimensional models of risk of developing cancer as a function of isotope and dose rate. The typical plot of lifespan vs. daily dose rate has three portions based on the cause of death, natural life-span, cancer, and acute radiation syndrome. According to Raabe, at low dose rates the animal's natural life-span is the cause of death before cancer can develop. As the daily

dose rate increases, a threshold is reached where cancer deaths dominate in a dose-responsive manner. Similarly, at high dose rates, a threshold is reached where acute radiation syndrome is the cause of death. These are lifetime studies involving a wide range of dose rates from very high down toward levels that humans may normally experience.

The mechanism by which cancer is induced in living cells is complex and is a topic of intense study. The accepted theory states that the induction of cancer by exposure to radiation takes place in three steps. The first step is initiation, which is a mutational event caused by the effect of the radiation interacting with the cellular genome. This may involve a single gene or multiple genes on one or many chromosomes, and may involve the activation of an oncogene or the mutation and subsequent inactivation of tumor suppressor genes. The mechanism may stall at this point, with the gene(s) either undergoing repair or remaining mutated and dormant. If repair fails to take place at all, if the repair is unsuccessful, or if cell division occurs before repair is complete, and the cell remains viable through future cell generations, the gene(s) appear in the progeny cells and will then enter into the stage of promotion. The second step, promotion, is generally thought to be unrelated to the dose of radiation (initiation step) received, even though thyroid cancer in children from ^{131}I or external exposure may suggest otherwise; therefore, the latent period is clearly independent of the initial dose of radiation received. This would be a reasonable explanation of why cancers develop at the ages that they would normally develop in unexposed populations, with the increased incidence of cancer related to the increased number of cell insults/injuries in the genome of the damaged cells. Several promotor agents have been identified, with some acting as both initiators and promotors. In the third step, cell transformation and proliferation, neoplasic cells are produced. More information on how radiation interacts with the genome and on the mechanisms by which it induces cancer is presented in Chapter 5 of this profile.

A few human studies are available that describe the incidences and types of cancers produced by some radionuclides. Osteogenic sarcomas were found in people whose average skeletal doses exceeded 1,380 rad (13.8 Gy) of alpha radiation following exposure to ^{226}Ra and ^{228}Ra via several routes of exposure (Aub et al. 1952; Evans 1966; Martland 1931; Rowland et al. 1978; Woodard 1980). ^{224}Ra, used in the treatment of ankylosing spondylitis, has also been implicated in producing osteosarcomas (Chemelevsky 1986; Mays 1988; Spiess and Mays 1970, 1973; Wick et al. 1986). One of the largest cohort of humans available for studying the effects of external radiation and cancer is the group of people exposed to the varying doses of radiation produced by the two atomic bombs detonated in Japan in August 1945. In this

population, an increase in leukemia incidence rate was seen only in those persons whose dose exceeded 10 rad (0.1 Gy). An increased incidence of solid tumors was seen only in those whose dose exceeded 40 rad (0.4 Gy).

Exposure to radiation can produce cancer at any site within the body; however, some sites appear to be more common than others. The BEIR V (1990) committee report came to some conclusions about which sites are more at risk than others in humans, and these data are summarized in Table 3-8. The relative risk of death normalized to a dose of 100 rad (1 Gy) from several types of cancer among 75, 991 atomic bomb survivors whose radiation doses are known are given in Table 3-9.

The conclusions of the BEIR V (1990) report were based on many human epidemiological studies over the past 70–80 years. Laboratory animal data have also proven useful for understanding human risks from radiation, particularly to the respiratory tract of humans, and were included when relevant. The use of human epidemiological data is certainly a valuable tool in determining the long-term carcinogenic effects from radiation. The BEIR V (1990) committee used human epidemiological data whenever possible; however, it also recognized its many limitations when attempting to draw conclusions about the carcinogenic effects of low doses of radiation. No increase in cancer has been observed at low doses. Therefore, for purposes of setting safety standards and public policy, we resort to mathematical models with a postulated zero threshold.

Most of the literature examined reported the effects of radiation in laboratory animal species, such as monkeys, dogs, rats, pigs, mice, and guinea pigs. The short- and long-term effects of radiation in these animals as a result of this research have been studied. When the laboratory animal data are examined more closely, the researcher and risk assessor are faced with a difficult and complex question: “Is this what happens when humans are exposed to this dose of ionizing radiation?” The answer will likely depend on a number of variables, including the toxicological end point being examined (in this case, cancer). The use of human subjects in scientific research is a highly regulated area and, for obvious moral reasons, is not an acceptable practice in the area of radiation biology unless there is full informed consent and the radiation doses are low. This normally leaves radiation biology risk assessors with the following sources of information from which to determine the risks associated with radiation exposure in humans: (1) extrapolation of data from laboratory animal models (which is associated with many uncertainty

Table 3-8. Summary of Risks of Developing Cancer After Exposure to Ionizing Radiation

Organ or system	BEIR Committee conclusions about risk	Cancer Relative Risk (RR) Factors (low dose/low dose rate) per 10^6 rad (10^4 Gy) [a]
Mammary/breast	1. The development of cancer from susceptible mammary cells due to exposure to ionizing radiation depends on the hormonal status of these cells. 2. The age-distribution of radiogenic breast cancers and those breast cancers from unknown causes is similar. 3. Women irradiated at #20 years of age are at higher risk than those irradiated later in life. 4. There is no evidence to suggest that radiogenic breast cancer will appear during the first 10 years after exposure to ionizing radiation. Peak incidences occur 15 to 20 years after exposure. 5. The data show little if any decrease in the yield of tumors when multiple radiation doses are compared to single, brief exposures to ionizing radiation.	92.5
Lung	1. Absolute risk of lung cancer from exposure to ionizing radiation is similar for both males and females. 2. The data suggest that smoking has a “greater than additive” effect on the development of lung cancer after exposure to ionizing radiation.	75.4
Stomach/digestive system	1. The incidence of stomach cancers increases with increased exposure to ionizing radiation. 2. Females are at greater risk for developing cancers than are males 3. The relative risk for developing cancer is higher for those exposed when 30 years of age or younger. 4. The baseline risk for digestive cancers increases with age; most of the excess cancers occur after middle age.	49.3
Thyroid	1. Susceptibility to radiation-induced thyroid cancer is greater in childhood. 2. Development of thyroid cancer is dependant on the hormonal status of the individual; sustained levels of TSH increase the risk of developing thyroid cancer. 3. For those exposed before puberty, the tumors do not appear until after sexual maturation. The risk is greatest for children exposed within the first 5 years of life. 4. Females are 2–3 times more susceptible than males to radiogenic (and spontaneous) thyroid cancer. 5. Radiogenic cancer of the thyroid is usually preceded by benign thyroid nodules and the frequency of hypothyroidism and goiter is increased in those exposed to large doses when very young.	32.1
Esophagus	1. Increased incidences of cancer of the esophagus have been observed to occur in humans receiving doses of ionizing radiation. 2. Little human data are available to make strong conclusions about the risk of developing esophageal cancer after exposure to ionizing radiation, although a risk estimate is available.	9.5

Table 3-8. Summary of Risks of Developing Cancer After Exposure to Ionizing Radiation (continued)

Organ or system	BEIR Committee conclusions about risk	Cancer Relative Risk (RR) Factors (low dose/low dose rate) per 10^6 rad (10^4 Gy) [a]
Small intestine (duodenum, jejunum, ileum)	1. Cancers of the small intestine have been produced in laboratory animals exposed to large doses of ionizing radiation. 2. None of the human epidemiological studies have conclusively demonstrated an increased risk of developing cancers of the small intestine after exposure to ionizing radiation.	NR
Large intestine (colon/rectum)	1. Data imply that there is an increased risk of developing either colon or rectal cancer after exposure to ionizing radiation 2. Based on human exposure data, the development of colon or rectal cancer is not apparent until 15 years after exposure or longer.	178.5
Skeleton	1. Large doses of low-LET ionizing radiation can result in the development of bone cancers. 2. The data suggest a threshold of between 4 Gy of low-LET or 13.8 Gy of high-LET radiation before increased bone cancers begin to occur.	1.3
Brain/central nervous system (CNS)	1. Increased incidences of CNS tumors have been observed in both humans and laboratory animals exposed to ionizing radiation. 2. Tumors are both malignant and benign. 3. The brain is considered to be relatively sensitive to developing cancer after exposure to ionizing radiation. 4. Increases have been reported when irradiated during childhood at doses less than 1–2 Gy.	NR
Ovary and uterus	1. There is no clear relationship between exposure to ionizing radiation and the development of uterine or ovarian cancers	23.8
Testis	1. There are few human data available for studying the relationship between exposure to ionizing radiation and testicular cancer. 2. The existing data suggest that the testis is relatively insensitive to the carcinogenic effects of ionizing radiation.	NR
Prostate	1. There is a weak association between cancer of the prostate and exposure to ionizing radiation. 2. The relative risk of cancer of the prostate due to exposure to ionizing radiation is small.	NR
Urinary tract	1. Exposure to ionizing radiation can cause cancer of the bladder, as well as cancers of the kidney and other urinary structures. 2. Women < 55 years old at the time of exposure are at greater risk than older women, with this risk increasing with time after exposure. 3. Gender appears to have little effect on the incidence of bladder cancer mortality.	49.7

Table 3-8. Summary of Risks of Developing Cancer After Exposure to Ionizing Radiation (continued)

Organ or system	BEIR Committee conclusions about risk	Cancer Relative Risk (RR) Factors (low dose/low dose rate) per 10^6 rad (10^4 Gy) [a]
Parathyroid glands	1. Increased incidences of hyperparathyroidism, parathyroid hyperplasia and parathyroid adenoma occur after exposure to ionizing radiation. 2. The data suggest that the incidences of hyperparathyroidism and parathyroid neoplasia increase with increasing doses of ionizing radiation. 3. Time to diagnosis normally is $30 years.	NR
Nasal cavity and sinuses	1. Little human data is available for analysis. Nasal and sinus tumors have been noted after human exposure to internally deposited ^{226}Ra and ^{232}Th. 2. The latency of these tumors is at least 10 years. 3. The risk of developing nasal and sinus cavity tumors from routes other than from internalized sources of alpha ion radiation are extremely low.	NR
Skin	1. Increased incidences of basal cell and squamous cell carcinomas of the skin have been reported after occupational and therapeutic exposures to ionizing radiation. 2. Incidence from radiation exposure may be 5 times greater if the skin is also exposed to sunlight	1.0
Bone marrow (leukemia, lymphoma, and multiple myeloma)	1. Examples include multiple myeloma, non-Hodgkins lymphoma, and chronic lymphocytic leukemia. 2. Multiple myelomas are observed to form after irradiation of the bone marrow. 3. The latent period for multiple myeloma is considerably longer than that of leukemia. 4. In Japanese A-bomb survivors, an excess of multiple myeloma cases did not appear until 20 years after exposure. 5. Excess mortality from multiple myelomas has been observed at doses as low as 0.5-0.99 Gy 6. No other form for lymphoma has been consistently observed in human populations exposed to excess amounts of ionizing radiation.	NR

Table 3-8. Summary of Risks of Developing Cancer After Exposure to Ionizing Radiation (continued)

Organ or system	BEIR Committee conclusions about risk	Cancer Relative Risk (RR) Factors (low dose/low dose rate) per 10^6 rad (10^4 Gy) [a]
Pharynx, hypopharynx, and larynx	1. Increased incidences of cancer do arise in these tissues after therapeutic radiation (i.e., ankylosing spondylitis) in the 30–60 Gy range. Increases in these cancers were not statistically significant at the $p<0.05$ level. 2. There were no increases in the incidences of these cancers in the Japanese A-bomb survivors exposed to <1 Gy. 3. The risk of developing cancers of these tissues after exposure to ionizing radiation appears to be very low.	NR
Salivary gland	1. The incidence of salivary gland tumors was increased in the Japanese A-bomb survivors, patients treated with x rays to the head and neck during childhood, and women treated with ^{131}I when middle-aged. 2. Increases in salivary gland neoplasia are dose-dependent in the Japanese A-bomb survivors, but with no detectable increases in excess mortality. 3. The salivary gland appears to be particularly susceptible to the development of cancer after exposure to ionizing radiation.	NR
Pancreas	1. An association between cancer of the pancreas and exposure to ionizing radiation has been suggested in some literature reports. 2. Pancreatic cancer has been found in occupationally exposed thorium workers. [b] 2. The existing data suggest that the pancreas is relatively insensitive to the carcinogenic effects of ionizing radiation.	NR

[a] Values from EPA Report 402-R-96-016, Radiation Exposure and Risk Assessment Manual, June 1996. Sum of all values = 760.6, including a remainder incidence risk of 173.4 for all other organs, including those listed in column 3 as NR.

[b] Polednak et al. (1980), *Health Physics* 44 (Suppl 1): 239-251.

Source: summarized from BEIR V 1990

LET = linear energy transport; NR = RR factor not reported.

Table 3-9. Summary of Radiation Dose Response for Cancer Mortality by Site[a,b]

Site of cancer	Number of deaths	Statistical p test[c]	Estimated relative risk at 1 Gy (100 rad)	Excess risk per 10^4 person-year Gy (PY Gy) (per 10^6 PY-rad)	Attributable risk (%)[d]
All malignant neoplasms	5936	0.0000	1.39 (1.23, 1.46)	10.0 (8.36, 11.8)	10.2 (8.50, 12.0)
Leukemia	202	0.0000	4.92 (3.89, 6.40)	2.29 (1.89, 2.73)	55.4 (45.7, 66.3)
All cancers except leukemia	5734	0.0000	1.29 (1.23, 1.36)	7.41 (5.83, 9.08)	7.86 (6.19, 9.64)
Digestive organs and peritoneum	3129	0.0000	1.24 (1.16, 1.33)	3.39 (2.27, 4.59)	6.58 (4.41, 8.91)
Esophagus	176	0.02	1.43 (1.09, 1.91)	0.34 (0.08, 0.67)	12.7 (2.92, 25.0)
Stomach	2007	0.0000	1.23 (1.13, 1.34)	2.07 (1.19, 3.05)	6.26 (3.61, 9.23)
Colon	232	0.0000	1.56 (1.25, 1.98)	0.56 (0.26, 0.91)	15.1 (6.96, 24.7)
Rectum	216	0.67	0.93 (, 1.27)[†]	-0.07 (, 0.25)[†]	-1.93 (, 7.12)[†]
Liver (primary)	77	0.57	1.12 (0.87, 1.70)	0.05 (-0.05, 0.25)	3.90 (-4.38, 20.5)
Gallbladder and bile ducts	149	0.13	1.37 (0.98, 1.96)	0.22 (-0.01, 0.53)	8.24 (-0.55, 19.5)
Pancreas	191	0.53	0.89 (, 1.23)[†]	-0.10 (, 0.20)[†]	-3.01 (, 6.21)[†]
Other (unspecified)	81	0.29	1.32 (0.87, 2.14)	0.11 (-0.05, 0.35)	7.73 (-3.29, 24.2)
Respiratory system	747	0.0000	1.40 (1.21, 1.63)	1.29 (0.71, 1.96)	10.1 (5.50, 15.3)
Lung	638	0.0000	1.46 (1.25, 1.72)	1.25 (0.70, 1.89)	11.4 (6.36, 17.1)
Breast (female)	155	0.0000	2.00 (1.48, 2.75)	1.02 (0.53, 1.60)	22.1 (11.4, 34.8)
Cervix uteri and uterus (female)	382	0.08	1.22 (1.01, 1.50)	0.60 (0.04, 1.29)	5.30 (0.34, 11.5)
Cervix uteri (female)	90	0.17	1.43 (0.93, 2.30)	0.26 (-0.04, 0.70)	10.0 (-1.68, 26.9)
Ovary (female)	82	0.03	1.81 (1.16, 2.89)	0.45 (0.10, 0.90)	18.7 (3.97, 37.7)
Prostate (male)	52	0.85	1.05 (, 1.73)[†]	0.03 (, 0.40)[†]	1.89 (, 24.8)[†]
Urinary tract	133	0.0000	2.02 (1.45, 2.87)	0.55 (0.26, 0.89)	22.7 (10.8, 37.1)
Malignant lymphoma	110	0.81	1.92 (, 1.40)[†]	-0.02 (, 0.18)[†]	-1.75 (, 13.6)[†]
Multiple myeloma	36	0.002	2.86 (1.55, 5.41)	0.21 (0.07, 0.39)	32.5 (11.3, 59.5)
Liver (including not specified as primary)	590	0.02	1.24 (1.06, 1.47)	0.63 (0.07, 1.18)	7.02 (1.87, 13.2)
Kidney	38	0.18	1.58 (0.91, 2.94)	0.09 (-0.02, 0.26)	15.7 (-2.77, 43.3)
Bladder	90	0.003	2.13 (1.40, 3.28)	0.41 (0.16, 0.70)	23.6 (9.31, 40.8)
Tongue	26	0.40	0.83 (, 1.49)[†]	-0.02 (, 0.06)[†]	-5.35 (, 14.1)[†]
Pharynx	23	0.61	0.83 (, 2.04)[†]	-0.02 (, 0.09)[†]	-6.14 (, 31.6)[†]
Nose	44	0.58	0.84 (, 1.67)[†]	-0.03 (, 0.12)[†]	-4.04 (, 14.5)[†]
Larynx	46	0.16	1.51 (0.95, 2.68)	0.10 (-0.01, 0.29)	13.4 (-1.47, 37.1)

Table 3-9. Summary of Radiation Dose Response for Cancer Mortality by Site[a,b] (continued)

Site of cancer	Number of deaths	Statistical p test[c]	Estimated relative risk at 1 Gy (100 rad)	Excess risk per 10^4 person-year Gy (PY Gy) (per 10^6 PY-rad)	Attributable risk (%)[d]
Skin (except melanoma)	21	0.69	1.17 (, 2.47)†	0.02 (, 0.12)†	5.60 (, 38.7)†
Bone	27	0.65	1.22 (, 2.79)†	0.02 (, 0.16)†	6.56 (, 42.9)†
Brain tumors	47	0.97	1.03 (0.51, 2.09)	0.01 (-0.12, 0.20)	1.0 (-13.0, 22.5)
Tumors of central nervous system (except brain)	14	0.08	3.09 (1.06, 9.74)	0.10 (0.00, 0.24)	35.9 (1.4, 82.2)
Other	907	0.03	1.20 (1.05, 1.38)	0.77 (0.19, 1.44)	5.65 (1.37, 10.5)

[a] Adapted from Shimizu et al. 1988. Number in parentheses indicate 90% confidence intervals.
[b] Data includes Hiroshima and Nagasaki, Japan, both sexes (unless specifically otherwise stated), all ages at time of bombing (ATB), from 1950 to 1985.
[c] p-value based on the test for increasing trend in radiation dose.
[d] Based on 41,719 human subjects exposed to $1 rad (average = 29.5 rad).
† Lower confidence limit not reported by study authors.

factors), (2) epidemiological studies of populations that live in high and low background areas, and of populations of accidentally or occupational exposed persons, and (3) data from patients who have received diagnostic radiation and radiotherapy.

The use of human data pools theoretically provides the most direct and informative approach to assessing the toxicity of radiation in humans. This would likely be the case in laboratories using controlled exposure scenarios. Much of the information regarding exposures to radiation does not use a controlled exposure situation. Most of the human information comes from epidemiological studies following the detonation of nuclear bombs (Hiroshima, Nagasaki, Bikini Atoll, etc.), from accidents involving the release of radionuclides (Palomares, Spain; Thule, Greenland; Rocky Flats, Colorado; Hanford, Washington and others), or from exposed radiation workers or patients.

Epidemiology is the study of the incidence of disease in groups of people. Epidemiologists attempt to determine the risk factors that may cause health effects by comparing the rate of occurrence of a disease among exposed and non-exposed populations with similar attributes. Epidemiologists prefer to compare the rate of occurrence of the effects under consideration. The major questions asked are: (1) Do the rates of occurrence differ between populations? (2) Are any noted differences a real effect or are they merely due to chance? and (3) Is there a relationship between an agent or other risk factor (such as radiation) and

the effect? In studying populations, epidemiologists must characterize the subjects based upon both the risk factor and the disease status. There are three main types of observational epidemiological studies: cohort, case-control, and prevalence (cross-sectional). Prevalence studies measure the presence or absence of a disease in a particular population at a particular time. Cohort (or incidence) is a prospective study that looks at the development of a disease in an initially disease free cohort in the context of postulated risk factors. Case-control studies compare a population with an existing disease to a sex- and age-matched disease-free population.

Prevalence, cohort, and case-control studies are the most likely types of epidemiological studies to be conducted in the case of exposure to ionizing radiation. Cohort studies follow a group of initially healthy persons with differing levels of exposure or risk factors and compare the rate of occurrence of disease in each population over time. Because exposure is assessed prior to development of the effect, there is less chance for bias; in addition, the relationship of other disease outcomes to the pre-assessed risk factors may also be studied. In case-control studies, a population with a particular disease and a matched (except for the disease) disease-free population are assessed for exposure or risk factors in order to determine whether a causal relationship exists. By studying populations after the development of the disease, the causes of relatively rare diseases can be assessed without following thousands of people; thus, a case-control study is a quicker and less expensive study than a cohort study. However, there is more opportunity for bias due to the fact that the disease has already occurred prior to determining exposure or risk factors. Also, only one disease may be investigated per study.

All epidemiological studies have inherent weaknesses due to the potential for bias in the experimental design or implementation. Common forms of bias include selection bias, recall bias, misclassification, and confounding factors.

Selection bias occurs when subjects are not recruited uniformly. When information about health and exposure status is not collected consistently or reliably, this will also artificially affect the outcome of the study. Recall bias occurs when subjects do not uniformly report the incidence or severity of exposures or health effects. Misclassification refers to mislabeling or incorrectly characterizing a study participant with regard to the toxic end point or outcome (disease). A common type of misclassification occurs in patients with cancer; the cause of death in these subjects may be complicated and classified as the result

of a secondary illness. Even when death is attributed to cancer(s), the specific cancer listed on the death certificate may be a secondary metastatic cancer. Exposure may also be misclassified, particularly when study subjects are aware that they are practicing risky behavior. Confounding refers to the interaction of multiple factors on a given effect and the possibility of attributing risk to an inappropriate factor. For example, when assessing the risk of a disease due to a factor such as the wire code of high power lines (involving non-ionizing radiation), one must consider that the wire code of power lines may be highly correlated with urbanization, heavy traffic, and increased pollution, and not associated with the actual electric and magnetic field strengths to which individuals are exposed. In such a case, an association between power lines and disease must be investigated while taking these other factors into account; otherwise, the results and any statistical correlation found may not be interpretable or appropriate.

Epidemiological studies should be carefully crafted to identify and account for appropriate confounders, and their unique data interpreted objectively. The following pages contain a synopsis of some of the more important human radiation epidemiological studies.

3.2.3.2 Nuclear Detonations of 1945 in Hiroshima and Nagasaki, Japan

The first atomic device was exploded in a test on July 16, 1945, in Alamogordo, New Mexico. The U.S. military, in an effort to bring a swifter end to the war and to avoid the casualties of a ground invasion of Japan (actually planned for November 1945), detonated a ^{235}U atomic bomb over the city of Hiroshima, Japan, on August 6, 1945. Three days later, another atomic bomb using ^{239}Pu was detonated over the city of Nagasaki, Japan. In both Hiroshima and Nagasaki, a total of 64,000 people within 1 km of the air detonation site (the air detonation side is designated as the "epicenter" and the point on the ground below the epicenter is designated as the "hypocenter" or "ground zero) were killed by a combination of the blast, intense heat, and to a much lesser extent gamma and neutron radiation emitted by these bombs. Blast, heat and light, and ionizing radiation accounted for 50%, 35%, and 15%, respectively, of the energy released by the bombs (Glasstone and Dolan 1977; Zajtchuk 1989). Survivors 1–2 kilometers away from the hypocenter received up to several hundreds of rad (several gray) of radiation and suffered the ill effects of ARS. The doses dropped off fairly rapidly with distance. In Hiroshima, the dose at 1 km was on the order of 100 rad (1 Gy), dropping to approximately 1 rad (0.01 Gy) at 2 km. For Nagasaki, the doses were on the order of 1,000 rad (10 Gy) and 10 rad (0.1 Gy), respectively. Those who survived the immediate effects, including those who were far enough away or shielded from a portion of the radiation,

were potential candidates for the latent effects of radiation. A more in-depth discussion of the events surrounding the creation of the atomic devices appears in Chapter 2 of this toxicological profile.

A few years after the atomic bombs were detonated, an effort was begun to study the effects that the different doses of ionizing radiation had on the surviving populations of Hiroshima and Nagasaki. This study was instituted by the Atomic Bomb Casualty Commission (ABCC) in 1950; the effects continue to be monitored today by the Radiation Effects Research Foundation (RERF). Periodic reports are published on the effects of ionizing radiation in the human populations of these cities in the main study, called the Lifespan Study (LSS). The LSS includes 120,321 individuals living in Hiroshima and Nagasaki in 1950; of these, 91,228 were exposed at the time of the bombing (BEIR V 1990).

At the time of the bombing of both cities, it was not possible to determine the exact doses of ionizing radiation each person had received; therefore, estimates were made as to the dose of radiation received by persons located at different distances from the hypocenter. The dose estimates, called the Tentative 1965 Dose (T65D), used the air dose (gamma ray + neutron kerma in air) adjusted for shielding by structures and natural terrain based on data obtained at the Nevada test sites, the Bare Reactor Experiment Nevada (BREN) experiment, and from large-scale shielding experiments. The accuracy of this computational system was questioned in 1978. After re-examining the available data, a new system of dose estimation, the Dosimetry System 1986 (DS86), was created and is available in its final format (Roesch 1987). The DS86 system provides more accurate radiation dose estimates than the T65D estimates because of improvements in assessing shielding of building materials, in verifying the gamma-ray component of the radiation doses to survivors using thermoluminescence of quartz crystals in roof tiles, and in considering the reduction in the neutron component of the radiation dose caused by the high humidity in Japan as compared to the Nevada desert. The DS86 data are currently being reevaluated, largely because of differing opinions on the magnitude of the Hiroshima neutron doses, which could produce small changes in the individual dose estimates, and because these doses directly affect the risk estimates

Based on the new dosimetry system, there are sufficient data from these large-scale human exposures to derive some conclusions about the cancer-inducing effects of external radiation. A report by Shimizu et al. (1988) used the exposure data from 75,991 survivors of the atomic bombs at Hiroshima and Nagasaki (based on the DS86 dosimetry) to estimate the risk of developing cancer when humans are exposed to radiation. Of these 75,991 exposed persons, 59,784 were distally exposed and 16,207 were proximally

exposed to the explosions. These persons are being followed to their time of death from 1950, with the specific types of cancers found through 1985 in these deceased individuals summarized in Table 3-9. The Radiation Effects Research Foundation (RERF) plans to continue studying the survivors and their offspring throughout the survivor lifespan in order to further refine the risk estimates.

As shown in Table 3-9, external radiation induces site-specific cancers in some organs but not in others. This extensive data set indicates that leukemia (acute and chronic myeloid and acute lymphocytic, but not chronic lymphocytic), cancers of the esophagus, stomach, colon, lung, female breast, ovary, and bladder, and multiple myelomas have statistically significant increases in incidences after exposure to radiation. The incidence of these types of cancer increases with the dose (as measured by estimated relative risk at 100 rad [1 Gy] and excess risk per 10,000 individuals each exposed to 100 rad [1 Gy] [10^4 person-year Gy]). Conversely, incidences of cancers of the rectum, gallbladder, pancreas, uterus, brain, and prostate, and incidences of malignant lymphoma do not appear to increase after exposure to ionizing radiation.

A number of other conclusions can be drawn from the data sets that are presented in many extensive tables in the Shimizu et al. (1988) report. Due to the size of these data sets, much of the raw data has been omitted from this toxicological profile.

Table 3-9 shows the risks associated with certain types of cancers over all age groups; when cancers are further classified by age at the time of death (ATD) and age at the time of the bombing (ATB), other trends are seen. For ATB <10 years, the risk of stomach cancer appears to be greater for those younger ATD groups (as observed for all cancers), but this trend is not statistically significant. No definable trends are observed for breast, lung, and colon cancers; this is most likely because in 1985, this age group had not yet reached the age where expression is likely. However, the relative risk of leukemia peaked at 6–8 years after the bombing and tends to decrease every year thereafter.

In humans, cancers do not begin to appear immediately after exposure to radiation; it is only after some minimum latent period (defined in this study as the time from exposure to the time of observation) that cancers induced by the effects of radiation will occur. This is the case with leukemia and with solid

tumors shown in Table 3-9. The incidence of radiation-induced leukemia began to occur 2–3 years after the detonation occurred, reached a peak within 6–8 years, and has been steadily declining ever since. A small (yet significant) excess in leukemia mortality still existed as of the writing of the Shimizu et al. (1988) report. This study also suggested that the incidence rate of radiation-induced cancers increases significantly only when the survivors reach those ages at which cancers normally develop. Thus, the minimum latent period is longer for the younger irradiated groups. These data also have demonstrated that the latent period for all the cancers shown in Table 3-9 (except for leukemia) appears not to be dose-dependent; the latency period is not affected by the dose. The latency period, however, is shorter among the young who were exposed to higher doses within the first 10 years of life. For the solid tumors (all but leukemia), the data from this study suggest that the minimum latent period is 15–19 years for stomach cancer, 20–24 years for lung and breast cancers, 25–29 years for ovarian cancer, and 30–34 years for cancers of the colon and urinary tract and for multiple myeloma. Some benefits of following this group until the last individual dies are (1) the improvement of radiogenic cancer risk estimates and (2) the possibility of verifying that certain cancer types whose incidence rates have not increased may have very long latency periods.

Other factors were examined in this cohort that may affect cancer rates. The relative risk of developing leukemia was not significantly different for males and females. For cancers other than leukemia, particularly those of the esophagus and lung, the relative risk is higher for females than for males. As for the effect of smoking on the rate of development of lung cancers, the relative risk of lung cancer at 100 rad (1 Gy) is greater for females than males. Adjusting for the effects of smoking in both males and females, the relative risk differences no longer are statistically significant. Also, no shortening of the lung cancer latency period was noted in male or female smokers.

The Shimizu et al. (1988) report addressed the occurrence of leukemia in the populations of Nagasaki and Hiroshima; the report did not elaborate on the specific types of leukemia found in those populations as a result of age and dose. Tomonaga et al. (1993) reported on the differential effects of radiation in inducing major leukemia types in these two cities using the DS86 dosimetry system. That study included 766 leukemia cases (249 among LSS subjects) occurring as of the end of 1980 in people who were exposed within a 9-kilometer radius of the detonation hypocenter. Bone marrow and blood specimens of

the registered cases were reassembled and re-examined for 493 of the 766 leukemia-diagnosed cases, including 177 of the 249 LSS cases, using the French-American-British classification system of leukemia diagnosis. Leukemias were further subclassified into a specific type of leukemia: acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and other leukemias (OTHER, including adult T-cell leukemia and other specifically diagnosed leukemias). Once a diagnosis was ascertained, the type of leukemia was correlated with the total body kerma received by that person, the city the dose was received in, and the elapsed time since exposure. Incidence estimates for each type of leukemia by exposure category and time period were determined (see Table 3-8) as well as incidence estimates for each type of leukemia by exposure category (see Table 3-9).

Meaningful statistical analysis on the leukemia data set could not be performed and should be taken as descriptive only. For the three lowest exposure categories, incidence rates were either similar or slightly increased over time; the two highest dose categories had incidence rates for all types of leukemias declining over time. CML and OTHER leukemia incidence rates returned to background levels during the late 1970s, while at the highest exposure levels ($150 rad [1.5 Gy]), the overall incidence rates of ALL and AML were 4–5 times higher than background levels from 1976 to 1980. The age at time of bombing seemed not to modify the temporal trends of leukemia in the three lowest exposure groups. Tomonaga et al. (1993) states in regard to this data, "In the two highest exposure groups, type-specific incidence rates declined with time in the youngest age-ATB group (0–15 years) for all types. In the young adult age-ATB group (16–35 years), however, this pattern held for ALL and CML in the two highest exposure categories and for OTHER in the 50–149.9 rad (0.5–1.499 Gy) group. The incidences of OTHER among those exposed to $1.5 Gy (150 rad) and of AML among those exposed to 50–149.9 rad (0.5–1.499 Gy) held nearly constant in time and that of AML among those exposed to >150 rad (1.5 Gy) increased. Among older adults (i.e., $36 years old ATB), there was either no change or an increase in incidence over time for AML and OTHER in the two highest exposure categories. CML and OTHER rates declined with time in the 50–149.9 rad (0.5–1.499 Gy) group, and CML and CML and ALL declined with time in the $150 rad (1.5 Gy) group. There was an increase over time in the excess rates of AML among those exposed to very high radiation levels ($150 rad [1.5 Gy]) at adult ages ATB. Thus age ATB appears to moderate the temporal patterns of incidence in the highest exposure groups." The incidence estimates for these types of leukemias suggest that the incidences for ALL, AML, CML, and OTHER were all greater in the higher dose categories. In the highest dose group, the estimated incidence

of ALL decreased with increasing age ATB, while those of ALL, CML, and OTHER were less dependent on age ATB. The risks of ALL and CML increased more rapidly with an increasing dose than did those of AML and OTHER. These findings suggest that ALL and CML leukemogeneses are more affected by atomic bomb radiation production than AML.

3.2.3.3 Human Exposures to ^{226}Ra and ^{228}Ra: The Radium Dial Painters

Radium was one of the first radioactive isotopes discovered (see Chapter 2). It was used in medicines and concoctions around 1900; however, the highest exposures to radium involved its use in dial paint. Martland (1931) reported that approximately 800 females employed in a factory in New Jersey painted the dials of watches and clocks with special luminous paint. The paint consisted of a crystalline, phosphorescent zinc sulfide, with the addition of varying amounts of radium and its progeny containing primarily ^{226}Ra, ^{228}Ra, and ^{228}Th, all in the form of insoluble sulfates in the paint. These young women "tipped" or pointed the end of the paint brush with their mouth and lips whenever needed to restore a sharp painting point. This resulted in oral ingestion of small amounts of radium, mainly ^{226}Ra ($t_{1/2}$ = ~1,600 years) and ^{228}Ra ($t_{1/2}$ = 5.75 years). In the women who died, deposits of these isotopes were found over the entire skeleton, and in particular in the cortical bone surface. Martland also estimated the total lifetime body burden of radium to be between 2 and 20 µg Ra in those exhibiting clinical signs of "radium poisoning." Radiation toxicity seemed more evident in those individuals who worked at the factory for >1–2 years or who had swallowed the paint for >1–4 years.

One of the main findings in this study was the increased incidence of death in some of the exposed women. Death was noted in 18 women in the study. Thirteen of the women who died also had jaw necrosis and anemias that developed within 4–6 years after they left the factory for other employment. The other eight deaths occurred at a later date. Jaw necrosis and anemia occurred with less severity and at lower levels; these individuals developed bone lesions which were characterized as radiation osteitis. Osteogenic sarcomas (scapula, knee, pelvis, femur, orbit) also developed in this study population.

A study by Evans et al. (1966) at the Massachusetts Institute of Technology (MIT) reported on the incidence of tumors in individuals exposed to ^{226}Ra and ^{228}Ra in both the radium dial painter population and other populations exposed to alpha emitters. The study included approximately 5,000 or more persons, including chemists who inhaled or ingested radioactive compounds, patients receiving

intravenous injections of ^{224}RaCl, those who ingested water containing ^{224}Ra, and the female radium dial painters. As a group, the total duration of exposure was usually less than 1 year but in some cases was as long as 20 years. The conclusion from this study confirmed the study findings of both Martland (1931) and Rowland et al. (1978)— people who inhale or ingest radium (^{224}Ra, ^{226}Ra, ^{228}Ra) have an increased chance of developing tumors of the bone or of the paranasal sinuses but little, if any, chance of developing leukemia from any of the doses studied. The data also supported the conclusion that the time required to develop these sarcomas or carcinomas tended to increase as the total activity of radium decreased. When all measured cases were included, the skeletal dose at which tumors began to be observed was 1,200 rad (12 Gy) of alpha radiation. No tumors were observed in the population that received less than 1,200 rad (12 Gy), the "practical threshold"; the tumor incidences began to climb in a linear dose-response manner from 1,200 to 50,000 rad (12–500 Gy) skeletal dose. Not all persons receiving a >1,200 rad (12 Gy) skeletal dose developed sarcomas or carcinomas; the tumor incidence at >1,200 rad (12 Gy) skeletal dose was placed at 40% at the time the study ended. Rowland et al. (1978) conducted a follow-up study on the incidences of osteosarcoma and "head carcinomas" (carcinomas originating in the mastoid air cells or paranasal sinuses) on this population of female dial painters. The data sets are shown in Tables 3-10 and 3-11.

Using statistics from the U.S. Department of Labor (DOL), it was estimated that approximately 2,000 individuals had been employed in the radium dial painting industry prior to 1929, with 1,474 workers identified who worked in the industry prior to 1930. Most of the dial workers were not located until as late as the 1960s. For the osteosarcoma analysis, the combined intake of radium (^{226}Ra + ^{228} Ra) ranged from <0.5 to $2,500 µCi (0.02–92 MBq), with the time-weighted average ranging from 0.74 to 3,602 µCi (0.03–133 MBq). The average age at first exposure to these two isotopes ranged from 18.4 to 19.8 years. For the head carcinomas, the intake of ^{226} Ra ranged from <0.5 to $1,000 µCi, with the time-weighted average ranging from 0.71 to 1,577 µCi. The average age at first exposure ranged from 17.8 to 22.3 years. The increased incidence of osteosarcoma in this exposed population can be attributed in part to radium's distribution and elimination kinetics. Radium has distribution patterns similar to those of calcium. Once ingested, radium distributes primarily to the bone surfaces and within about 10 µm from the osteogenic cells (the target cells for radium toxicity). The range of alpha particles in soft tissue is estimated to be approximately 30–70 µm (see Chapter 2), well within the range of these radiosensitive

Table 3-10. Distribution of Osteosarcomas in a Population of Female Dial Painters Exposed to ^{226}Ra and ^{228}Ra

Systemic intake[a] (^{226}Ra + 2.5 ^{228}Ra)[b]							
Activity range (μCi)	Activity weighted average (μCi)	Number of cases	Average age at first exposure (years)	Number of bone sarcomas	Person-years	Person-years at risk	Sarcomas per 1,000 person-years at risk (10^{-3} years $^{-1}$)
$2500	3602	16	18.5	4	299	219	18.3
1000–2499	1675	22	19.2	15	529	419	36.8
500–999	675	18	19.7	8	700	610	13.1
250–499	375	32	19.8	9	1409	1249	7.21
100–249	171	27	18.4	2	1299	1164	1.72
50–99	68.0	21	18.6	0	1082	977	0.00
25–49.9	35.2	45	19.5	0	2331	2106	0.00
10–24.9	16.3	71	19.2	0	3642	3287	0.00
5–9.9	7.04	66	19.1	0	3378	3048	0.00
2.5–4.9	3.63	83	18.8	0	4217	3802	0.00
1.0–2.49	1.56	101	18.9	0	5240	4735	0.00
0.5–0.99	0.74	52	18.4	0	2731	2471	0.00
<0.5	---	205	19.0	0	10535	9510	0.00

[a]estimated amount that entered the blood after oral exposure

[b]dose adjustment factor for ^{226}Ra (and daughters) energy (29.4 MeV) and $t_{1/2}$ (1600 years), in relation to ^{228}Ra (and daughters) energy (10.6 MeV) and $t_{1/2}$ (5.75 years)

Source: Rowland et al. 1978

cells but outside the range of red marrow cells from which leukemias would originate. The osteogenic cells initially receive a large radiation dose after each intake of ^{226}Ra and/or ^{228}Ra. Owing to the long physical $t_{1/2}$ of both ^{226}Ra (- 1,600 years) and ^{228}Ra (5.75 years), both radionuclides will eventually redistribute throughout the bone matrix over time, moving out of range of the osteogenic cells but continuing to irradiate other less sensitive cells and tissues within a 70-μm radius of each atom of radium. A similar proximity of exposure scenario is likely true for the development of the head carcinomas in this population of exposed workers. The most likely explanation for the head carcinomas is that they are due to accumulation of ^{222}Rn gas and radon daughters in the mastoid air spaces of the sinus cavities. This explains the lack of effect of ^{224}Ra and ^{228}Ra, which transform through ^{220}Rn by short half-life transitions, and which produce much lower doses in the parasinal cavities than from ^{222}Rn (Rowland 1994).

Table 3-11. Distribution of Head Carcinomas in a Population of Female Dial Painters Exposed to ^{226}Ra

Systemic intake[a] (^{226}Ra)							
Activity range (μCi)	Activity weighted average (μCi)	Number of cases	Average age at first exposure (years)	Number of head carcinomas	Person-years	Person-years at risk	Carcinomas per 1,000 person-years at risk (10^{-3} years $^{-1}$)
$1000	1577	10	17.8	3	264	164	18.3
500–999	584	11	22.3	2	385	275	7.27
250–499	366	25	20.1	5	1062	812	6.16
100–249	176	31	18.3	5	1255	945	5.29
50–99	68.3	23	18.2	1	1123	893	1.12
25–49	35.5	34	18.8	1	1666	1326	0.75
10–24.9	15.9	59	19	0	3025	2435	0
5–9.9	6.99	41	18.4	0	2114	1704	0
2.5–4.9	3.52	70	19.6	0	3558	2858	0
1.0–2.49	1.55	145	19.3	0	7531	6081	0
0.5–0.99	0.71	73	18.7	0	3799	3069	0
<0.5	–	227	18.9	0	11624	9354	0

[a] estimated amount that entered the blood after ingestion

Source: Rowland et al. 1978

The data presented in both tables show that a dose response is present when comparing the weighted-average dose to the number of osteosarcomas or head carcinomas observed throughout the lifespan of these exposed individuals. In addition, a dose-squared-exponential function most closely described the bone sarcomas induced by these two radionuclides. In contrast, a linear dose-response function was found to best describe the head carcinoma data.

3.2.3.4 Human Exposures to ^{224}Ra via Injection

During 1944–1951, injections of ^{224}Ra were administered to approximately 2,000 German adults and children as a treatment modality for several debilitating diseases, including tuberculosis and ankylosing spondylitis. A report by Spiess and Mays (1970) summarized the health effects of 925 humans (708 adults and 217 children) injected with ^{224}Ra who received alpha doses of up to 5,750 rad (57.7 Gy). The duration of treatment ranged from a few weeks to a few years, depending on the disease being treated.

For this study, treated individuals were classified by age and dose received during the treatment period(s). These subpopulations are shown in Tables 3-12 and 3-13.

As was the case with ^{226}Ra and ^{228}Ra, the critical organ for ^{224}Ra was bone tissue, with an overall increased incidence of osteosarcoma in the exposed population. Tables 3-12 and 3-13 report the dose parameters and incidences of osteosarcomas induced by ^{224}Ra by age distribution. These data show that the lowest dose that resulted in a detectable osteosarcoma was 90 rad (in an adult). The incidence of osteosarcoma in this population increased in a dose-responsive fashion, with a 0.7% rise in incidence of osteosarcomas per 100 rad (1 Gy) skeletal dose from ^{224}Ra in adults and a rise of 1.4% per 100 rad (1 Gy) in children (see Table 3-13). The ability of ^{224}Ra to induce bone tumors in males and females, with or without pre-existing bone disease, was equal in all instances. At the time of publication of the Speiss and Mays (1970) report, no head carcinomas or leukemias attributable to ^{224}Ra exposure had been observed.

The lowest alpha dose to induce osteosarcoma in this population exposed to ^{224}Ra was 90 rad (0.9 Gy), significantly lower than the 1,200 rad (12 Gy) (skeletal dose at death) required to induce osteosarcoma in the radium dial painters (^{226}Ra and ^{228}Ra). The answer lies in the physical half-life of ^{224}Ra, and the total dose to the critical tissue. ^{224}Ra distributes in an identical fashion within the bone matrix as does ^{226}Ra and ^{228}Ra, with the initial deposition of each of these isotopes within 10 μm from the osteogenic cells on the bone surface. In cases of ^{226}Ra and ^{228}Ra exposure, the dose of radiation was initially received by the osteogenic cells; however, as time progressed, natural bone formation (remodeling) resulted in the redeposition of these isotopes (and other minerals) away from these target cells and into the mineral volume of the bone, out of the range of the alpha particles (50–70 μm) emitted by these isotopes. These longer-lived isotopes continued to transform for several years; however, many of the radium atoms were out of range of the target tissues (osteogenic cells) and not likely to cause bone cancer. This was not the case with those exposed to ^{224}Ra. ^{224}Ra deposits initially on bone surfaces as does ^{226}Ra and ^{228}Ra; however, the half-life of ^{224}Ra is 3.62 days and the dosimetery is quite different from other radium isotopes. The local dose to the skeleton of ^{224}Ra within 0–10 μm is estimated to be nine times the average skeletal dose of ^{226}Ra (because the radiation dose is almost exclusively delivered to the osteogenic cells during ^{224}Ra's short half-life). However, the dose from ^{226}Ra to the critical osteogenic cells is only 0.63 times the average skeletal dose, which is randomly distributed throughout the bone matrix.

Table 3-12. Alpha Doses from Injected ^{224}Ra (in rad) by Age Group, Number, and Percentage of Subpopulation Developing Osteosarcoma

		Age at first injection of ^{224}Ra					
Dose range (rad)	Parameters	1–5 years	6–10 years	11–15 years	16–20 years	All children (1–20 years)	Adults (>20 years)
0–89	Average rad dose	46	ND	24	55	47	53
	No. of persons	1	ND	1	3	5	210
	% Bone sarcomas[a]	0.00	ND	0.00	0.00	0.00	0.00
90–199	Average rad dose	152	126	ND	148	146	139
	No. of persons	2	1	ND	4	7	229
	% Bone sarcomas	0.00	0.00	ND	0.00	0.00	1.3
200–499	Average rad dose	446	397	344	342	363	306
	No. of persons	2	9	7	17	35	214
	% Bone sarcomas	0.00	0.00	29	0.00	5.7	1.9
500–999	Average rad dose	860	703	727	719	727	650
	No. of persons	7	30	22	17	76	55
	% Bone sarcomas	0.00	10	5	0.00	5.3	5.5
1000–1999	Average rad dose	1426	1381	1340	1246	1345	ND
	No. of persons	16	19	18	19	72	ND
	% Bone sarcomas	38	26	22	21	26.4	ND
2000–5750	Average rad dose	3491	3451	2550	3100	3329	ND
	No. of persons	9	9	3	1	22	ND
	% Bone sarcomas	22	67	0.00	0.00	36.4	ND
All persons with a known dose of ^{224}Ra	Average rad dose	1662	1207	984	747	1103	204
	No. of persons	37	68	51	61	217	708
	% Bone sarcomas	22	21	14	7	15.2	1.4

[a] % of bone sarcomas as of 1969 ND = No data available

Source: adapted from Speiss and Mays 1970

Table 3-13. Age Distribution, Alpha Dose (in rad), and % Incidence of Osteosarcomas Induced by ^{224}Ra Injection

Age (years)	Exposed patients	Sarcoma cases	% Incidence	Average dose (rad)	% Incidence per 100 rad
1–5	37	8	21.6	1662	1.30
6–10	68	14	20.6	1207	1.70
11–15	51	7	13.7	984	1.39
16–20	61	4	6.6	747	0.88
All children	217	33	15.2	1103	1.38
Adults	708	10	1.4	204	0.69

Source: adapted from Speiss and Mays 1970

Other similar studies include those involving tinea capitis treatment (Albert et al. 1986; Harley et al. 1983; Ron and Modan 1984), uranium miners (NIH 1994), and iron miners (Radford and Renard 1984).

3.2.3.5 Other Human Cancer Studies

Cancer data from other sources are available in the open literature. Sorahan and Roberts (1993) performed a case-control study examining the association between childhood cancer and the occupational exposure of the child's father to radiation. Data from the Oxford Survey of Childhood Cancers collected from 1953 to 1981 were used. There was a total of 15,279 cases and the same number of matched controls (matched for sex, date of birth, and local area). Estimates of exposure were completed based on job descriptions. Dose groups were: not exposed (<0.1 rem, 0.001 Sv), 0.1–0.4 rem (0.001–0.004 Sv), 0.5–0.9 rem (0.005–0.009 Sv), and $1 rem (0.01 Sv). There were also 27 case fathers and 10 control fathers who had been exposed to radionuclides. Based on the information gathered, it was determined that 67 fathers of children with cancer and 50 fathers of controls were exposed to external radiation within 6 months of conception of their children. Relative risks for estimated external radiation doses and all childhood cancers were near one, and none of the specific types was statistically significant. Among fathers with likely exposure to radionuclides (from unsealed radioactive material), the relative risk for all childhood cancers was statistically significant at 2.87 (95% CI 1.15–7.13). There is considerable uncertainty associated with this value, and the findings are not supported by those in the studies of the survivors of the atomic bombings in Japan. Cancer incidence during the first 20 years of life among the children of parents who suffered a mean gonadal dose of 43 rem (0.43 Sv) was 43 cases in 31,150 offspring, and there were 49 cases among 41,066 offspring from the control population. For leukemia,

there were 16 cases among 31,150 children of exposed parents and 21 cases among the 41,066 children from the unexposed controls (Yashimoto et al. 1991).

In 1991, Matanoski (1991) reported on the health effects of low-level radiation exposure to shipyard workers. Many of the earlier human radiation studies had been of groups exposed to large doses of radiation where there was a clear dose response for cancer induction. The typical dose response curve assumes a linear no-threshold shape that starts with zero effect at zero dose and extends linearly upward to intersect the measured effect at doses above 10–40 rad (0.1–0.4 Gy). Previous attempts to demonstrate the shape of the curve at low and occupational doses had not produced a clear result. The purpose of the Matinoski study was to better define the upper and lower bounds of risk associated with radiation exposure using a relatively large population group whose radiation doses had been measured carefully, many of which were elevated above ambient levels, and for which there was an adequate control population. The selected group was workers in public and private U.S. shipyards involved in the overhaul and refueling of nuclear-powered warships. Concern over the risk to these workers had been raised earlier in a limited study of deaths among Portsmouth, New Hampshire, shipyard workers (Najarian 1978). Also, a report had been released on an apparent leukemia excess among U.S. military veterans (Caldwell 1980). However, a subsequent cohort study by Rinsky (1981) did not observe a relationship between exposures and leukemia. These groups had received approximately the same radiation dose. The Matinoski study group involved workers at eight nuclear facilities throughout the United States, who had been occupationally exposed from 1957 through 1981. The study group was divided into dose groups and exposures were lagged by 2 years for leukemia and lymphoma, and 5 years for lung cancer to account for disease latency. The numbers in each of the three major dose groups were: 32,510 non-radiation workers, 10,348 radiation workers whose doses were below 0.5 rem (0.005 Sv), and 27,872 radiation workers whose doses were over 0.5 rem (0.005 Sv). The data were analyzed statistically using methods suggested by Gilbert (1983). In this manner it was estimated that the statistical power had a 79% probability of finding a risk of leukemia from cancer if the risks were as large as five times the linear model estimates in BEIR III (1980). For those whose doses exceeded 0.5 rem (0.005 Sv), the death rate from leukemia was only 91% of the normally expected death rates from that disease (95% confidence interval = 56–139%), and the death rate from lymphatic and hemopoietic cancers was 82% (95% confidence interval = 61–108%) of the normally expected death rates from those diseases. The death rates from these diseases in the less than 0.5 rem (0.005 Sv) group were similar to those in the above 0.5 rem (0.005 Sv) group. Standard mortality ratios (SMRs) for the lower-dose group were similar. This

indicates the risks of these diseases is lower among shipyard workers than in the general population. The risk of lung cancer, however, was significantly higher ($p<0.05$) in the non-nuclear work group and slightly higher in the nuclear work groups than for the public. Mesothelioma was selected as a biological marker for the presence of asbestos exposure in the population, and a high SMR for mesothelioma (>5 for radiation workers and 2.4 for non-radiation workers) suggests that the excess is due to asbestos exposure and not to radiation. The radiation worker population did not show a significant increase in the risk of any of the cancers studied, except for mesothelioma which was attributed to asbestos. The data suggest that there is a threshold greater than 0.5 rem (0.005 Sv) for leukemia, and lymphatic and hemopoietic cancers.

In another human study, Checkoway et al. (1988) used a historical cohort mortality study of 8,375 workers at the Y-12 plant at Oak Ridge who were exposed to gamma radiation and/or alpha radiation by inhaling uranium compounds. The population studied included employees who had worked for at least 30 days between May 1947 and December 1974. The median duration of exposure in that study was 9.2 years. There were 862 deaths in the cohort, which was composed of 6,781 white males. The majority of the cohort was followed for 10 years. Exposure from gamma radiation was measured with dosimeters or film badges, and internal alpha contamination was estimated with urinalysis for uranium (reported as cumulative radiation dose). Mortality was compared with both U.S. and Tennessee rates. For all causes there were fewer deaths than expected (Standardized Mortality Ratio [SMR] 0.89, 95% CI 0.84–0.96). These findings are consistent with the healthy worker effect. There were a total of 196 cancer deaths in the population compared to 193 expected, (SMR 1.01). Relative to U.S. white males, there were statistically significant excesses of lung cancer (SMR 1.36, 95% CI 1.09–1.67) and possibly cancers of the and central nervous system (SMR 1.8, 95% CI 0.98–3.02). Cancer SMRs for Tennessee white males were lower than those for the U.S. white male referent population. A trend was observed for increasing lung cancer deaths with increasing radiation dose, although the trend was greater with a zero-year latency assumption than for a 10-year latency assumption. Mortality for brain and central nervous system cancers was unrelated to either the alpha or gamma dose. The authors point out that the dose-response trend for lung cancer mortality should be viewed with some caution because the rate ratio estimates are imprecise, as reflected by the wide confidence limits because of small numbers. Also, the dose-response gradients are reduced considerably when a 10-year latency is assumed. No data on cigarette smoking were included in the study. Other studies have also shown that the lung is the primary target organ of airborne radon when mixed with diesel fumes, cigarette smoke and silica dust related to uranium mining, but not from uranium itself (BEIR IV 1988), which was the most important airborne radioactive material at this

plant. Readers are referred to the effects of cancer induced by the chemical and radiological effects of uranium mining in the ATSDR *Toxicologic Profile for Uranium* (ATSDR 1999b).

In a later related report, Kneale et al. (1981) responded to criticism of previous reports of a study of cancer risks from radiation to workers at Hanford using the method of regression models in life-tables. The population included employees up to 1975 who wore film badges for their external dosimetry record and included deaths through 1977. Some internal monitoring was also completed: individuals for whom internal monitoring was completed tended to have higher external exposures. Cause of deaths was classified into three categories: (1) cancers of radiosensitive tissues (stomach, large intestine, pancreas, other intestinal, pharynx, lung, breast, lymphoma, myeloma, myeloid leukemia, other reticuloendothelial system cancers, and thyroid); (2) other cancers; and (3) non-cancer. The reported risk per unit of radiation dose for cancers of radiosensitive tissues was much greater than the generally accepted risk based on other studies which had been used in setting safety levels for exposure to low-level ionizing radiation. The estimated risk calculated from this study was about 10–20 times greater than would have been expected by extrapolating downward from higher doses analyzed in previous studies, notably studies of the atomic bomb survivors. The authors suggested that after statistically controlling for a wide range of possible interfering factors, there was a significant downward curve at about 10 rem (0.1 Sv) in the dose-response relationship. Therefore, the agreement with other studies, conducted at higher doses, may be stronger than is widely assumed. The authors also point out that the findings on cancer latency (about 25 years) and the effect of exposure age (increasing risk with age) are in general agreement with other studies. The unexplained finding is a significantly higher dose for all workers than for workers who developed cancers in tissues that are supposed to have low sensitivity to cancer induction by radiation. The “healthy worker effect” was very large in this study—the SMR for all causes of death was 75. Therefore, the fact that living workers at Hanford in Washington State have higher radiation doses than workers who died could reflect a healthy worker effect. Using a model that allowed for cancer latency and variation in sensitivity to radiation with age of exposure, investigators estimated a doubling dose for cancer of 15 rad (0.15 Gy) with a 95% CI of 2–150 rad. The interval between cancer induction and death was estimated (maximum likelihood estimate) to be 25 years. The investigators also discuss the fact that Japanese bomb survivor data and ankylosing spondylitis data indicate that the doubling dose is about 200 rem (2 Sv). No records of smoking were available for the Hanford population. Internal monitoring showed evidence of internal exposure in only 225 of the Hanford workers; the investigators indicate that

the effects were a result of external rather than internal radiation. The authors pointed out that the Hanford study could not distinguish between effects of neutron and gamma radiation.

3.2.3.6 Laboratory Animal Reports

Cancer is a major latent biological effect of inhaling many of the various isotopes and chemical forms of radioactive materials. The literature contains many studies describing the onset and specific types of cancers that occur after inhalation exposure(s) (see the ATSDR profiles on uranium and radon for more complete information). The vast majority of reports concerning the inhalation of radionuclides with the subsequent development of cancer dealt with alpha and beta particle emitters incorporated into soluble or insoluble particles of varying sizes for an acute duration of delivery (usually only a few minutes to achieve the desired initial lung burdens) followed by a long-term exposure of the tissues. Due to the large database describing the neoplasia associated with exposure to ionizing radiation, only a cross-section of these reports will be discussed in some detail here.

Cancer has been reported in laboratory animals after inhalation of different radionuclides (see Table 3-1). For example, isotopes of strontium (^{85}Sr and ^{90}Sr) have strong affinities for bone; therefore, it is reasonable to expect that the initial site of neoplasia formation will be in bone tissues. Metastases may occur to more distant organs at a later time, depending on the type of tumor induced. For example, Gillett et al. (1987b) studied the late-occurring biologic effects in Beagle dogs given graded levels of $^{90}SrCl_2$ via single brief inhalation exposures and then observed for their lifespans. The cumulative absorbed beta dose to bone ranged from 12 to 1,200 rad (0.012–12 Gy) at 30 days and from 200 to 170,000 rad (92–1,700 Gy) at 1,000 days after exposure. The most frequent cause of death in exposed dogs was primary bone cancer (30 of the 66 exposed dogs). Bone-tumor-related deaths occurred from 759 to 3,472 days after exposure. Four additional animals developed carcinomas in soft tissues adjacent to the bones of the skull (invasive baso-squamous carcinoma, transitional carcinomas of the nasal cavity, and an adenocarcinoma in the maxilloturbinate region). The remaining exposed and control dogs died from a variety of other causes not related to ^{90}Sr exposure. Radiation-induced lesions were confined to the bone, bone marrow, and adjacent soft tissue. Forty-five primary bone tumors occurred in 31 of the 66 exposed dogs (47%). Metastasis occurred from 21 tumors, with the lungs being the most frequent site of metastasis (76%). Twenty-seven tumors were classified as different subtypes of osteosarcoma, 14 as hemangiosarcomas, 3 as fibrosarcomas, and 1 as a myxosarcoma.

Using ^{241}Am, Gillette et al. (1985) determined the retention, translocation, and excretion of inhaled monodisperse (1.8 μm AMAD) or polydisperse aerosols (AMAD 0.75, 1.5, 3.0 μm) and explored the development of osteosarcomas in dogs. ^{241}Am was soluble and transported in blood and deposited in the liver and skeleton. Two years after exposure, 0.5–3.0% of the initial lung burden was present in the lung, 10–47% was in the liver, and 10–36% in the skeleton. Four of 15 dogs developed osteoblastic osteosarcomas #1,000 days after exposure to ^{241}Am. Three of these were in the 1.8-μm AMAD group and one was in the 3.0-μm AMAD group. Initial lung burdens for all 15 ranged from 1.0 to 6.2 μCi (0.04–0.2 MBq). Radiation doses to 1,000 days for dogs ranged from 185 to 1,260 rad (1.85–12.6 Gy) to the lungs, 180 to 1,070 rad (1.8–10.7 Gy) to the liver, and 67 to 410 rad (0.67–41 Gy) to the skeleton, while the skeletal doses to death for the 4 dogs developing osteosarcoma were 500, 300, 240, and 180 rad (5, 3, 2.4, and 1.8 Gy). Metastasis was evident in only 1 of the 4 dogs.

Neoplastic formation after exposure to ^{238}Pu and ^{239}Pu has been extensively studied in Beagles. Hahn et al. (1981) exposed 72 Beagle dogs by inhalation to monodisperse aerosols of $^{238}PuO_2$ measuring 1.5 μm and another 72 dogs to particles measuring 3.0 μm. Twenty-four control dogs inhaled an aerosol produced from a diluent solution. Equal numbers of males and females were used. Groups of 12 dogs were exposed to concentrations expected to produce initial lung burdens of 0.56, 0.28, 0.14, 0.07, 0.029, 0.01, and 0 μCi/kg (0.021, 0.010, 0.0052, 0.0826, 0.0011, 0.00037, and 0 MBq/kg). However, mean actual initial lung burdens were 0.97, 0.43, 0.26, 0.11, 0.055, 0.017, and 0 μCi/kg (0.0359, 0.0159, 0.0096, 0.0041, 0.0020, and 0 MBq/kg), respectively, for 1.5 μm particles, and 1.2, 0.57, 0.30, 0.14, 0.069, 0.024, or 0 μCi/kg (0.044, 0.021, 0.011, 0.0052, 0.0026, 0.00089, or 0 MBq/kg), respectively, for 3.0 μm particles. Necropsy and histopathological examinations were performed at death. Primary bone cancers developed in Beagle dogs briefly exposed by inhalation to aerosols of $^{238}PuO_2$. $^{238}PuO_2$ was initially deposited in the respiratory tract where it was retained with a half-time greater than 100 days. A portion of the ^{238}Pu was solubilized and translocated to the liver and skeleton; 46 of 144 exposed dogs and 2 of 24 control dogs died (as of date of publication). Deaths unrelated to bone tumors are as follows: 7 of the 144 dogs died from severe radiation pneumonitis and pulmonary fibrosis 536–1,213 days after exposure (3,700–8,600 rad [37–86 Gy] to lungs) and 4 of the 144 dogs died of pulmonary carcinomas 1,319–2,143 days after exposure (2,100–5,900 rad [21–59 Gy] to lungs). Five years after exposure, 46 osteosarcomas developed in 35 of 144 exposed dogs. The cumulative absorbed radiation doses to the skeleton for these dogs ranged from 210 to 830 rad (21-83 Gy), and time from inhalation exposure to death ranged from 1,125 to 2,078 days. Of the 46 bone tumors, 22 originated in the vertebrae (49%),

12 in the humeri (26%), 6 in the pelvis (13%), and 6 in miscellaneous long and flat bones (13%). Most of the tumors were well differentiated sarcomas. Only 10 of the tumors metastasized; the lung was the organ most often invaded. Bone tumors were associated with lesions of radiation osteodysplasia. The number of bone tumors found in this study indicated that inhaled $^{238}PuO_2$ was an effective skeletal carcinogen. The authors noted that the rate of solubilization in the lungs and translocation to the bone may be factors in the radiation dose pattern and the type and location of bone tumors that developed after inhalation of $^{238}PuO_2$.

In another study, Muggenburg et al. (1994) exposed 144 Beagle dogs to $^{238}PuO_2$ aerosols; 72 of these dogs inhaled monodisperse aerosols of $^{238}PuO_2$ with AMADs of 1.5 µm, and 72 dogs inhaled 3.0-µm AMAD particles. For each particle size, dogs were exposed to achieve one of the following six graded activity levels of initial lung burden: 0.57, 0.27, 0.14, 0.08, 0.03, or 0.01 µCi of $^{238}PuO_2$/kg. These dogs were observed for biological effects (cancerous and non-cancerous effects) over their natural lifespan. The $^{238}PuO_2$ aerosol exposures resulted in initial lung burden ranging from 37 to 0.11µCi and from 1.50 to 0.01 µCi (1.4–0.004 and 0.06–0.0004 MBq) of $^{238}PuO_2$/kg of body mass for the 1.5- and 3.0-µm particles, respectively. The particles were found to dissolve slowly, resulting in translocation of the Pu to liver, bone, and other tissue sites. The principal late-occurring effects were tumors of the lung, skeleton, and liver. Lung tumors were detected in 47 of the exposed dogs; within this group, lung tumors were the primary cause of death in 8 dogs that died from 3.6 to 12.3 years after exposure. Twenty-seven dogs that died from bone tumors also had lung tumors. Lung tumors were primarily bronchoalveolar carcinomas and papillary adenocarcinomas. Skeletal tumors were detected in 92 dogs; of this group, bone tumors were the primary cause of death in 89 dogs that died from 3.1 to 13.2 years after exposure. These tumors were primarily osteosarcomas that occurred in the axial skeleton and head of the humerus. Liver tumors were detected in 19 dogs and caused the death of 2 dogs that died from 6.6 to 13.2 years after exposure. Thirteen of these dogs had a variety of malignant liver tumors and 6 had only benign liver tumors. Risk factors estimated for these cancers were 2.8 lung cancers per 10^6 dog-rad, 8.0 liver cancers per 10^6 dog-rad, and 6.2 bone cancers per 10^6 dog-rad.

Using a different isotope of Pu, Muggenburg et al. (1988) exposed 216 Beagle dogs to $^{239}PuO_2$ aerosols. The $^{239}PuO_2$ aerosols were monodisperse with AMADs of 0.75, 1.5, or 3.0 µm. After the inhalation was completed, all animals were matched by age and sex (6 males and 4 females in each group). Group I dogs had initial pulmonary burdens (IPBs) of 8.91–109.9 µCi (0.3–4 MBq) of $^{239}PuO_2$/kg of body mass with a mean of 42.9 µCi/kg (1.6 MBq/kg). Group II dogs had IPBs of 2.97–52.9 µCi (0.1–2 MBq) of $^{239}PuO_2$/kg

of body mass with a mean of 15.9 µCi/kg (0.6 MBq/kg). The plutonium particles produced protracted alpha irradiation of the lungs over the course of several years. The average alpha dose to the lungs to 2,600 days after exposure for the dogs in group I ranged from 230 to 3,200 rad and for the dogs in group II, 80 to 1,570 rad. Five dogs died within 1 year of exposure. Lung carcinomas were observed in 3 dogs (2 males and 1 female) from group I (2,900–3,200 rad) and in 1 dog (male) from group II (1,000 rad). These 3 dogs from group I had the highest doses and had many small, dense, parenchymal scars and small foci of alveolar septal fibrosis scattered throughout the lungs. Alveolar epithelial hyperplasia was associated with many of the fibrotic foci. Oral melanoma was found in one dog (male) from group II that died (190 rad).The authors note that these findings indicate that alpha irradiation of the lungs of humans could produce restrictive lung disease at long times after initial exposure. Other studies in dogs have demonstrated that exposure to ^{239}Pu can induce lung cancer (Boecker et al. 1988; Galvin et al. 1989).

In addition to Pu, other radionuclides have been shown to induce cancer in dogs. Hahn et al. (1977) reported on a series of lifespan studies initiated to study the biological effects of beta emitters using aerosols of insoluble fused-clay particles containing ^{90}Y, ^{91}Y, ^{144}Ce, or ^{90}Sr. AMADs ranged from 0.8 to 2.7 µm and the duration of exposure was 2–48 minutes. ^{90}Y exposures resulted in a range of initial lung burdens of 0 or 80–5,200 µCi/kg body weight; ^{91}Y exposures resulted in a range of initial lung burdens of 0 or 11–360 µCi/kg; ^{144}Ce exposures resulted in a range of initial lung burdens of 0 or 0.0024–210 µCi/kg; and ^{90}Sr exposures resulted in a range of initial lung burdens of 0 or 3.7–94 µCi/kg. The approximate effective half-lives in the lungs of insoluble ^{90}Y, ^{91}Y, ^{144}Ce, and ^{90}Sr are 2.6, 50, 180, and 400 days, respectively. Dogs exposed to ^{144}Ce or ^{90}Sr generally had more active inflammation and pulmonary fibrosis than dogs exposed to ^{90}Y or ^{91}Y, perhaps due to their longer average survival time after inhalation exposure and the influence of the continuous irradiation. Primary malignant lung tumors were found in 5 of the ^{91}Y exposed dogs (cumulative lung doses to death of 16,000–25,000 rad), 9 of the ^{144}Ce exposed dogs (22,000–61,000 rad), and 14 of the ^{90}Sr exposed dogs (34,000–68,000 rad). Several dogs died with primary hemangiosarcomas of the heart or mediastinum, and several died with primary bone tumors or epithelial tumors associated with the nasal cavity. Exposure to ^{144}Ce or ^{90}Sr, with dose rates that decreased slowly, induced pulmonary hemangiosarcomas. Pulmonary irradiation from ^{91}Y, with a rapidly decreasing dose rate, resulted in bronchoalveolar carcinomas. Benjamin et al. (1978) exposed dogs to ^{144}Ce in fused aluminosilicate particles with particle sizes ranging from 1.4 to 2.7 µm. Radiation pneumonitis and pulmonary fibrosis were evident in 13 of 14 dogs that died. Additionally, there was one bronchoalveolar-squamous carcinoma and four pulmonary hemangiosarcomas. The tumors observed

developed within a time period when the dogs showed severe lymphopenia and also were likely to have immune suppression. These studies suggest that chronic pulmonary irradiation from internally deposited radionuclides may have a dual effect in terms of combined carcinogenic and immunosuppressive effects.

Other species exposed to Pu isotopes show similar results. Brooks et al. (1992) exposed male monkeys by nose-only inhalation to an aerosol of soluble $^{239}Pu(NO_3)_4$ to produce projected initial lung burdens of either 1.08, 0.27, or 0.1 μCi (0.04, 0.01, or 0.004 MBq). Total skeletal plutonium activity was nearly constant for the first year after exposure; however, the skeletal burden at sacrifice increased with time up to 99 months after exposure to 1.08 μCi (0.04 MBq) because of transfer from other organs. ^{239}Pu in the liver peaked at 1 year and then decreased to about 10% of the peak value at 99 months postexposure. In the testes, Pu was localized in the interstitial tissue with only 0.01–0.002% of the projected lung burden remaining in the testes at 99 months after inhalation. Animals exposed to 1.08 μCi (0.04 MBq) died (3 of the 8) of radiation-related pulmonary pneumonitis and fibrosis, and a primary papillary adenocarcinoma of the lung was identified in one animal in that group. Of 2 animals exposed to 0.27 μCi (0.01 MBq), 1 developed fibrosis and 1 developed fibrosis and pneumonitis. Of those exposed to 1.08 μCi (0.04 MBq), 6 developed pneumonitis, 9 developed fibrosis, 7 developed alveolar epithelial proliferation, and 1 developed lung cancer. Overall, results of this study indicate that the lungs, the bone, and the liver are the major sites of deposition following inhalation of soluble plutonium in monkeys. The primary biological effects, pneumonitis and pulmonary fibrosis, were seen in monkeys with large initial plutonium burdens. There was little indication of chromosome damage at levels of plutonium at which there were no major histological changes in the lungs.

Hahn et al. (1987) exposed 16 male Rhesus monkeys to particles laden with $^{239}PuO_2$ via inhalation (AMAD 1.6 μm). Initial lung burdens ranged from 0.0018 to 1.8 μCi (0.00007–0.07 MBq). A pulmonary fibrosarcoma of bronchial origin was discovered in one monkey that died of pulmonary fibrosis after 9 years (3,277 days) with a radiation dose to the lungs of 1,400 rad (14 Gy). The fibrosarcoma proliferated around the major bronchus of the right cardiac lung lobe and extended into the bronchial lumen and surrounding pulmonary parenchyma. The time-dose relationship for survival is consistent with that of dogs and baboons that inhaled plutonium dioxide and died with lung tumors.

In addition to dogs and monkeys, induction of cancers in rats irradiated with different radionuclides has also been studied. A lifespan study was conducted by Lundgren et al. (1981) in CFW random-bred male

mice for the toxicity of ^{90}Y (AMAD 0.7–1.4 μm) inhaled in insoluble fused aluminosilicate particles. Groups of 25–393 mice were exposed to achieve initial lung burdens of 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, and 61–140 μCi (0.04–0.4, 0.4–0.7, 0.8–1.1, 1.2–1.5, 1.5–1.8, 1.9–2.2, and 2.3–5.2 MBq). Exposures were 10–20 minutes. Control mice (n=763) were either unexposed, sham exposed, or exposed to nonradioactive Y in fused aluminosilicate particles. At death, animals were necropsied and major organs examined. Mean absorbed dose to the lungs to death were 1,100, 2,300, 3,800, 6,000, 7,200, 8,800, and 14,000 rad (11, 23, 38, 60, 72, 88, and 140 Gy) for initial lung burdens of 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, and 61–140 μCi (0.04–0.4, 0.4–0.7, 0.8–1.1, 1.2–1.5, 1.5–1.8, 1.9–2.2, and 2.3–5.2 MBq), respectively. The cumulative survival rates of mice in groups with initial lung burdens up to 20 μCi (0.7 MBq) that produced lung doses as large as 2,300 rad (23 Gy) were not significantly different from that of controls. Larger lung burdens caused lung doses >3,000 rad (30 Gy) and resulted in radiation pneumonitis and a significant shortening of the lifespan ($p<0.05$). Median survival time ranged from 12% to 2.1% of controls at initial lung burdens of more than 20 μCi, and median time of survival after exposure ranged from 66 to 12 days for these dose levels. Radiation pneumonitis was observed in 75–100% of mice at these dose levels. The incidences of all lung tumors and other lesions in exposed mice were similar to those of controls, except for pulmonary adenomas, which were found more frequently in groups of mice with initial lung burdens of as large as 20 μCi (0.7 MBq). The early occurring biological effects observed in mice in this study were similar to those observed in Beagle dogs exposed to ^{90}Y.

Hahn and Lundgren (1992) also studied lung cancers induced in rats by inhaled $^{144}CeO_2$. Rats were exposed once or repeatedly by inhaling $^{144}CeO_2$ and observed over their natural lifespan. Three groups (a total of 314 rats) were exposed once, briefly, to $^{144}CeO_2$ to achieve lung burdens of 0.06, 0.32, 1.16, or 6.48 μCi (0.002, 0.01, 0.04, and 0.24 MBq). Another group of 201 rats was repeatedly exposed briefly once every other month for 1 year (7 exposures) to initially establish and subsequently re-establish desired lung burdens in groups of 18–38 males and 19–38 females of 0.35, 1.30, 5.67, or 32.4 μCi (0.01, 0.05, 0.2, and 1.2 MBq). There was significant life shortening only in those rats exposed repeatedly at the highest radioactivity level (32.4 μCi, 1.2 MBq). In these rats, there was a high percentage of squamous cell carcinomas of the lungs, as well as much lower percentages of adenocarcinomas of the lungs, hemangiosarcomas of the lungs, and pleural mesotheliomas. At lower doses, adenocarcinomas were the predominant tumor, with alveolar, papillary, tubular, or undifferentiated adenocarcinomas most commonly observed histologically. The lung neoplasms induced by this beta-emitting radionuclide are

similar in nature to those induced by alpha-emitting radionuclides deposited in the lung in rats. However, the radiation-induced squamous cell carcinomas of the lungs differed from those induced by nonradioactive compounds.

Many other studies also confirm the formation of cancers of the respiratory tract in laboratory animals (Benjamin et al. 1975, 1978, 1979; Boecker et al. 1988; Gillette et al. 1992; Hahn et al. 1976, 1980, 1988; Lundgren et al. 1974, 1980a, 1983, 1991; McClellan et al. 1973).

Skin and bone cancer have been demonstrated after external exposure to radionuclides, particularly those that are beta and gamma emitters. Ootsuyama and Tanooka (1989) exposed female mice to beta irradiation from 40,000 µCi (1,500 MBq) of ^{90}Sr and ^{90}Y which delivered a surface dose rate of 228 rad/minute (2.28 Gy/min) and a 20–80% lower dose rate to the top of the vertebrae. Mice were irradiated three times weekly at skin entrance doses per exposure of 135, 150, 250, 350, 470, and 1,180 rad (1.35, 1.5, 2.5, 3.5, 4.7, and 11.8 Gy), respectively, and irradiation was continued until a palpable tumor appeared (up to 86 weeks). Tumors that formed in the irradiated area were of skin and bone origin. Most mice had either an osteosarcoma or a skin tumor, while some mice had both osteosarcomas and skin tumors. Osteosarcomas were induced most frequently with skin surface doses of 250–350 rad (2.5–3.5 Gy) per exposure. These doses were 20–80% lower at the depth of the bone. The skin is incidentally irradiated in the radiotherapy of deep tumors. Repetitive irradiation was essential, or at least more effective, for induction of osteosarcomas, as well as for skin tumors, and the carcinogenic dose for osteosarcoma was less than that for skin tumors.

Hulse (1966) irradiated female mice with ^{204}Tl and then allowed them to live out their natural life (unless they were moribund or sacrifice was deemed necessary). Nominal doses ranged from 750 to 12,000 rad (7.5–120 Gy). ^{204}Tl beta particles have a low energy (mean 0.24 MeV) and a maximum range in soft tissue of 3 mm. Doses to the dermis and epidermis were 69–72% and 40–70%, respectively, of the epidermal entrance dose. Mice were irradiated on one or two zones. The single-zone exposure included the middle of the trunk, and the two-zone exposure included the thorax (with proximal forelimbs) and pelvis (with hindlimbs), with an intervening unirradiated gap of about 1 cm. In one group, two zones were arranged to be immediately adjacent (thorax-midtrunk, midtrunk-pelvis) with the potential for slight overlap due to the movement of the mice. The percentage of mice irradiated on one zone only and dying with skin tumors was 7, 25, 42, and 57 for the 1,500-, 3,000-, 6,000-, and 12,000-rad (15, 30, 60, and 120

Gy) dose groups, respectively. In mice exposed to two separate zones, the percentage dying of skin tumors was 3, 17, and 50 for the 750-, 1,500-, and 3,000-rad (7.5, 15, and 30 Gy) dose groups, respectively. Mice that were irradiated on two adjacent zones received 1,500 rad (15 Gy) only. Twenty percent of these mice died with skin tumors. A total of 133 tumors arose in tissues which were affected by the irradiation, and 7 tumors arose in similar tissues outside the irradiated zones. There were 20 epidermal tumors: 2 benign and 18 squamous cell carcinomas, which were situated on the torso. There were 96 dermal tumors; 77 of those were malignant and of those 74 were fibrosarcomas. Five fibrosarcomas occurred beneath the irradiated skin and 12 breast tumors occurred. No tumors of the epidermis or dermis were seen in the unirradiated control mice. The maximum incidence of dermal tumors in all dose groups occurred during the third year after irradiation. Increasing the number of irradiated zones from one to two zones, which doubled the exposed skin area, essentially doubled the animal's chance of dying from skin cancer.

In summary, cancer is the major latent biological effect in several studies identified in this profile after inhalation, ingestion, or external exposure. Reports of cancer induction after ingestion and the more unconventional exposure routes are numerous (Evans et al. 1966; Martland 1931; Raabe 1994; Rowland et al. 1978; Speiss and Mays 1970). Excess cancer has been reported in humans after exposure to varying amounts of radiation during the Hiroshima and Nagasaki atomic blasts (Shimizu et al. 1988), which has provided risk assessors a unique data set to determine the short- and long-term biological effects of radiation in humans. Several other studies that monitored cancer death rates from radiation exposure in humans were also located (Checkoway et al. 1988; Kneale et al. 1981; Sorahan and Roberts 1993). Reports of humans receiving an acute inhalation, oral, dermal, or external dose of radiation under controlled conditions were not identified in the open literature. Levels of Significant Exposure to Radiation and Radioactive Material tables that describe Cancer Effect Levels (CELs) from exposure to radiation in humans and laboratory animals are provided in Chapter 8 of this profile.

Many laboratory animal inhalation exposure studies were identified that described increased incidences of cancer developing in a variety of species after exposure to alpha, beta, and gamma radiation. Many of these studies were selected for discussion in this profile because they were lifespan studies, concentrating on the effects of alpha (^{238}Pu, ^{239}Pu) and beta (^{90}Sr, ^{144}Ce, ^{91}Y, ^{137}Cs) emitters. The main animal model, the Beagle dog, has lungs that are similar anatomically, physiologically, and morphologically to human lungs, making them an ideal lung model to study the potential effects of inhaled nuclides in humans. The nasopharageal structure of the Beagle is significantly different from a human's; therefore, comparisons of nasal tissue and bone cancers between the species are not practical at this time. These studies provide

valuable data on the long-term toxicity of many radionuclides that would be likely to be inhaled in soluble and insoluble forms during a nuclear fallout or an acute exposure event, as well as low-level radionuclide exposure from fallout and natural in the atmosphere. Biennial reports of these lifespan studies that summarize the most recent findings from these laboratory animal studies are available.

These animal studies, especially the Beagle dog studies, clearly demonstrate that the inhalation of very large amounts of radionuclides in soluble or insoluble forms, which results in very high absorbed doses to the lungs, has the potential to produce lung cancer and to induce cancers in other organs. These cancers are the same cancers that would normally appear with a lower frequency in an unexposed animal population. After exposure(s) to one or to a combination of radionuclides, the incidence of these naturally occurring cancers tend to increase, though the latent periods do not change. This observation was demonstrated by the studies performed by many investigators in which $^{238}PuO_2$ and $^{239}PuO_2$ exposed dogs had increases in lung, skeletal and liver tumors after exposures to varying doses of these nuclides (Boecker et al. 1988; Brooks et al. 1992; Gillett et al. 1985; Hahn et al. 1987, 1981; Muggenburg et al. 1994). This trend, also noted with the cancers that were produced in those individuals exposed to external sources of ionizing radiation after the atomic blasts in Hiroshima and Nagasaki, Japan, in August 1945, is discussed in more detail below (Shimizu et al. 1988).

The sites where these cancers occurred in exposed laboratory animals depended largely on (1) the dose, which depends on the quantity of radioactive material, (2) the physical properties of the particle (or vapor) they were incorporated into, (3) the solubility of the particle, (4) the particle size, and (5) the radiological and biological properties of the material. For example, for dogs exposed to insoluble aerosols of ^{238}Pu (1.5 and 3.0 μm), it may be reasonably surmised that these animals would develop lung tumors based on the physical half-life of the radionuclide, the insoluble nature of the particle, the small particle size (long retention times), the dose, and the tissues at risk of receiving large doses of radiation within a short distance of the particle retention site. Lung tumors did in fact develop in these animals at an increased incidence rate many years after the initial exposure. Liver and bone tumors also developed in conjunction with some of these lung tumors. Over a period of time, the particles slowly dissolved and the ^{239}Pu was transferred to the hepatic and skeletal tissues, subsequently irradiating other susceptible tissues and inducing cancers of the liver and osteosarcomas of the bone (Muggenburg et al. 1994). Metastasis also is a factor in the appearance of cancer in some organs.

External exposure has also been found to induce cancers in both humans and laboratory animals. A few human studies that involved external exposures to radiation and resulted in cancer were identified, but the best study available to date is the Life Span Study (LSS) currently being conducted by the Radiation Effects Research Foundation (RERF) with the survivors of the atomic bombings of Japan in 1945. A large database is available from the persons exposed to radiation from the atomic bombing of Hiroshima and Nagasaki. According to DS86 doses, the major type of radiation was gamma emissions, with lesser amounts of neutron radiation than originally anticipated using T65D dosimetry assumptions; the estimates of doses to these individuals are still being refined today. Exposures are considered to be mostly from external radiation, with much smaller amounts of internal radiation from inhalation and oral exposure routes, due to relatively little fallout from those atomic blasts. In Nagasaki, however, survivors were exposed to the "Black Rain," which is fallout radioactivity mixed in a rain shower. Many of these individuals received high doses to their unprotected skin and even to skin under water-saturated clothing due to the high-activity, beta and gamma-emitting fission products. This ongoing epidemiologic study provides an excellent source of data for use in studying the delayed effects of radiation in humans.

As with cancers induced after inhalation of radioactive material by laboratory animals, cancers in humans or animals exposed to external radiation do not appear immediately after the initial exposure. In the Hiroshima and Nagasaki atomic bombing survivors, and in the dog studies discussed above, there was no dose-dependent shortening of the latent periods for cancer induction, except possibly for those individuals exposed to radiation within the first 10 years of life (which was dose-dependent). This observation may reflect a higher sensitivity to the effects of radiation in very young humans. Cancers were also of the type that are normally found in unexposed individuals, but they occurred with some increasing frequency. These cancers occur only when those individuals reach an age when these cancers normally would be expected to develop (except for leukemia). For example, a female #10 years of age who was exposed to external gamma radiation from the atomic blast and survived the acute effects of the initial radiation exposure would have an increased probability of developing (and dying from) breast cancer as a result of the latent radiation effects, but not before she reached the age at which the majority of unexposed women would be expected to start developing this specific cancer. The same would be true for the other types of cancers as well, except for leukemias. Deaths due to leukemia did exhibit a minimum latent period (2–3 years). The incidence of the cancer increased to a peak at 6–8 years after exposure and the incidence declined after that. A slightly significant increase in deaths due to leukemia existed at least through 1980

(the cut-off date for much of the DS86 dosimetry system data), some 35 years after the initial exposure; this increase was independent of the age at which the initial exposure had occurred.

In another report by Upton (1991) and in the report by Shimizu et al. (1988), the same cohort was reported to show linear dose-mortality relationship responses for cancers (other than leukemia) ranging from 40 to 300 rad (0.4–3 Gy). In the most recent report on this cohort, solid cancer excess deaths increased greatly in the last 5-year study period, 1986–1990; for those exposed as children, 50% of the excess deaths occurred during this period (Pierce et al. 1996). For all cancers, most of the excess deaths were due to leukemia and most leukemias occurred in the 15 years following exposure. Though excess relative risk for those exposed as children declined over the recent years, the excess absolute risk increased rapidly and excess absolute risk is seen to be an important measure of radiation's population impact. Solid cancer excess lifetime risk per sievert was estimated at 0.10 for males (10 cancers per 100 people) and 0.14 for females, and still shows a linearity up to about 3 Sv (Pierce et al. 1996). However, leukemia showed nonlinearity of risks: risk at 0.1 Sv was 1/20 of the risk at 1 Sv.

Cancer mortality due to ionizing radiation has been evaluated extensively (BEIR V 1990; Shimizu et al. 1988; Upton 1991). In summary, for the Japanese atomic bomb survivors, the relative risk for the whole exposed population (all ages and both sexes) for malignant neoplasms (including leukemia) for the years 1950–1985 has been estimated to be 1.39 (range 1.32–1.46) per 100 rad (1 Gy), corresponding to an absolute risk of 13.1 (10.1–15.9) excess deaths per million person rad (10^4 person-Gy)/year. When leukemia is excluded from the previous estimates, the relative risk for the whole exposed population (all ages and both sexes) for solid cancers is estimated to be 0.41 (0.32–0.51) per 100 rad (per Gy) organ-absorbed dose, corresponding to a lower absolute risk of 10.13 excess cancer deaths per million person rad (10^4 person-Gy)/year organ-absorbed dose. When total cancer mortality (including leukemia) is reexamined on the basis of sex, sex ratios of radiation-induced cancers at specific sites are not significantly different from those of the unexposed general population. The relative risk for some epithelial tumors tends to be somewhat higher in females than in males (Upton 1991). Finally, when the data are re-examined as to cancer mortality and age at exposure, the current data suggest that the lifetime risk of developing radiation-induced cancer is substantially lower in those persons exposed during their adult years than in those exposed during childhood or adolescence, a conclusion supported by BEIR V (1990). Several types of

cancer were observed with increased frequencies in this exposed population and are summarized in Table 3-8.

CELs from exposure to ionizing radiation in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

3.3 IDENTIFICATION OF DATA NEEDS

The database appears to have a sufficient volume of information for regulators to allow workers to work safely with radiation sources. This is verified by the fact that the nuclear power industry has the best overall safety record of all industries. This good safety record, with a Standardized Mortality Ratio (SMR) of less than 100 is usually attributed to the "Healthy Worker Effect." However, for scientific reasons, the following have been identified as potential data needs regarding health effects that may be associated with exposure to ionizing radiation:

- Since somatic and reproductive cell chromosomes are radiosensitive tissues that can sustain damage after exposure to ionizing radiation, damage to the chromosomes and the genes on them in exposed populations has potentially serious implications. Better methods are needed by which to estimate the levels of exposure to ionizing radiation that may result in an increased risk of hereditary disease.

- Important gaps in knowledge should be filled to permit more reliable estimation of genetic and hereditary risks. In some cases this might include collection of new data that could remove or refine assumptions needed in the direct and indirect (doubling-dose) methods of hereditary risk estimation. In other cases, gaps in knowledge could be filled by the reevaluation of the masses of data collected in the past (for example, specific-locus experiments) in the light of new understandings about hereditary risk. In addition, information gathered as part of the Human Genome Project may lead to improvements in the existing methods or to entirely new methods of estimating hereditary risk.

- The largest group of workers that receive elevated doses of ionizing radiation are airline air crews. Assuming a dose of 1 mrem/hr (0.01 mSv/hr) and 72–100 hours/month airtime for 11 months, this leads to an approximate dose of 800–1,100 mrem/year (8–11 mSv/year), about twice the annual dose of an average nuclear power plant worker. There is a need to determine whether or not this long-term, continuing, low-level radiation dose rate leads to harmful effects.

- The mechanisms by which cancer is induced in living cells are complex and an area under intense study. More research is required to better understand the mechanisms by which cancer is induced after exposure to chemical carcinogens and to ionizing radiation. This would include the identification of unique biomarkers and biochemical pathways at the cellular and tissue level, and the study of radiological and chemical mixtures.

- Regarding radon exposure, several studies involving underground-miner surveys need to be completed and the data analyzed for the interaction between radon and smoking. These studies should also provide more information on radon dosimetry and narrow some uncertainties in applying the lung-cancer risk data derived from the miner data sets to estimation of risk of radon exposure in the general population.

- Epidemiological studies need to continue in order to more firmly describe the risks of lung cancer in underground miners and the risks of indoor home radon exposure to those potentially exposed to radon and radon progeny. In addition, adding a thoron (^{220}Rn- and ^{220}Rn- plus decay products) study to the radon studies would be of benefit, because thoron is hard to get into the home. If it does, the decay products are long-lived; there are limited data on in-home thoron and thoron decay product levels.

- Further modeling of the indoor air environment is needed to assess potential health consequences of indoor radon exposure.

- The role of ^{210}Po in tobacco smoke and lung cancer should continue to be evaluated; this includes bronchial and lung dosimetry, identification and characterization of target cells, and the role of cofactors in the carcinogenic response.

- The deterministic acute and delayed health effects from ^{210}Po, particularly those affecting the renal, cardiovascular, and reproductive systems, should continue to be investigated.

- More quantitative information regarding the ^{224}Ra, ^{226}Ra, and ^{228}Ra human exposures is needed to more adequately evaluate the magnitude of some dosimetric uncertainties and what impact these uncertainties have on quantitative risk estimation.

- The bone cancer information from all of the human ^{224}Ra, ^{226}Ra, and ^{228}Ra exposures should be integrated and more adequately analyzed.

- Research should continue on identifying the cells at risk after exposure to radium. This should include cell behavior over time, changes in cell behavior, location of cells in relation to the microenvironment of the radiation field, responses of the cell to the radiation, and the time course and distribution of radioactivity in the bone.

- The dosimetry of the mastoids should be examined in order to calculate the risk per unit of epithelial tissue and per unit of cell dose.

- Data should be obtained from the five major epidemiological studies of Thorotrast-exposed patients and the data analyzed to develop risk models for liver and other cancers.

- The dosimetry of the thorium isotopes at the cellular level in target organs should be closely examined.

- The mechanism of uranium deposition and redistribution in bone should be further investigated in order to more accurately define the potential carcinogenic effect of natural uranium based on results obtained from enriched uranium or other alpha particle emitters.

- The current epidemiological studies of worker populations exposed to transuranic elements should be continued.

- The current lifespan studies with dogs should be completed and the results reported.

- The current lifespan studies of the Japanese atomic bomb survivors should be continued and the results reported regularly every 5 years.

- Studies should continue regarding the genetic effects of low-level exposure to ionizing radiation, particularly in the second generation offspring of the Japanese atomic bomb survivors. Better methods for extrapolating data from animal studies for applications in human genetic risk assessment are also needed.

- It would be useful to have some information on induced dominant damage in female mice for use in the direct method of hereditary risk estimation, as none has been known to have been collected. Presently the application of the direct method to females assumes that the relative risks of the sexes are the same for serious dominant mutations as they are for specific-locus mutations, which are recessives.

- Efforts to assess the carcinogenic risks of exposure to low levels of ionizing radiation, for both single dose and protracted and fractioned doses, should continue.

- The carcinogenicity of neutron radiation exposure in human populations should continue to be examined. Similarly, the mutagenicity of low doses of neutron radiation should continued to be investigated in order to more comfortably predict the potential genetic risks observed in laboratory animals and extrapolate those findings to human populations.

3.4 CONCLUSIONS

This chapter has provided an overview of the health effects related to ionizing radiation exposure in humans and laboratory animals. These effects can be both non-carcinogenic and carcinogenic in nature. Non-carcinogenic effects primarily result in immediate effects, mainly to organs with rapidly dividing cells, which include the hematopoietic system, gastrointestinal tract, and skin, or delayed effects such as cataracts and embryo/fetal development problems. Carcinogenic effects also may occur in any number of organ systems. This end point may not be expressed for several years after the initial exposure. The dose-response relationships for these effects are known from the massive amount of data from studies on both humans and animals. Epidemiology studies are not likely to provide significant refinement of radiation risk estimates. The most fruitful approach to further understanding risk from exposure to ionizing radiation is through molecular studies, including the identification of unique biomarkers and pathogenic pathways at the cellular and tissue levels.

4. RADIATION ACCIDENTS

Radiation accidents may be viewed as unusual exposure events which provide possible high exposures to a few people and, in the case of nuclear plant events, low exposures to large populations. A number of radiation accidents have occurred over the past 50 years involving radiation producing machines, radioactive materials, and uncontrolled nuclear reactors. These accidents have resulted in a number of people being exposed to a range of internal and external radiation doses, and those involving radioactive materials have involved multiple routes of exposure. Some of the more important accidents involving significant radiation doses or releases of radioactive material, including any known health effects, are discussed below. It is important to carefully and critically assess each individual accident in order to identify the causes and then to implement indicated corrective measures that will prevent a recurrence. An analysis of the common characteristics of accidents is useful in resolving overarching issues, as has been done following nuclear power, industrial radiography, and medical accidents. Success in avoiding accidents and responding when they do occur requires planning in order to have adequately trained and prepared health physics organization; well-defined dose limits and action levels; a well-developed instrument program; close cooperation among radiation protection, experts, local and state authorities, and emergency responders; and solid communication among response groups, the medical community, the media, and the public (Morgan and Turner 1973). Focus is given to the successful avoidance of accidents and the response in the event they do occur. Examples of some accidents are discussed below.

4.1 PALOMARES, SPAIN

From the 1950s through the late 1960s, the Strategic Air Command (SAC) conducted Operation Chrome Dome which, in the interest of national defense, required the Air Force to fly aircraft carrying nuclear weapons around the world 24 hours a day. On January 16, 1966, two B-52 airplanes, each carrying four thermonuclear weapons containing ^{239}Pu, flew to the southern fringes of the former Soviet Union. On their return trip to the United States, one collided in mid-air with a KC-135 tanker aircraft during a refueling operation over Spain. After fire erupted on the planes, the B-52 broke apart and scattered all four nuclear weapons. The weapons were dispersed over Palomares, a town located in a remote area of Spain. Two weapons landed without incident, one in the water and the other on the beach near Palomares, and both were recovered. The third weapon landed in low mountains west of the town, and the fourth landed on agricultural land to the east. The high explosives in these last two weapons

detonated and burned, causing some of the plutonium inside to also burn and spread plutonium contamination throughout the area. There were chemical but no nuclear explosions (Civil Defense Technology Workshop 1995).

Partial chemical burning of the fissile material from the two bombs that had been blown apart by their high explosive charges resulted in a cloud formation which was dispersed by a 35-mph wind. Approximately 2.25 km^2 of farmland was contaminated with plutonium at levels of 50–500 $\mu g/m^2$ (3–32 $\mu Ci/m^2$), and low levels of plutonium were detectable for a distance of 2 miles. Initially, 630 acres of land were reported to be contaminated; however, an additional 20 acres were subsequently classified as contaminated due to resuspension by the wind. The primary form of income for the citizens of Palomares was their tomato crop. The U.S. government purchased the tomato crop for a total of $250,000. These mildly contaminated tomatoes were washed free of contamination and were considered safe to eat. Crops in highly contaminated fields where levels exceeded 5 µg/m2 (0.3 $\mu Ci/m^2$) were dug up and burned in open-pit fires, which further spread the contamination.

An agreement between the United States and Spain called for removing the top 10 cm (4 inches) of soil in areas contaminated with more than 32 $\mu Ci/m^2$ (500 $\mu g/m^2$). This resulted in the removal of 1,100 m^3 of soil. The decontamination procedure required 747 people and 8 weeks of labor and resulted in the filling of 4,879 metal 55-gallon drums with contaminated soil. Soil with surface contamination levels between approximately 5 and 500 $\mu g/m^2$ was mixed with petroleum oil, plowed under to a depth of 8 inches, and then covered over with another layer of top soil. Following this decontamination, the concentration of activity in surface soil averaged 1 µg/g, with a maximum of 40 µg/g. The plutonium concentration in plants ranged from uncontaminated to 30 times the ambient level in Spain. The Air Force contracted 140 trucks to move 3,400 truck loads of replacement soil from a dry river bed. These actions essentially destroyed all of the indigenous population's crop lands. All soil levels greater than 462 $\mu g/m^2$, together with other contaminated materials, were transferred to the United States for burial. All but two of the barrels were shipped to the Savannah Naval Storage Facility in Aiken, South Carolina. The other two barrels were sent to Los Alamos National Laboratories in New Mexico, where they are still being monitored and tested (Civil Defense Technology Workshop 1995; Shapiro 1990; UNSCEAR 1993). No plutonium was found in the 100 residents of Palomares who were the most likely to have been exposed. The potential dose to the lungs, bone surface, and bone marrow of the local residents has been estimated to be much less than the ICRP recommended limits (Iranzo et al. 1987). Follow-up studies on this group

of exposed individuals are not likely to provide useful information on the long-term effects of plutonium exposure in humans.

The Spanish government, concerned about public perception and panic, prohibited the U.S. Air Force cleanup crews from wearing anti-contamination suits or full face masks. Only uniforms, hats, and surgical gloves with tape over the openings between gloves and clothing were permitted. This resulted in internal contamination of some service members, who were monitored by urinalysis for plutonium content. Data indicate that a small number registered readily measurable levels, and some of those levels decreased to below detection limits in a few months. Long-term monitoring of the others was eventually discontinued. Counter to U.S. recommendations, civilians were not restricted in their movements in or around the area. In the hilly, rocky area surrounding the impact site of the fourth weapon, it proved impossible to reach the initial cleanup standards set by the Spanish Government, so the limits for this area were adjusted to meet the conditions, with the agreement that the area would not be used for agriculture. Where the soil could not be removed, the workers soaked it with water to force the contamination into the soil. This area has never been restricted by local authorities, and, although the local population was warned that the area was contaminated, Spanish citizens eventually began to farm some of this land (Civil Defense Technology Workshop 1995). Six years after the incident, follow-up studies found that there was little change in the community and in exposed persons (Shapiro 1990). Of the 714 people examined through 1988, 124 had urine concentrations of plutonium greater than the minimum detection limits (MDLs).

4.2. GOIANIA, BRAZIL

On September 13, 1987, two scavengers found an abandoned teletherapy device in an abandoned medical clinic in Goiania, Brazil. The machine contained a radioactive ^{137}Cs source with an activity of 1,375 Ci (50.9 TBq) in the form of powdered and soluble $^{137}CsCl$. After removing the source from its shield, they took it home and, in a crude attempt to break it apart, managed to rupture the source and spread pieces about the property. Both became ill within hours. Either 1 or 5 days later, according to various versions of the story, the device became the property of a junk dealer. This dealer noticed a luminescence emanating from the unit and used tools to cut the unit apart to gain access to the material inside. The rupture allowed the $^{137}CsCl$ powder to disperse easily and be further distributed by wind suspension and rainwater runoff. Several land areas and 129 people were significantly contaminated, resulting in four deaths and one forearm amputation (Amaral et al. 1991; Rosenthal et al. 1991).

Initial External Response. On September 29, 1987, the Secretary of Health for the State of Goiania allowed a local physicist to notify the Department of Nuclear Installations (DNI) which, in turn, notified the National Nuclear Energy Commission (CNEN) in Rio de Janeiro. The Director of DNI and technicians from the Institute of Nuclear Energy research (IPEN) left that day and arrived in Goiania the next morning (Moreira 1991). The abandoned hospital was searched first, but there was no source of contamination. Next, the houses of presumably contaminated patients were checked and contamination was found. A detailed search found 7 highly contaminated areas that included 2 houses, 4 lots, and the Public Hygiene Control Unit. Part of the original source was found at this unit. Testing showed maximum radiation readings of 1,000 rem/hr (10 Sv/hr) on contact and 40 rem/hr (0.4 Sv/hr) at 1 meter. The source was shielded with concrete for personnel protection. That night the Goiania task force developed its site action plan.

Initial Patient Management. The accident primarily exposed or contaminated about 80 people, who were all related, and an additional 170 were later contaminated to much lower levels. Initially, 11 individuals who had handled the source and who were the most highly contaminated were taken to the Hospital of Tropical Diseases or to the Santa Maria Hospital. The most highly contaminated of these were then transported to the Marcilio Dias Naval Hospital in Rio de Janeiro. People from the primary contamination zones were assessed and, based on clinical findings, sent to Goiania Hospital, FEBEM, or the House of the Good Shepherd. Twenty-two people who were evacuated from contaminated homes were taken to Olympic Stadium, and others who were in the vicinity were encouraged to go there. In a prioritized manner, the contaminated victims were provided with medical care, clean clothing, nourishment and orientation, and contamination monitoring; the public was informed. Because of exaggerated claims of water contamination by the press, an additional 112,000 unaffected individuals went to Olympic Stadium for monitoring. A total of 249 were found to be contaminated. About half had shoe and clothing contamination, that could have been picked up from walking in the stadium. Of the other 129, who were both internally and externally contaminated, 21 required intense medical treatment. Ten of these were seriously compromised, four died, and one required forearm amputation (Brandao-Mello et al. 1991; Oliveira et al. 1991a, 1991b).

Contamination Spread. The ^{137}Cs contamination was spread by social contacts, the sale of contaminated material, the movement of pieces of the source, and wind and rain dispersal (Amaral et al. 1991; Becker et al. 1991; da Silva et al. 1991; Godoy et al. 1991). Contamination was found on 7 major properties; in 42 residences, including 22 homes of family and friends who were evacuated and 20 others where radiation levels ranged from 0.1 to 1 rem/hr (1–10 mSv/hr); and on 68 of the more than 10 million currency bills tested. The population was internally exposed by inhalation and the ingestion of fruits and vegetables, and externally exposed to the penetrating ^{137}Cs gamma radiation, but the drinking water supply was found to be clean.

Contaminated materials in the environment were removed from the various sites and loaded into containers, with liquids being immobilized in concrete. Decontamination limits for solids were set by the national standard. Anything contaminated below 74 kBq/kg was considered to be clean and unaffected by the accident. Contamination level was characterized by the contact radiation level, with values of 0.2 and 2 rem/hr (2 and 20 mSv/hr) being the respective limits for low- and medium-level contamination. An estimated 1,200 Ci (44 TBq) of ^{137}Cs was recaptured during the decontamination effort, which left the area with no significant residual hazard (Rosenthal et al. 1991).

The type of media coverage of this accident caused a psychological impact on a community with recent memories of the Chernobyl reactor accident in the former Soviet Union. The situation improved when the news media refocused their efforts toward balanced reporting and public education.

4.3 THULE, GREENLAND

In January 1968, a U.S. Air Force plane experienced an on-board fire and subsequently crashed while attempting an emergency landing near Thule, Greenland. The plane was carrying four unarmed 1.1-megaton nuclear weapons; although the nuclear weapons did not detonate, the conventional explosives of the weapons exploded on impact, depositing an inventory of 1 TBq (27 Ci) combined ^{239}Pu and ^{240}Pu, 0.02 TBq (0.54 Ci) ^{238}Pu, and 0.1 TBq (0.27 Ci) ^{241}Am; igniting fuel; and creating an intense fire that burned for almost 4 hours. The force of the crash and explosions resulted in the spread of plutonium-laden debris over an area approximately 100 m by 700 m. The burning plutonium was converted mainly into insoluble oxides and dispersed as fine particles. Measurements of ^{239}Pu and ^{240}Pu

indicated that the radionuclides preferentially deposited in the fine-grained bottom sediments covering the basins in the vicinity of the crash site. Follow-up investigations found that plutonium levels in bivalves and crustacea to be increased by a factor of 10–1,000 over pre-accident levels (Aarkrog 1971, 1994; Handler 1992; Shapiro 1990; Smith et al. 1994).

The cleanup effort, called project Crested Ice, lasted 8 months and resulted in the shipping of almost 240,000 tons of contaminated ice and snow to the United States. About 99% of the plutonium was contained in the blackened ice at the crash site; this was recovered by road graders and mechanized loaders scraping away the affected ice. A total of sixty-seven 25,000-gallon fuel tanks were filled with debris and four additional containers were used for storing contaminated recovery equipment and gear. The materials were shipped to the United States for disposal. Although low-level contamination was detected on land close to the crash site, it is believed that minimal amounts of plutonium escaped from the crash site. No significant radionuclide exposure and no long-term effects to neighboring populations were expected (Handler 1992; Shapiro 1990).

4.4 ROCKY FLATS, COLORADO

The Rocky Flats Nuclear Weapons Plant, located approximately 15 miles from Denver, Colorado, occupies approximately 2 square miles of federally owned land. Approximately 2.2 million people from the 8-county Denver metropolitan area live within a 52-mile radius of the facility. As of December 1995, there were approximately 4,700 employees at the Rocky Flats facility. Since beginning operations in 1953, the plant has been a major processor of plutonium. During the Cold War, Rocky Flats was responsible for the fabrication of the hollow plutonium sphere, or "pit," that serves as nuclear fuel for nuclear warheads. Rocky Flats also was responsible for recycling plutonium retrieved from retired nuclear warheads. A high-tech machine shop produced other weapons parts from stainless steel, beryllium, depleted uranium, and other metals.

Due to its proximity to an urban area (Denver, Colorado) and because its property boundaries border two creeks feeding public waters, there is a potential for public exposure to radioactive material following an accident at this plant. Several significant incidents have occurred at this plant: two fires in 1957 and 1969 and leakage of plutonium-contaminated cutting oils from storage drums (Rocky Flats Citizens Advisory Board 1995; Shapiro 1990).

Probably no individual location at the Rocky Flats site has achieved more attention than the site known as the 903 Pad. In the late 1950s and early 1960s, Rocky Flats stored barrels at this location which were filled with plutonium-contaminated oil left over from the pit manufacturing operations. Over time, many of the oil barrels had corroded, allowing the contaminated oil to spill out onto the ground. The leakage was first detected in 1964, and efforts to prevent the spread of leakage were initiated the same year. Managers at the site attempted to solve the problem by removing all of the barrels and cleaning up the storage area. However, the cleanup effort resulted in the disturbance of the contaminated soil, and the radioactive dust was picked up and spread further by the high winds that are common at Rocky Flats. The Health Advisory Panel overseeing the Dose Reconstruction Project for the Colorado Department of Public Health and Environment lists the 903 Pad as one of the major contributors to off-site contamination from Rocky Flats (Rocky Flats Citizens Advisory Board 1995; Shapiro 1990).

The first of two major fires at the Rocky Flats facility occurred on the evening of September 11, 1957, when some of the plutonium on the glove box line spontaneously ignited. Although the area was designed to be fireproof, it was soon engulfed in flames. Firemen switched on ventilating fans, which ultimately spread the flames to contact more plutonium. Attempts to quench the fire with carbon dioxide also failed. Meanwhile, the filters designed to trap plutonium escaping up the stacks caught fire. The shift captain and other observers reported a billowing black cloud pouring some 80–160 feet into the air above the 150-foot-high stack. When the carbon dioxide gas failed to extinguish the fire, the firefighters began pouring water into the blaze. The fire was extinguished roughly 13 hours after it began. Some 14–20 kg of plutonium were estimated to have burned in the fire, not including plutonium liberated from the burning filters. In addition, the water used to extinguish the fire became contaminated with radioactive material, and approximately 30,000 gallons of it escaped unfiltered, spreading contamination into local streams and into the water table. Although some of the buildings were heavily contaminated, plutonium pit production was back under way within a few days (Wasserman et al. 1982).

The fire in 1969 also started with the spontaneous ignition of plutonium metal. Several kilograms of plutonium burned and the resulting smoke plume spread to surrounding areas. Soil samples collected from 15 locations ranged from background levels of 20 pCi/kg (0.7 Bq/kg) of material to 6,000 pCi/kg (220 Bq/kg) in the top centimeter; 7 water samples ranged from 0.001 to 0.2 pCi/L (10^{-5} to 10^{-2} Bq/L. Another study in 1970 of soil samples to a depth of 20 cm found levels up to 2 Ci/km^2 (70,000 MBq/km^2) at sites adjacent to the property boundaries (Shapiro 1990).

Johnson (1981) examined the relation between cancer rates and plutonium exposures using cancer diagnosis data for 1969–1971 and plutonium exposures estimated from an analysis of soil samples collected near Rocky Flats in 1970. Johnson claimed to have found increases in many cancer types for persons in exposed areas, as compared with those for unexposed areas. However, a feasibility study for an epidemiologic study of persons who lived near the plant concluded that exposures were not high enough to be evaluated statistically (Dreyer et al. 1982). Cobb et al. (1982) compared plutonium concentrations in autopsy samples from persons who lived near Rocky Flats with those who lived far from the plant. A weak relation between plutonium concentrations in autopsy samples and distance from Rocky Flats was detected; however, these authors did not believe that the elevated concentrations could be conclusively linked to emissions from Rocky Flats. Crump et al. (1987) re-evaluated cancer diagnosis data for 1969–1971 and for 1979–1981 using the study designed by Johnson (1981). For both study periods, the authors found no increase in cancer rates for combined cancers, for radiation-sensitive cancers, or for cancers of the respiratory system in those living within 10 miles of Rocky Flats. A National Cancer Institute (NCI) study of cancer incidence and mortality around nuclear facilities in the United States found slight elevations for some cancers in some age groups among those living near the Rocky Flats facility; however, the study should be interpreted with caution because county-by-county cancer mortality data were used and because of limited information on potential confounding factors (Jablon et al. 1990), and because it appears that plutonium exposures were not detectable.

4.5 THREE MILE ISLAND, PENNSYLVANIA

On March 28, 1979, an accident occurred at the unit 2 civilian nuclear power reactor at Three Mile Island (TMI). Figure 4-1 is a simplified diagram of the TMI pressurized water nuclear reactor design. Under normal operating conditions, the control rods are withdrawn from the reactor core to produce power, and water from the principal source (#1) circulates through the core and a primary heat exchange loop. A secondary water source (#2) is in standby. To prevent a major accident, it is imperative that the reactor core be submerged in water at all times. Although the water should never be allowed to boil inside

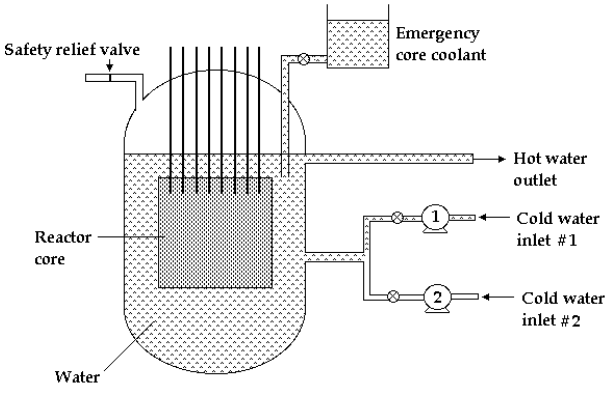


Figure 4-1. Schematic of Three Mile Island Unit 2 Nuclear Reactor (adapted from PSU 1999)

the pressure vessel, a pressure safety relief valve exists to release steam to an alternate collection location in the event of inadvertent boiling; during normal operation, this valve is closed. During shutdown, there is no chain reaction, but the cooling water continues to circulate through the core to remove the heat generated by the decay of the radioactive fission products in the fuel rods.

In the TMI incident, water from supply #1, which returns condensed steam from the steam generators, was interrupted because the feed water pumps that pumped water from the reactor to the reactor's steam generators stopped. The loss of water flow resulted in a loss of cooling of the reactor core. The operators immediately switched on the emergency feedwater pumps. However, the water did not enter into the cooling loop because the valve was accidentally left closed the previous day following a scheduled maintenance activity (the reactor operators didn't realize this). Emergency water injection pumps started automatically, but an operator misinterpreted the gauge readings and reduced the flow. The water overheated and steam bubbles began forming. The operators responded improperly, draining water out of the system, exacerbating the coolant problems. The fuel heated up and partially melted, releasing radioactive material into the remaining coolant, which continued flowing out of the reactor through the relief valve and onto the containment room floor (Eisenbud 1987; PSU 1999; Shapiro 1990).

The cleanup is still in progress at a cost that has already exceeded 1 billion dollars. The high cost is not only due to the cleanup itself, but to the research into the materials and their behavior during the accident. This has made the cleanup a huge research project. However, very little radioactivity was released to the environment. The main contaminants reaching the environment were ^{133}Xe and ^{131}I, with total releases of approximately 370 PBq (10 MCi) and 550 GBq (14.85 Ci), respectively. The actual quantity of ^{131}I released was much smaller than the overconservative models of the time projected. Subsequent research confirmed previous scientific studies which showed that hot iodine is very reactive; during the accident, much of the iodine plated out on the concrete and structural metal components inside the containment dome, greatly limiting the quantity released. The average dose to the general public within 80 km was estimated to be 0.0015 rem (0.000015 Sv), and the highest dose was estimated to be 0.085 rem (0.00085 Sv), mainly in the form of external gamma radiation. In contrast, the average annual radiation dose from natural radiation is approximately 0.3 rem (0.003 Sv), of which 0.036 rem (0.00036 Sv) is from radioactive material naturally inside the human body (PSU 1999; UNSCEAR 1993). No radiation effects have been reported among the surrounding population because population exposures were small relative to normal background radiation. Psychological effects have been documented at TMI. One cause was the very large ^{131}I release estimates that were projected using models known to be overconservative, and

another was the emotional political response and media coverage which projected fetal health outcomes based on those projected releases and uninformed reporting. Public panic ensued despite the small radiation doses. Research in the aftermath led regulators to accept more realistic radionuclide release models on which to base emergency response recommendations. Lessons learned from this event include the need to accurately project releases of radioactive material and to keep the news media accurately informed of the situation and response actions. The media must then make the decision to provide fair and balanced coverage in the public interest.

4.6 CHERNOBYL, UKRAINE

In April 1986, an accident at the civilian nuclear reactor facility at Chernobyl in the former USSR, resulted in the largest accidental release of radioactive material to date. The RBMK-1000 reactors utilized at Chernobyl have a design flaw that makes their operation at low power unstable. In this mode of operation, any increase in the production of steam can boost the rate of energy production in the reactor. If that extra energy generates still more steam, the result can be a runaway power surge. While performing an unauthorized engineering test on a generator, instabilities developed in the reactor system which could not be controlled; the operators had deliberately disabled safety systems that could have averted the reactor's loss of control because the safety systems might have interfered with the performance of the test. At 1:23 a.m, an operator pressed a button to activate the automatic protection system, but by this time it was too late.

Within 3 seconds, the fission rate in the reactor dramatically increased to hundreds of times the normal operating level. The fuel temperature consequently rose within seconds to beyond the melting point of uranium dioxide (2,760 EC; 5,000 EF). The resulting steam explosion lifted the 90-ton covering of the reactor, destroyed the roof, and ejected fuel debris from the facility (Figure 4-2). Molten nuclear fuel and graphite from the reactor core caused fires in and around the reactor that burned for 10 days.

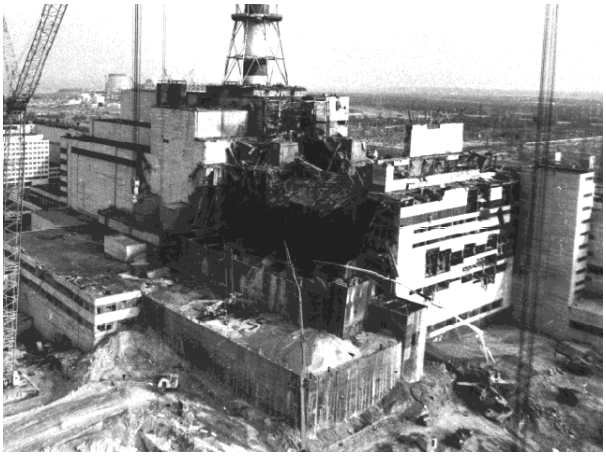


Figure 4-2. Aerial View of the Damaged Chernobyl Reactor Facility (adapted from http://193.125.172.36/www-klae/POLYN/history.html)

Efforts to quench the flames included dumping 5,000 tons of various materials (boron carbide, dolomite, sand-clay mixture, and lead) by helicopter. By the time the fires were extinguished, 250 tons of graphite had been consumed by the fires (Shapiro 1990; Shcherbak 1996). The total release of radioactive material from Chernobyl was estimated to be 1–2 EBq (27–54 MCi). The major radionuclides released were ^{131}I (630 PBq; 17.0 MCi), ^{134}Cs (35 PBq; 0.95 MCi), and ^{137}Cs (70 PBq; 1.9 MCi). A plume containing these radionuclides moved with the prevailing winds to the north and west, and then east around the world, transporting the radioactive material thousands of miles (Figure 4-3).

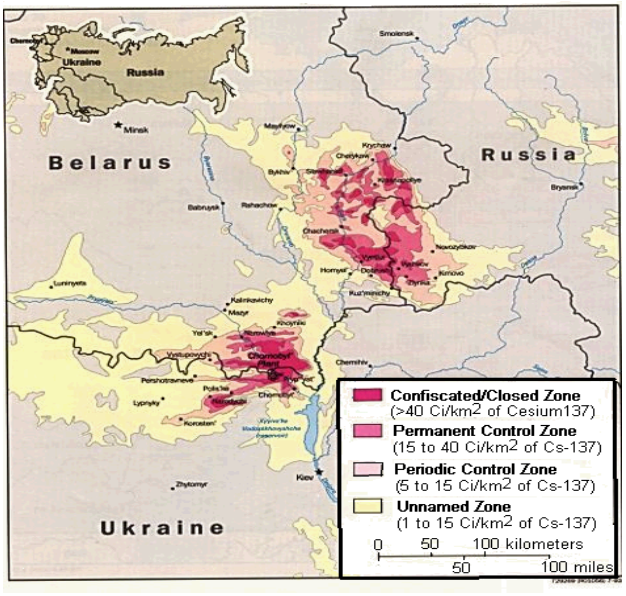


Figure 4-3. Hot Spots of Radioactivity in Regions Surrounding the Chernobyl Facility (BRAMA 1996)

The deposition on the ground varied considerably during the accident due to variations in temperature and other atmospheric conditions during the release. ^{137}Cs was the main contributor to the radiation doses received by the population once the short-lived ^{131}I had decayed. The three main areas of ^{137}Cs contamination resulting from the Chernobyl accident were identified as the Central, Bryansk-Belarus, and Kaluga-Tula-Orel spots. The central spot, formed during the initial, active stage of the release, had ground depositions of ^{137}Cs of more than 40 kBq/m^2 (1.1 µCi/m^2) over large areas of Northern Ukraine and Southern Belarus. The most highly contaminated area was the 30-km zone surrounding the reactor, where ^{137}Cs ground depositions exceeded 1,500 kBq/m^2 (40.5 µCi/m^2). The Bryansk-Belarus spot, centered 200 km to the north-northeast of the reactor, was formed as a result of rainfall on the region. The ground depositions of ^{137}Cs in the most highly contaminated areas reached 5,000 kBq/m^2 (135.1 µCi/m^2) in some villages. The Kaluga-Tula-Orel spot, approximately 500 km northeast of the reactor in Russia, was also formed as a result of rainfall; the levels of ^{137}Cs deposition in this area were usually less than 600 kBq/m^2 (16.2 µCi/m^2). Outside the three main hot spots there were many areas in the European territory of the former Soviet Union contaminated with ^{137}Cs at levels ranging from 40 to

200 kBq/m^2 (1.1–5.4 μCi/m^2). Overall, the territory of the former Soviet Union initially contained approximately 3,100 km^2 contaminated by ^{137}Cs at levels exceeding 1,500 kBq/m^2 (40.5 μCi/m^2); 7,200 km^2 with levels of 600–1,500 kBq/m^2 (16.2–40.5 μCi/m^2); and 103,000 km^2 with levels of 40–200 kBq/m^2 (1.1–5.4 μCi/m^2) (NEA 1995). The regions affected included not only the Ukraine, Belarus, and Russia, but also Georgia, Finland, Poland, Sweden, Germany, Turkey, and other countries. Even such distant lands as the United States and Japan received measurable amounts of radioactive material. In Poland, Germany, Austria, and Hungary as well as in the Ukraine, some crops and milk were contaminated and had to be destroyed, while others were destroyed out of panic. In Finland, Sweden, and Norway, carcasses of reindeer that had grazed on contaminated vegetation were destroyed (Shcherbak 1996; UNSCEAR 1993).

A total of 237 plant workers and firefighters suffered from ARS (Shapiro 1990). Within 3 months, the death toll from the incident was 30 persons; all of the deceased were either plant operators or firefighters (UNSCEAR 1993). Approximately 15,000 persons from the plant or surrounding communities were reported to have lost their ability to work as a result of diseases which they claimed could be attributed to radiation exposure including: gastrointestinal (inflammatory immediately after the accident and ulcerative in later years); immunological; metabolic (5–6 year latency period); respiratory (chronic obstructive bronchitis); hemopoietic (increase or decrease in white blood cell numbers); and neuropathologies (reduced mental capacity, inability to estimate one's own abilities). In addition, 12,000 children received large doses to the thyroid, and 9,000 persons were exposed *in utero*. An increase in thyroid cancer among those who had been exposed as children is the only major public health effect documented and authenticated to date. An investigation of brain damage *in utero*, performed by the International Programme on the Health Effects of the Chernobyl Accident (IPHECA), found some evidence of retarded mental development and deviations in behavioral and emotional reactions in exposed children; however, the extent to which radiation contributed to these problems could not be determined due to the lack of individual dosimetry data (Bebeshko 1995; WHO 1995). By 1992, the frequency of occurrence of thyroid cancer had increased dramatically in the children of Belarus, but these data may be difficult to interpret because of endemic goiter in the population. The pattern of the increases was not uniform but was correlated with those areas in the direct path of the radioactive fallout (Kazakov et al. 1992). Other health-related side effects of the accident included: radiophobia, an increase in stress-related illnesses due to both fear of radiation and to the dislocation of people; poor diets due to stringent safeguards against potentially contaminated food, that may have led to vitamin deficiencies; the aborting of as many as 200,000 healthy fetuses because of concern that they might have been damaged in the womb by minor radiation exposures; and an increase in alcoholism following the accident (Atomic Energy Insights 1996).

About 200,000 people involved in the initial cleanup received an average whole-body dose on the order of 10 rem (0.1 Sv). An exclusion zone (within 30 km [18.6 mi] of the reactor) was established that required the evacuation of 116,000 of the surrounding residents. Fewer than 10% of these people received doses greater than 5 rem (0.05 Sv), and the dose to more than 95% of these was less than 10 rem (0.10 Sv), but exceeded 30–40 rem (0.3–0.4 Sv) in some cases. In contrast, the average annual radiation dose from background radiation is approximately 0.36 rem (0.0036 Sv). A total of 786 settlements in Belarus, the Russian Federation, and the Ukraine were declared strict control zones. In the settlements, food consumption was restricted as a protective measure. The average dose during the first year to persons in these settlements was 3.7 rem (0.037 Sv); in 2 subsequent years, average annual doses were approximately 2.3 rem (0.023 Sv) (UNSCEAR 1993).

The collective dose (the sum of all individual doses) from the Chernobyl accident has been estimated to be 600,000 man•Sv. The majority of this dose is expected to be received by the population in the former USSR (40%) and Europe (57%). The remainder (3%) is expected to be dispersed over other countries of the northern hemisphere (UNSCEAR 1993). Direct costs of the accident, due to loss of the facility, firefighting, and relocating citizens, approached $7 billion (Shapiro 1990). This figure does not include current or predicted future medical expenses. The explosion left approximately 180 metric tons of fuel exposed to the atmosphere. In an attempt to prevent the further escape of radiation, the Ukrainian government built a concrete covering over the entire facility, referred to as the sarcophagus (Figure 4-4), beginning in May 1986 and completed in November of that year. However, the sarcophagus is not leak-tight. There is concern that rainwater and wind might enter the structure and disperse some of the residual contamination to the environment (NEI 1995).

Figure 4-4. A View of the Sarcophagus Covering the Chernobyl Reactor Facility
(adapted from http://193.125.172.36/www-kiae/POLYN/history.html)

4.7 KYSHTYM

In September 1957, a major accident occurred at the Chelyabinsk-40 military plutonium production facility near Kyshtym in the southern Ural mountains of the former Soviet Union. The facility, built in 1953, had a number of underground steel storage tanks equipped with cooling systems to store high-level waste so that it would not be dumped in the River Techna. These high-level wastes overheated when the cooling system failed. The heat buildup resulted in evaporation of the coolant water, which allowed the sediment to heat further and dry. The chemicals in the tank exploded on September 29, 1957, with an explosive power of 70–100 tons of TNT, which hurled the 2.5-m-thick concrete lid 25–30 m away. The radioactive cloud from the explosion reached about 1 km. Due to calm wind conditions, about 90% of the materials deposited locally, while 100 PBq (2.7 MCi) was dispersed away from the plant in an oblong fallout pattern about 300 km in length, including parts of Chelyabinsk, Sverdlovsk, and Tyumen counties. Almost all of the radioactive fallout occurred within the first 11 hours (UNSCEAR 1993; Wasserman et al. 1982).

The major contaminants released were ^{144}Ce, ^{95}Zr, ^{95}Nb, and ^{90}Sr. Most fission products deposited on the ground, allowing the strontium isotopes to enter the food chain. A ban on food containing ^{90}Sr at concentrations greater than 2.4 Bq/g (64.8 pCi/g) resulted in the destruction of 10,000 tons of agricultural produce in the first 2 years. All stores in Kamensk-Uralskiy which sold milk, meat, and other foodstuffs were closed as a precaution against consuming radioactive material, and new supplies were brought in 2 days later by train and truck. Approximately 10,000 people were evacuated from the high-contamination area, while approximately 260,000 people remained in less contaminated areas. The highest individual doses were experienced by those evacuated within a few days of the accident. These individuals received an average external dose of 17 rem (0.17 Sv) and an average internal (gastrointestinal) dose of 150 rem (1.5 Sv); the average effective dose equivalent was approximately 52 rem (0.52 Sv). The average 30-year committed dose for persons living in areas with a ^{90}Sr surface contamination level of 40–70 kBq/m^2 (1.1–1.9 μCi/km^2) was estimated to be 2 rem (0.02 Sv) (CIA 1959; UNSCEAR 1993).

4.8 WINDSCALE, U.K.

In October 1957, the first substantially publicized release of radioactive material from a nuclear reactor accident occurred at the Windscale nuclear weapons plant at Sellafield in the United Kingdom. During a routine release of stored energy from the graphite core of a carbon dioxide-cooled, graphite-moderated

reactor, operator error allowed the fuel to overheat. This led to uranium oxidation and a subsequent graphite fire. Attempts to extinguish the fire with carbon dioxide were ineffective. In the end, water was applied directly to the fuel channels but not before the fire had burned for 3 days, resulting in the release of ^{131}I (740 TBq; 20 kCi), ^{137}Cs (22 TBq; 0.6 kCi), ^{210}Po (8.8 TBq; 0.2 kCi), ^{106}Ru (3 TBq; 0.08 kCi), and ^{133}Xe (1.2 PBq; 32.4 kCi). The fire consumed much of the uranium fuel, and some of the resulting fallout was in the form of flake-like uranium oxide varying in size from 1 to 25 cm (Schultz 1996; UNSCEAR 1993).

The contamination of pastureland was widespread; for those in close proximity to the accident, the greatest threat of exposure was considered to be from ^{131}I via contaminated cow's milk. Those living farther from the accident were exposed to significant amounts of ^{131}I via milk consumption and air inhalation. The consumption of cow's milk was quickly banned; this lessened the exposure to ^{131}I. The highest individual doses (approximately 100 mGy) were to the thyroids of children living near the accident site. The collective dose equivalent received in the United Kingdom and the rest of Europe was estimated to be 2,000 man•Sv, of which 900 man•Sv was from inhalation, 800 man•Sv was from ingestion, and 300 man•Sv was from external exposure. The main radionuclides contributing to the exposures were ^{131}I (37%), ^{210}Po (37%), and ^{137}Cs (15%) (UNSCEAR 1993). There has been no detected impact on the health of the public from this accident.

4.9 TOMSK

An incident occurred at a plant near Tomsk in the Russian federation in 1993 in which individual exposures were low and few in number. The Tomsk site featured one of Russia's three operating plutonium production reactors. The Tomsk reactors were built to produce plutonium and to supply steam for the city's district heating plant. Reprocessing, which involves the use of chemical processes to separate uranium and plutonium from spent nuclear fuel, occurs at the plant. Under certain conditions, the chemical solutions can cause an explosion. In April 1993, a tank containing a blend of paraffin and tributyl phosphate chemically exploded, resulting in the involuntary release of uranium, plutonium, niobium, zirconium and ruthenium. The tank had a volume of 34.1 m^3, and held 25 m^3 of solution. The solution contained 8,773 kg of uranium, and about 310 kg of plutonium. The total amount of radioactivity in the solution was approximately 20.7 TBq (559.3 Ci). The explosion caused substantial damage to the facility and contaminated a largely unpopulated area of about 123 km^2. The release from the tank was estimated to be 4.3 TBq (115 Ci) of long-lived isotopes. Radioactive material spread to the north-east and

fallout was detected over an area of 120 km^3. Gamma radiation 20 times higher than the norm was measured in the area that received the most fallout. The personnel who assisted in putting out the flames received the maximum radiation dose of 2 mSv (200 mrem). The accident could have had more serious local consequences if the wind had carried the contamination to two large nearby cities. In June 1993, DOE officials visited Tomsk to investigate the accident. Although they were not permitted to view the chemical tank that had exploded, they did see other parts of the facility. Several operational errors, such as improper mixing of chemicals in the reprocessing tank, and possible design flaws, such as inadequate tank ventilation, were identified as contributors to the accident (GAO 1995; Nilsen 1997; OTA 1994; UNSCEAR 1993).

4.10 LOST INDUSTRIAL OR MEDICAL SOURCES

Four incidents in which sealed sources of radiation intended for industrial or medical use were lost or damaged have occurred since 1982.

In 1983, an obsolete teletherapy machine from a hospital in Ciudad Juarez, Mexico, containing 16.7 TBq of ^{60}Co was sold as scrap metal. As a result, thousands of tons of steel products sold in Mexico and the United States, as well as several foundries and streets and hundreds of houses, were contaminated and approximately 1,000 people were exposed to an approximate dose of 0.025 rem (0.25 mSv). About 80 people received doses of 0.25–3 Sv (25–300 rem), and 700 people received doses of 0.005–0.25 Sv (0.5–25 rem) (UNSCEAR 1993). No deaths resulted from this exposure.

In 1984, a family in Morocco found and kept within their house a sealed radiography source containing ^{192}Ir. The source was used to radiograph (make x-ray-like pictures) to noninvasively check the integrity of metal welds at construction sites. The capsule holding the source became disconnected from the restraint system inside the source shield and fell out of the shield. A passer-by found the source and took it home, consequently exposing himself and his family. The resultant effective doses were estimated to be 800–2,500 rem (8–25 Sv); 8 members of the family died (UNSCEAR 1993). A poorly designed source- capsule-locking device along with personnel error on the part of the contractor led to these deaths and injuries. Radiography source-locking mechanisms have been redesigned to help prevent such accidents from occurring.

In Goiania, Brazil, in 1987, 54 people were hospitalized and 4 died after removing a teletherapy source containing ^{137}Cs from its enclosure. Individual doses were estimated to range up to 500 rad (5 Gy) (UNSCEAR 1993). This accident is described in more detail in Section 4.2.

In 1992, in the Shanxi province of China, three people in one family died after a member found a ^{60}Co source. The U.S. Nuclear Regulatory Commission has published a safety document that describes the acute health effects of these types of radiation accidents (USNRC 1982).

4.11 IDENTIFICATION OF DATA NEEDS

The following has been identified as a potential data need regarding health effects associated with exposure to ionizing radiation.

A number of people have been exposed to a range of radiation doses as a result of the accidents discussed in this chapter. Some human data do exist on the health effects associated with acute exposure to ionizing radiation (see Chapters 3 and 5); however, most of the radiological effects have been derived from laboratory animal data. It would be helpful to estimate the dose of radiation each of these individuals was exposed to and monitor these people over the long term to determine what health effects (if any) these doses of ionizing radiation had on lifespan, cancer rates, and reproductive effects. There is ongoing research in these areas, mainly the observation of the survivors of the nuclear bombings in Japan and their children and grandchildren by the Radiation Effects Research Foundation (RERF). The RERF is a binational agency that is supported by the United States and Japan.

4.12 CONCLUSIONS

Although most radiation to which the public is exposed is of natural origin, that portion arising from human activities, particularly accidental releases, is perceived by the public to be a very serious threat to health. For the majority of the world's population, less than 1% of radiation exposure arises from nuclear weapons testing fallout and the generation of electricity in nuclear, coal (many coal-fired electric generating stations emit more radioactivity than do nuclear stations), and geothermal power plants. Selected military and civilian accidents have resulted in the exposure of certain populations to substantial amounts of radiation. Few exposures of general populations have been of sufficient size to produce quantifiable deleterious effects. The thyroid cancer rates (the only type of excess cancer seen to date) associated with the Chernobyl accident have begun to rise. After the Hiroshima and Nagasaki bombings, there was a surge of childhood leukemia cases into the 1950s (Pierce et al. 1996). There are also elevated incidence rates for some cancers in the population exposed by the Hiroshima and Nagasaki bombings. To date, there have been about 500 excess deaths from cancer among the survivors of the bombings. The circumstances and results of nuclear power plant accidents indicate that rapid mobilization of clean-up efforts, imposed dietary restrictions, and evacuation of residents (especially pregnant women) minimizes

the public risk. Three-Mile Island and Chernobyl are cases in which the evacuations caused a health detriment and a health benefit, respectively.

4.13 OTHER SOURCES OF INFORMATION

This chapter provided a brief synopsis of population exposures to ionizing radiation. Readers are encouraged to read Chapters 2 through 6 of this toxicological profile for more in-depth information on the basic principles of ionizing radiation, the health effects of ionizing radiation, and the sources of population exposure to ionizing radiation. Further scientific information can be obtained from the United Nations specialized agencies, such as the World Health Organization (WHO), Geneva, Switzerland, and the International Atomic Energy Agency (IAEA), Vienna, Austria. Readers are also referred to the Internet sites listed in Table 4-1 for further information on the general principles and health effect issues involving the different types and doses of ionizing radiation. These sites are sponsored by scientific, government, and academic organizations.

Table 4-1. Internet Sites Pertaining to Population Exposures to Ionizing Radiation

HyperText Transfer Protocol (HTTP) Address	Web Page Contents
http://www.hps.org	The Health Physics Society, a scientific organization dealing with radiation safety
http://www.rerf.or.jp	Atomic bomb survivor studies provide by Radiation Effects Research Foundation, a joint Japanese-U.S. sponsored research organization
http://www.sandia.gov/LabNews/LN01-19-96/palo.html	A newspaper for the employees of Sandia National Laboratories and recounts the Palomares incident
http://fema.gov/home/fema/radiolo.htm	Federal Emergency Management Agency information on how to prepare for an emergency and what to do if an accident occurs
http://www.radres.org/intro.htm	The Radiation Research Society
http://www.afrri.usuhs.mil/www/index.html	The Armed Forces Radiobiology Research Institute
http://cedr.lbl.gov	Comprehensive epidemiologic data resource related to radiological releases from sites
http://radefx.bcm.tmc.edu/	Radiation Health Effects Research Resource page. A comprehensive page on radiation and health effects, including extensive literature searches on Chernobyl health effects

5. MECHANISMS OF BIOLOGICAL EFFECTS

5.1 INTRODUCTION

Radiation ionizes cellular atoms and molecules; if immediate recombination does not occur, these can manifest as some type of molecular, cellular, or organic system alteration. An ionizing event can cause a variety of damage scenarios: (1) no damage if the ionized molecule reforms immediately; (2) repairable damage that causes no clinical effects if repaired; (3) repairable damage to DNA, which can be tumoriginic or carcinogenic if not repaired prior to cell division; (4) irreparable small-scale damage which causes cell death to a small population of cells that is insignificant and produces no clinical effects; and (5) irreparable large-scale damage that kills enough cells within an organ system to produce deterministic threshold effects such as cataracts and acute radiation syndrome

A very large radiation dose received in a short enough period of time to preclude significant repair can cause cellular walls to collapse and disrupt organ systems, producing deterministic effects such as acute radiation syndrome, cataracts, and teratogenesis (mental retardation, IQ reduction, microencephaly, stunted growth). These effects can be caused by acute exposure to sources of high intensity radiation, such as can be found in hospitals, government, and industry. Overexposure events which have caused such effects are not applicable to NPL site residual radioactive contamination. The discussion below largely relates to lower radiation doses and dose rates which can cause non-deterministic effects and which are more relatable to radiation exposure from NPL sites.

A number of direct and indirect radiation interaction pathways can produce damage to the DNA of irradiated cells. DNA damage occurs by indirect action (mediated through radiolytic products in water) or direct ionization. Cells depend on their DNA for coding information to make various classes of proteins that include enzymes, certain hormones, transport proteins, and structural proteins that support life. When the genetic information containing the “blueprint” for these substances is disrupted, cell homeostasis is disrupted, resulting in a wide-range of immediate and/or delayed toxicological effects. Direct and indirect ionization of DNA is ultimately responsible for the DNA alterations that adversely affect the structural and genetic integrity of the system. These alterations can be repaired, or can result in mutations in the genetic coding that can be passed on to daughter somatic cells or to progeny offspring

from reproductive cells. These alterations can result in the wide range of somatic and reproductive effects described in greater detail in Chapter 3.

The human body has nearly 10^{13} cells. Each somatic cell (cells other than sperm and eggs) contains 23 pairs of chromosomes. Each cell (except for red blood cells) contains a nucleus that houses these chromosomes. The total chromosomal content of a cell involves approximately 10^5 genes in a specialized macromolecule of deoxyribonucleic acid (DNA). DNA is composed of alternating sugar and phosphate groups, with the sugar attached to 1 of 4 possible nucleotide bases (adenosine, cytosine, guanine, thymidine). These bases attach to each other in a specific pattern: adenosine:thymidine and cytosine:guanine. Genetic sequences of the bases are read in groups of three (called a triplet), with a possibility of 64 configurations or "words" in which to code information.

Specialized cell structures called ribosomes are the cellular organelles that actually synthesize the proteins (RNA transcription). RNA polymerases read the codes from specific areas of the DNA and transcribe the information into a mRNA copy of the DNA. At the ribosome, the processed mRNA is translated to produce proteins from amino acid units. When the genetic information containing the "blueprint" for these substances is disrupted, cell homeostasis is disrupted, with a wide range of possible non-carcinogenic and carcinogenic toxicological effects. These effects were described in some detail in Chapter 3. Radiation can disrupt the structure of the DNA (and other macromolecules), thereby disrupting normal cell and organ functions.

Direct macromolecule damage by radiation involves partial or complete energy transfer to one or more electrons on the molecule. Each electron that is given enough energy to overcome the attractive forces of the nucleus escapes from the DNA or other macromolecule and leaves it in the form of a charged ion; this process, called "ionization," is the source of the term "ionizing radiation" (see Chapter 2). Unlike non-ionizing radiation (such as microwaves and ultraviolet radiation), which has insufficient energy to eject molecular electrons, ionizing radiation deposits sufficient energy to remove electrons from atomic orbits and create molecular ion pairs along particle tracks.

Ionizing radiation can exert a number of adverse toxicological effects on many tissues in the body by ionizing and subsequently altering the DNA in the nucleus and other macromolecules of the irradiated

cell and possibly even the cytoplasm itself. This radiological toxicity occurs independently of, and in addition to, whatever chemical toxicological effects are produced by internally deposited radionuclides. Chapter 3 describes in some detail the biological effects of radiation in different organ systems in humans and laboratory animals and demonstrates that some systems or tissues are more sensitive to the effects of radiation than others. Chapter 3 also provides some general explanation for the presence of marked toxicity differences. DNA damage and cell wall destruction are the likely bases for lethality due to radiation; however, other molecules and cellular organelles may be damaged by radiation. These other molecular alterations may also result in adverse cellular activity and may be responsible for some of the biological responses observed after exposure to radiation. This chapter is an overview of the specific mechanisms that result in the non-carcinogenic and carcinogenic biological effects.

5.2 EVIDENCE OF THE EFFECTS ON DNA

Before any mechanism of action of ionizing radiation on DNA can be presented, it is necessary to demonstrate that DNA is indeed the critical molecule after exposure to radiation. Indirect evidence comes from studies which show that cells that divide frequently (undergo mitosis or meiosis in the case of spermatogonia) are the most sensitive to the effects of radiation. This phenomenon is described in Table 5-1. Conversely, structures that undergo less frequent mitotic cycles (myocytes, connective tissue, nervous tissue) are relatively more resistant to the effects of radiation. Early experiments, in which either the cytoplasm of the cell (not the nuclear material) or the nucleus only were irradiated with alpha radiation, demonstrated that the DNA is the most critical cellular component in radiation toxicology (Munro 1970). Those experiments showed that, although some minor effects could be induced after exposing the cytoplasm to alpha radiation, the nucleus (and the genome) were many times more sensitive to the effects of ionizing radiation. Recently developed research techniques, which allow precise irradiation of individual cell components with a predetermined number of alpha particles, have also concluded that cellular cytoplasm is less radiosensitive than DNA (Miller et al. 1999; Wu et al. 1999). These alterations are what ultimately gives rise to lethal or phenotypic genetic alterations of the DNA and may lead to the induction of many types of cancers in the irradiated individual (see Chapter 3 of this profile).

Table 5-1. Relative Sensitivities of Major Organs and Tissues to the Effects of Ionizing Radiation

Radiosensitivity category	Organ system	General cell type affected	Frequency of mitosis
High	Lymphoreticular	Lymphocytes	Very frequent
	Hematological	Immature hematopoietic cells	
	Reproductive	Spermatogonia	
		Ovarian follicular cells	
	Gastrointestinal	Intestinal epithelium	
		Esophageal epithelium	Frequent
		Gastric mucosa	
	Renal	Urinary bladder epithelium	
	Dermal	Epidermal epithelial cells	
		Mucous membranes	
	Ocular	Epithelium of optic lens	
Medium	Circulatory system	Endothelium	
	Musculoskeletal	Growing bone and cartilaginous tissues	Moderately frequently
	Brain/CNS	Glial cells	
	Dermal	Glandular epithelium of the breast	
	Respiratory	Pulmonary epithelium, tracheobronchial epithelium	
	Renal	Renal epithelium	
	Hepatic	Hepatic epithelium	
	Endocrine	Pancreatic epithelium	
		Thyroid epithelium	
		Adrenal epithelium	
Low	Hematological	Mature hematopoietic cells (erythrocytes, neutrophils, eosinophils, basophils, macrophages)	Infrequently/rarely
	Musculoskeletal	Myocytes, osteocytes	
		Mature connective tissues	
		Mature bone and cartilage	
	Brain and peripheral nervous system	Ganglion cells	

Other evidence exists to support the thesis that radiation's toxicological effects are intimately related to nuclear DNA damage. For example, when non-radioactive thymidine is incorporated into the DNA of a cell, no change in the cell's lifespan is encountered; however, when the same thymidine is labeled with radioactive tritium (^{3}H), which emits short-range beta particles (see Chapter 2), cell lethality dramatically increases. Coupled with the other indirect evidence, this suggests that the low-energy beta particles are

ionizing the nuclear DNA, resulting in increased incidences of cellular death. Additionally, work involving radioactive material in viruses and plants has shown a strong correlation between the chromosome volume of a cell with radiosensitivity—the larger the volume of chromosomal material, the greater the relative radiosensitivity of the cell. Radiosensitivity is relative to a specific biological end point. For instance, sperm have a high radiosensitivity with respect to mutation induction but a very low sensitivity with respect to cell killing. A direct correlation has been demonstrated between aberrant chromosome formation at the first cell division after irradiating hamster cells. These and many other studies provide strong evidence that exposure to radiation has detrimental effects on cellular DNA (Hall 1988).

5.3 INTERACTIONS OF IONIZING RADIATION WITH DNA

Chapter 2 provides an overview of the types of radiation and their ability to transfer energy when ionizing biological matrices. The interaction of radiation with all molecules (including DNA and other cellular components) may be classified as either direct or indirect interactions. Each produces damage by a specific pathway (or mechanism) that is described in more detail in this section.

Depending on the energy of alpha and beta particles when they are formed, the initial velocity of an alpha particle can be a few tenths the speed of light and that of a beta particle can approach the speed of light; however, these velocities reduce toward zero as they interact with the medium through which they pass, losing energy as they excite and ionize molecules along their paths. Since gamma rays are electomagnetic radiation, they travel at the speed of light even as their energy is transferred to the medium. As described above, a direct interaction occurs when an alpha particle, beta particle, or gamma ray hits and ionizes an atom or molecule. Both high and low LET radiation can directly ionize a molecule at the point of impact, producing two adjacent pieces which are chemically reactive. If the two pieces immediately recombine to reproduce the same original molecule, no damage results. Alternately, the pieces may drift apart, engaging neighboring atoms and molecules in any stabilizing chemical reactions that are thermodynamically feasible. Each chemical reaction produces a different molecular species. In the case of high LET radiation or high intensities of low LET radiation, the distance between ionizing events is short enough that the radiation can ionize adjacent molecules or even multiple bonds on the same molecule. For a large macromolecule such as DNA with its multistrand arrangement in chromosomes, these actions can damage the molecular structure in a number of ways. Radiation can remove large or small pieces of the molecules, and can open purine rings (leading to depurination) and break phosphodiester bonds. This action may result in the genetic effects listed in Tables 3-4 and 3-5.

Genotoxic effects are a major toxicological end point for exposure to ionizing radiation and are likely involved in the induction of cancer in humans. The data from Tables 3-4 and 3-5 demonstrate that the typical genotoxic effects associated with radiation exposure of genetic material primarily consist of deletions, mutations, chromosomal aberrations, and breaks, resulting in reciprocal translocations, sister chromatid exchanges, dominant lethal mutations, and sperm anomalies. When the cell enters a mitotic cycle, these damaged chromosomal units have an increased probability of failing to replicate properly due to structural damage unless chromosomal repair mechanisms repair the damage prior to entering mitosis. If the repair mechanisms fail to perfectly and seamlessly repair the damage to the chromosome, restoring it to its original preionized structure, or do not repair the damage at all, the chromosome may not replicate properly. This results in critical portions of that chromosome being deleted during the replication cycle, resulting in cell death (which equates to no damage at low doses) or genetic mutations in cell progeny. Table 5-1 shows that those cells that undergo rapid mitotic cycles (intestinal crypt cells, fetal cells, and other rapidly dividing cells) have less time for repair mechanisms to reverse the radiation damage to the nuclear DNA, making chromosomal anomalies more likely to be present during subsequent mitotic cycles and increasing the chances for cell death, genetic mutations, and abnormal cell functions in cell progeny. Ionizing radiation can affect other macromolecules in a similar fashion; these effects are discussed in Section 5.4.

Indirect interactions are molecular disruptions occurring at distances from the radiation's direct interaction site. Indirect interactions are mediated by radiation-produced chemical species (free radicals and oxidizers) with sufficient life-times and reactivity to diffuse away from the primary site and disrupt molecules with which they collide. Some of the radiation degradation (radiolysis) products of water, including the hydrogen and hydroxyl radicals produced by the reactions below, are recognized cytotoxins, and oxygen enhances these effects. Thus, oxygenated tissue is more radiosensitive than anoxic tissue. Water comprises approximately 60% of the total body mass of humans and laboratory animals, and 75–80% of the chemical composition of the living cell. When radiation interacts with water molecules surrounding DNA, the end products diffuse away and react with any DNA that is in their paths. Biological material that has a low water content, such as spores, exhibits a greater resistance to radiation effects.

Radiolysis of water

$$H_2O + IR \rightarrow e^- + H_2O^+$$
$$e^- + H_2O \rightarrow H_2O^- \rightarrow OH^- + H^\cdot$$
$$H_2O^+ \rightarrow H^+ + OH^\cdot$$

In the first reaction, radiation interacts with free cellular water to produce one free electron (e^-) and one ionized water molecule (H_2O^+), a reaction commonly known as radiolysis. This free electron is highly reactive and interacts with another un-ionized water molecule to produce a negatively charged and highly unstable water molecule. This molecule quickly decomposes to form the OH^- ion and the $H^\bullet$ free radical; the $H^\bullet$ radical is reactive, but the OH^- ion is more stable and can then diffuse out into the cellular fluid and interact with any number of macromolecules it encounters in its path, such as molecules of DNA. The remaining H_2O^+ molecule can also transform into a free and ionized hydrogen ion (potentially affecting intracellular or extracellular pH) and the hydroxyl radical. From these reactions, four products of radiolysis can occur after ionizing radiation interacts with a water molecule: $H^\bullet$, $OH^\bullet$, H^+, and OH^-.

Of the radiolysis products, 55% are either $H^\bullet$ or OH^- and are the most important species biologically; however, they have lifetimes of approximately 10^{-11} seconds, which is long enough to produce damage to DNA and other macromolecules. These ionized particles will react with DNA, resulting in the addition of atoms or loss of atoms or pieces of the molecule; this will ultimately result in structural degradation, cross-linking, breakage of chemical bonds, and a host of other adverse effects. $H^\bullet$ or OH^- may also interact with each other, to form an innocuous water molecule.

In the presence of water and oxygen, radiation can produce another set of reactions that have more potentially destructive capabilities within the cell. The radiolysis reaction, in the presence of molecular oxygen, results in the formation of three chemical entities: hydrogen peroxide (H_2O_2), hydroperoxy radicals ($HO_2^\bullet$), and hydroperoxy ions (HO_2^-). All have potent oxidizing potential and lifetimes of approximately 10^{-11} seconds. With an extended lifetime (when compared to the 10^{-11} second half-lives of $H^\bullet$, $OH^\bullet$, H^+, and OH^-), there is a greater diffusion length and potential for interacting with and inducing more damage to the DNA. Oxygen is, therefore, considered a radiosensitizing agent, associated with the production of relatively longer-lived and more potent by-products than in tissues containing less oxygen. The oxygen-water-ionizing radiation interactions have practical applications in clinical medicine. Radiotherapy is often used to treat large cancerous tumors in humans. Oxygen tension is lowest at the center of these large cancers, due to an inadequate blood supply to the cancer, compression from surrounding cells, or altered aerobic metabolism in these cancerous cells. Many of these masses may have liquified and necrotic centers as well. Low oxygen tension in these cancers may not result in the production of significant amounts of hydrogen peroxide and hydroperoxy ions/radicals to damage macromolecules within these abnormal cells and, therefore, may limit the efficacy of radiotherapy in

these patients. The use of oxygenating chemicals to offset this oxygen deficit and enhance the oxygen tension can make cancer tissue more radiosensitive than the surrounding healthy tissue.

Radiation frequently produces an important type of change to DNA at the molecular level by removing a base to form an apurinic or apyrimidinic site. The deletion or total destruction of DNA bases, destruction of deoxyribose residues, and deamination of cytosine or adenine are a few of the many ways radiation can alter the DNA at a molecular level. The attack by direct and indirect radiation action results in the degradation of bases and sugars, breakage of the hydrogen and sugar-phosphate bonds, and cross-linkages, all of which are deleterious to the structural integrity of the DNA macromolecule. Significant amounts of damage make the DNA unable to successfully replicate during mitosis and/or unusable for transcription into RNA. The magnitude of the damage is dose-dependant. A more in-depth discussion of the alterations at the DNA level by radiation, including a few of the known DNA repair mechanisms, is presented in BEIR V (1990).

DNA base damage is the most predominant type of DNA damage, followed (in decreasing order of incidence) by single-strand breaks, DNA-protein cross-linkages, and double-strand breaks. In base damage, thymidine appears to be the most radiosensitive base, followed by cytosine, adenine, and guanine. A 100-rad (1 Gy) dose of low LET radiation can produce 63–70 double-strand breaks per cell and 1,000 single-strand breaks (Cockerham et al. 1994). In addition, it was noted that there were 440 sites of multiple DNA strand lesions that are in close proximity to each other that interact in such a way to cause cell death (called Locally Multiple Damaged Sites [LMDS]). It would appear that simple single- or double-strand breakage is responsible for cell death; however, in cases of genotoxicity after chemical exposure, single-strand breakages have numbered into the hundreds of thousands, suggesting that the relatively low number of single-strand breaks after exposure to radiation is not likely to be the primary cause of cell toxicity, probably because of the presence of repair systems. Double-strand breaks are likely too few to be of consequence for cell death, but they are critically important in cancer initiation. Given that there are only three types of damage to the DNA that could be responsible for cell death, this leaves LMDS as the primary cause for cell death (Faw and Shultis 1993).

Strand breakage is also responsible for chromosomal anomalies, some of which were listed in Tables 3-4 and 3-5. DNA strand damage is a serious cellular event; however, the cell comes equipped with chromosomal repair mechanisms. Without them, the damage that occurs to the entire organisms's DNA every day could prove lethal. Chromosomal repair mechanisms provide a mechanism for minimizing the

adverse DNA effects of radiation on the genome, providing that the dose is not so large as to overwhelm the inherent repair mechanisms. However, like many other biological functions, they are not always 100% efficient at performing this task. Single-strand breaks stand a better chance for repair by the cellular DNA repair enzymes (DNA ligase) than do double-strand breaks. First, with single-strand breaks, only one strand of the double-stranded DNA is broken, whereas both strands are broken with double-strand DNA damage. Because one strand is still intact, single-strand breaks are usually stable and within a reasonable distance from each other for repair enzymes to function; however, this is not always the case with double-strand DNA breaks. Secondly, there is a template on the adjacent strand in single-strand DNA breaks to determine where various bases go on the missing strand. The ionizing event that produces a double-strand break may leave the displaced sections close enough together to rejoin with minimal repair, or it may displace large sections, leaving no template for repair enzymes to follow in order to replace the missing segments. Because single-strand breaks in DNA are more easily repaired, cells can tolerate much more of this type of strand breakage before the repair mechanisms are overwhelmed.

Chromosomal aberrations and chromatid aberrations are the two most common types of chromosomal anomalies that can be visibly observed during the metaphase or anaphase stages of the cycle. Chromosomal aberrations are a result of a cell that was irradiated early in the interphase cell cycle (G1 or early S phase), prior to the chromosome being duplicated. Chromatid aberrations are commonly observed when the damage was received in the later stages of interphase (late S or G2 phase) after the chromosome has duplicated and consists of two strands of chromatin. Specific radiation-induced aberrations in chromosome and chromatid structure have been discussed in more depth by Hall (1988). These aberrations may or may not result in the disruption of normal cellular functions, depending on which chromosome the breakage occurred in and where on the chromosome the damage occurred. When examined more closely, the broken ends of the chromosomes appear "sticky" and may fail to mitotically separate with the proper chromatid (Hall 1988). However, when the cell enters a mitotic cycle, these damaged chromosomal units will ultimately fail to replicate properly unless chromosomal repair mechanisms can repair the damage prior to entering mitosis/meiosis. If the repair mechanisms fail, cell death or genetically deficient progeny cells result. Of the single and multiple gene mutations that result, point mutations and small deletions usually involve a small number of bases (~20 to 60), whereas large base deletions or base rearrangements may involve several hundred or many thousands of bases. The mutation frequency increases with the radiation dose (Borek 1993). The cells that undergo more frequent mitotic cycles (intestinal crypt cells, fetal cells, and other rapidly dividing cells) have less repair time, and

a resulting increase in sensitivity to radiation induces genetic mutations and abnormal cell functionality. Cells with less frequent mitotic activity (nerve, lens, musculoskeletal) are conversely less radiosensitive.

The types of genetic damage described above for radiation exposure are also caused by other environmental agents, and their rates are in addition to a high rate of spontaneous production. An average of 200,000 repairs per hour are made to spontaneously occurring damage to DNA in humans. Actually, the damage occurs at a much greater rate than can be observed because the damage is simultaneously being repaired by many physiological mechanisms. Damage is expressed when the rate at which the damage is produced exceeds the body's natural repair mechanisms or when those mechanisms fail.

5.4 EFFECTS ON OTHER CELLULAR MACROMOLECULES

DNA is the most critical molecule for damage from radiation. A number of other critical cellular components have been reported; some effects on these molecules are outlined in Table 5-2.

Table 5-2 shows that a wide range of molecules, varying in both size and molecular weight, can be adversely affected by exposure to radiation. The mechanisms by which each is affected are the direct and indirect effects of radiation discussed for DNA. The end results are broken chemical bonds, cross-linkages, and conformational changes. These changes may affect the molecule's biological function; for example, a conformation change in the structure of an enzyme or protein could affect its ability to perform a critical function in a metabolic pathway and thereby halt a certain function.

Amino acids and their larger counterparts, peptides, polypeptides, and proteins, are also susceptible to radiation damage. Irradiation of these molecules frequently results in breakage of hydrogen bonds, disulfide bridges, and cross-linking with DNA or with other proteins. All of these effects can result in conformation changes and alterations in function. Radiation causes the depolymerization of glycogen and cleavage of α-glycosidic bonds within glycogen and other molecules containing α-glycosidic bonds. Glycogenesis and gluconeogenesis pathways within the cell are activated; insulin and blood glucose levels also rise due to increased release of insulin and adrenocorticoid release. By comparison, radiation doses that are orders of magnitude larger than required to produce these effects are used in industry to polymerize monomers to produce hard plastics and bond materials. Even larger doses are required to inactivate bacteria and viruses during sterilization of medical equipment, spices, vegetables, and meat.

Table 5-2. Some Effects of Ionizing Radiation on Molecules in Animal Tissues

Molecule	General effects
Amino acids	Production of ammonia, H_2S, pyruvic acid, CO_2, hydrogen molecules
Carbohydrates	Cleavage of glycosidic bonds, depolymerization of monomers, oxidation of terminal alcohols to aldehydes
Deoxyribonucleic acid (DNA)	Degradation from base loss and modification, breakage of hydrogen bonds and sugar-phosphate bonds; DNA-DNA and/or DNA-protein cross-linking; single- or double-strand breakage; formation of guanyl, thymidyl and sugar radicals
Lipids	Peroxidation and carbon bond rearrangement: conjugated diene formation, aldehyde formation, β-scission, lipid cross-linking, increased microviscosity, cell membrane rupture
Proteins	Degradation and modification of amino acids, chain scission, cross-linkage; denaturation, molecular weight modifications, changes in solubility
Thiols	Redox reactions, radical formation, cross-linkages, inhibit thiol from mediating damage to lipids

Source: adapted from Cockerham et al. 1994.

Lipids are ubiquitous macromolecules that participate in a number of cell process. They comprise cell membranes, disruption of which leads to disruptions of homeostasis, cellular dysfunction, and death. Lipids are also involved in the production of prostaglandins, which modulate a number of biological functions, including digestion, reproduction, and neural function. Lipid peroxidation occurs primarily through free-radical attacks at double-bond sites and at carbonyl groups, and starts a chain reaction within cells. When a lipid radical interacts with another organic molecule, that molecule is transformed to a free-radical state which then interacts with another molecule. Given this chain of events, the damage induced after lipid peroxidation can be formidable. Fortunately, animals have several mechanisms by which to slow or stop this chain reaction. A number of free-radical scavengers such as vitamin A, vitamin E, and thiols are available to inhibit the chain reactions. Other detoxification systems that can inhibit the effects of lipid peroxidation include metallothionine, glutathione transferase, reduced NADPH-dependent glutathione reductase, selenium-dependant glutathione peroxidase, ferric manganese and copper-zinc superoxidase dismutases, and catalase. A more in-depth discussion on the specific mechanisms by which each system functions is available (Cockerham et al. 1994). Several of these systems and a number of chemicals have been more closely studied in order to potentially decrease the harmful effects of moderate to high doses of radiation in humans and animals, but results have been mixed (Biambarresi and Walter 1989).

5.5 MECHANISMS OF CARCINOGENESIS

The exact mechanism(s) by which cancer is produced are not clearly understood, but over the years, several theories and models have been developed that describe the events that scientists suggest must take place in order for cancer to occur. Some of the more traditional carcinogenesis models are briefly summarized in Table 5-3. A number of factors have been identified (such as diet; hormonal status; genetics; and exposure to some solvents, chemicals, and ionizing radiation) that appear to predispose some individuals to developing cancer. Both chemicals and ionizing radiation are known to induce many types of cancer and much of the evidence for this observation was discussed in Chapter 3 of this profile.

Cancer is the major latent effect after exposure to radiation, with the critical molecule being the DNA. Cells depend on their DNA for coding information to make very specific enzymes, proteins, hormones, vasoactive substances, and a host of other chemicals in order to live. When the genetic information containing the "blueprint" for these substances is disrupted, cell homeostasis is disrupted, with a wide range of carcinogenic and non-carcinogenic toxicological effects that have been described in Chapter 3.

Not all alterations in the genome will result in the expression of immediate adverse events. Radiation may cause genetic damage, which includes gene deletions, point mutations, frameshift mutations, and "nonsense" coding of some genes on one or many chromosomes. These alterations occur by the same direct and/or indirect mechanisms outlined in Section 5.3. If these genes are not used by the cell or if their mutation or total absence is of little consequence to normal cell function, no immediate effects may be incurred. Cell function and homeostasis is not disrupted. These seemingly inconsequential genetic effects may initially be of minimal importance. However, with spontaneous changes in the genetic apparatus of somatic cells continuing over time and with further exposure to environmental carcinogens, the amount of misinformation in the genetic apparatus continues to increase within the cell's DNA. If this misinformation affects the DNA coding that either controls or suppresses an oncogene, then oncogenic lesions may be initiated.

The formation of cancer has been an area of intense research in the scientific community for centuries. In 1775, Percival Pott was the first to report that cancer could be caused by environmental factors. Pott described a number of cases of cancer in men employed as chimney sweeps sometime during their life. Pott concluded from his observations that their exposure to soot was in some way related to their developing

Table 5-3. Some Models That Describe the Induction of Cancer in Animals

Model	Model type and premise	Model characteristics
Single Hit [a]	Mechanistic model: One "hit" is sufficient for a cell to mutate and then transform into a neoplastic cell.	Tumor development depends only on the total dose received and not on the pattern of exposure; yields high estimations of risk compared to other models
Multi-Hit	Mechanistic model: A critical number of hits must occur before the cell becomes neoplastic.	May produce very high or very low "safe-dose" estimates; doesn't easily account for dose-response relationships that are linear at low doses; begins to curve as dose increases
Multistage/ Linearized Multistage (LMS)	Mechanistic model (based on the model of Armitage and Doll 1957): A progression of orderly events must occur in a cell in order for cancer to occur.	Use of upper bounds results in a model less sensitive to changes in data; multi-degree polynomials are fitted using only 2 or 3 dose levels; a constant dose rate is assumed (which is not always the case); does provide conservative risk estimates
MVK	Mechanistic model; Two-stage model: Similar to the LMS, but it assumes that altered cells have a selective advantage over normal cells.	Assumes tumors come from mutations of anti-oncogenes; assumes 2 events must occur for malignant transformation; allows for cell kinetic information and mutations to be incorporated into the model
Probit	Statistical model	Estimates probability of a response at a given dose; may not reflect scientific observations of dose-response when extrapolating from a 50% response dose to a 1/1,000,000 risk estimate
Logit	Statistical model	Derived from chemical kinetic data; used to derive "virtually safe doses" by some government agencies until the late 1970's; similar to Probit model
Weibull	Statistical model	Used to derive "virtually safe doses" by some government agencies until the late 1970s; uses power transformations to describe the data; greater flexibility than either the Probit or Logit models; risk estimates range between the LMS and multihit mechanistic models; dose and time relationship are described

[a] A "hit" is defined as a critical cellular interaction, such as a gene mutation, that alters the cell's DNA (Faustman and Omenn 1996).

Source: summarized from Faustman and Omenn 1996 and Rees and Hattis 1994

cancer of the scrotum. Since that time, a number of chemical, environmental, and lifestyle factors have been identified as either be directly or indirectly implicated in producing different types of cancer. Many of these chemicals have similar physico-chemical and structural characteristics.

Today, the induction of cancer from exposure to some chemicals is believed to be a multi-stage process that involves at least three distinct phases and multiple steps. Some chemicals or agents may be capable of inciting one, two, or all three of these steps. It is believed that exposure to ionizing radiation involves the same multi-step process as does the chemical carcinogen exposure, and that radiation can induce each

step. The first stage is initiation, which is characterized by the fixation of a somatic mutational event in the cell's DNA. This damage may occur by direct, indirect, or a combination of the events described in Sections 5.2 and 5.3. This initiation may occur at one or multiple sites within the genome and may affect any gene on any chromosome in any exposed cell. Once exposed, certain outcomes are possible. In cases of high doses of radiation, the cell may sustain such extensive genetic damage that the cell is unable to perform its functions or sustain itself metabolically, in which case it simply dies. High doses may kill so many cells that the organism shows signs and symptoms, but lower doses can kill few enough cells that effects are not readily observed. The cell may attempt to repair the damage using alkyltransferases, base excision repair, nucleotide excision repair, mismatch repair, or other innate repair mechanisms inherent to that cell. If all of the damage is repaired correctly, the cell is considered normal and not at risk for developing cancer. However, repair mechanisms are not always 100% effective and may result in incorrect repair or no repair at all. In this case, the cell may either live and tolerate the damage to the genetic material or undergo apoptosis (programmed cell death). Only the cells that continue to live and reproduce can potentially produce cancer. Exposure to ionizing radiation can result in changes to a cell's genetic apparatus and can act as an initiating agent in the development of cancer. Additional information about the ability of radiation to inflict damage on the DNA structure is presented in Chapters 2, 3, and earlier in this chapter.

Initiation requires at least a partial failure of gene repair mechanisms and one or more cell mitotic cycles before the genetic alteration can be "fixed" into place. Initiation is an irreversible process once this fixation occurs. Whatever the mechanism, the end product is a mutation of the cell's DNA that the cell's innate repair systems failed to restore to the normal genetic state. This mutation is considered an adverse event; however, the initiation or "genetic recoding" alone is not sufficient to produce cancer.

The initiation step must be followed by the second stage, promotion. A promoting agent is one which stimulates the initiated (or pre-neoplastic) cell to divide or otherwise provides certain conditions that allow the preferential selection of mutated cells to survive over unmutated cells in the tissue. In contrast to initiation, the promotion step is a reversible step both at the DNA and cellular level, and depends on continuous exposure to the promoting agent. This reversibility is a characteristic of the promotion stage of carcinogenesis. For promoting agents, there is no evidence to suggest that these chemicals or other factors must interact directly with the DNA to affect cell proliferation. Promoters need not necessarily be carcinogenic agents themselves. Many chemicals (phenobarbital, dioxins, cholic acid), as well as some hormones (estrogen and thyroid-stimulating hormone) are not carcinogenic themselves, but have been

found to promote carcinogenesis after certain cells have undergone the initiation process in some species of animals. Promoting agents may also be species specific. A promoting agent for cancer in laboratory animals may not necessarily be a promoting agent in humans. Although some promoters are actually non-carcinogenic when administered by themselves, other promoters can act as both initiators and promoting agents. Radiation is an excellent example of an agent that can act as both an initiator (producing gene mutations and chromosomal alterations) and as a promoting agent by stimulating cell division after exposure.

The last stage of carcinogenesis is called progression. Progression agents cause uncontrolled and extensive proliferation of abnormal cell types. During this stage, a specific phenotype of mutated cells is selected that effectively evades the host defense mechanisms and then undergoes massive proliferation. Arsenic salts, asbestos fibers, benzene, benzoyl peroxide, and hydroxyurea have all been identified as proliferation agents associated with cancer formation. This uncontrolled and extensive proliferation of abnormal cell types leads to the formation of solid tumors (adenomas, squamous cell carcinoma, adenocarcinomas, etc.) or non-solid tumors (leukemia, lymphoma, etc.) at one or multiple locations throughout the body. How locally invasive the tumor is (aggressiveness) or the ability of the tumor to relocate to sites distant from the site of initial formation (metastasis) depends on the type of tumor formed. If the progression becomes widespread throughout the body or causes severe harm to vital organ functions, the organism will eventually succumb to organ failure and die. Radiation is capable of acting as a proliferation agent in the formation of cancer in the skin of mice.

Gene mutation is a key step in the formation of cancer. Any gene or any locus on the DNA can be affected by a genotoxic agent and undergo. Certain gene mutations and chromosomal irregularities are associated with specific cancers in humans and laboratory animals. These genes are called proto-oncogenes, oncogenes, and tumor suppressor genes. Proto-oncogenes are similar to viral oncogenes. Proto-oncogenes are considered normal genes. When mutated, proto-oncogenes become oncogenes, which, in turn, initiate carcinogenesis. Both proto-oncogenes and oncogenes are dominant genes that normally function to regulate cell growth, signal transduction, and nuclear transcription (Pitot III and Dragan 1996). Mutations in these genes result in the activation and subsequent neoplastic transformation of cells containing these mutated genes. Conversely, tumor suppressor genes are recessive genes which normally function to slow cell growth. When these genes mutate, cells lose this capacity to down-regulate cell growth, which results in the activation and subsequent neoplastic transformation of the mutated cells. Radiation may cause mutations in proto-oncogenes, oncogenes, and tumor suppressor genes.

Environmental factors have also been shown to play a role in lung carcinogenesis, particularly in the promotion stage. These environmental factors include tobacco, silicon dust, diesel fumes, and possibly other toxicants found in the breathable air of mines. Other factors that have been related to chemically-induced cancers include alcohol use, food additives, diet, sexual behavior, occupation, air and water pollution, pharmaceuticals, and bacterial and viral infections.

5.6 IDENTIFICATION OF DATA NEEDS

The following has been identified as a potential data need regarding health effects associated with exposure to ionizing radiation.

Environmental factors, such as tobacco, silicon dust, diesel fumes, and possibly other toxicants found in the breathable air of mines, together with radiation, have been shown to play a role in the development of lung cancer. More research is needed on biomarkers as identifiers of unique DNA and cellular changes associated with exposure to radiation. More research is also needed to determine possible interactions between other carcinogens and ionizing radiation.

Human epidemiological studies have clear limitations in the low-dose range, and mechanistic studies may be important in further clarifying the true effects at low doses. In this regard, there is a need to more fully understand the role of DNA repair at low dose, gene expression in carcinogenesis, and the role of radiation in cancer promotion and progression. Mechanistic studies should be considered for non-carcinogenic effects such as human developmental radiobiology, particularly for internal emitters.

5.7 SUMMARY

This chapter summarized the major mechanisms by which ionizing radiation exerts it toxic effects on cell structure. Macromolecules, in particular DNA, are the critical molecules for damage from radiation. The method by which radiation interacts with a biological medium may be direct or indirect. Damage can occur due to direct ionization of the DNA molecule itself or indirectly through the formation of toxic products, such as free radicals, hydrogen peroxide, hydroperoxy radicals, and hydroperoxy ions, that diffuse from the site of formation and interact with any molecules in their path. Since cells rely heavily on their DNA for instruction information, when the genetic information containing the “blueprint” for this information is disrupted, cell homeostasis is disrupted, and a wide range of biological responses is

encountered. These responses include non-carcinogenic and carcinogenic end points. Other molecules, such as lipids, proteins, thiols, amino acids, and carbohydrates, can also be damaged when irradiated. A number of models were presented that reflect possible mechanisms of cancer induction, as well as a brief discussion of the three steps of cancer formation. By knowing the specific mechanisms by which radiation produces carcinogenic and non-carcinogenic end points, research can focus on identifying biomarkers of effect with which to better assess the effects of low-level radiation exposure.

6. SOURCES OF POPULATION EXPOSURE TO IONIZING RADIATION

6.1 OVERVIEW

All organisms (e.g., bacteria, plants, or animals, including humans) are exposed everyday to varying amounts of ionizing radiation. Figure 6-1 shows average contributions from various sources of radiation to which the average U.S. citizen is exposed during his or her lifetime. Approximately 82% of the radiation dose is from natural sources: 55% from radon (see Figure 1-3), 8% from cosmic radiation (from the sun and stars), another 8% from terrestrial sources (radioactive material in rocks and soil), and 11% from internal sources (radioactive materials, primarily potassium-40, from food and water consumed in the daily diet).

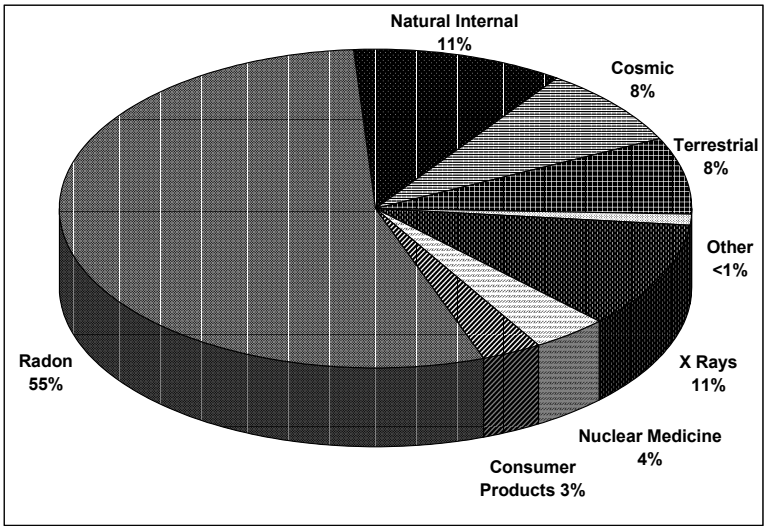


Figure 6-1. Radiation Exposure to the Average U.S. Citizen
adapted from (NCRP1987a)

The remaining 18% of the dose comes from anthropogenic (man-made) sources such as medical x ray exposure (11%), nuclear medicine procedures exposure (4%), consumer products (3%), and other sources (<1%). These other sources include occupational exposure, nuclear fallout, and the nuclear fuel cycle. The total average annual effective dose equivalent for the population of the United States, natural and anthropogenic, is approximately 360 mrem (3.6 mSv) and is described further in Chapter 1 of this profile (BEIR V 1990).

The majority of exposure to radiation comes from natural sources. With the exception of indoor radon exposure (and to some extent exposure from terrestrial sources), exposure to natural radiation is only moderately controllable. Controllability in relation to radon refers to mitigation of radon concentrations in buildings and homes. The average annual effective dose equivalent from all natural sources combined is approximately 3 mSv (300 mrem). Of this amount, approximately 98 mrem (98 mSv) is due to

background radiation; this includes cosmic rays, 29 mrem (0.29 mSv); terrestrial gamma rays, 29 mrem (0.29 mSv); and naturally existing radionuclides within the body, 40 mrem (0.40 mSv). Individual doses from natural sources may be much greater. The magnitude of natural exposures depends upon numerous factors such as geographic location, height above sea level, and the construction and ventilation of buildings. For instance, the average annual radiation dose received by a person living in Boston, Massachusetts, is approximately 300 mrem (3 mSv), while people living in Denver, Colorado, and Kerala, India, receive average annual doses of approximately 600 mrem and 1500 mrem, respectively. The difference in these doses is due mainly to greater concentrations of radioactive materials found in the soils of the Colorado and Kerala areas and to a smaller extent the increase in cosmic radiation at higher altitudes in these areas (BEIR V 1990; Eisenbud 1987; Harvard Medical School 1996; UNSCEAR 1993).

Commonly used terms and scientific unit symbols and abbreviations used in this chapter are defined in Table 6-1 and Table 6-2, respectively. These and other terms may also be found in the glossary in Chapter 9 or in the index at the end of this toxicologic profile. The following sections discuss natural external exposures (Sections 6.2 and 6.3), natural internal exposures (Section 6.4), and internal and external man-made/industrial exposures (Sections 6.5, 6.6, and 6.7).

6.2 COSMIC RADIATION EXPOSURE

Cosmic radiation contributes an estimated 8% to the average population radiation dose. It is primarily composed of galactic radiation originating outside the solar system in addition to a varying degree of solar radiation. The primary cosmic rays that arrive in the upper atmosphere are high-energy subatomic particles—primarily protons, but also nuclei and electrons— moving almost at the speed of light; these primary rays create secondary rays that bathe the atmosphere in radiation. Austrian physicist Victor Hess discovered cosmic rays in 1912 when he and two assistants flew a balloon to an altitude of 16,000 ft (4,877 meters). Hess proved that the source of a mysterious radiation previously detected over the ocean, where terrestrial radiation levels were expected to be very low, was actually coming from outside the atmosphere; he also found that the rate of decline in radiation as the balloon ascended over land was slower than would be expected if the radiation emanated from the earth. The difference is caused by the cosmic rays. Only a small fraction of cosmic radiation originates from the sun; however, the proportion of cosmic radiation contributed by the sun increases during periods of increased sunspot and solar flare activity, which run in

Table 6-1. Common Terms and Abbreviations

becquerel (Bq)	SI unit for quantity of radioactive material; 1 Bq equals that quantity of radioactive material in which there is 1 transformation or disintegration per second (dps).
curie (Ci)	Conventional unit for quantity of radioactive material. One Ci is the quantity of any radionuclide in which there are 37 billion transformations or disintegrations in 1 second. This is the activity of 1 gram of ^{226}Ra.
rad	The unit of absorbed dose equal to 0.01 Joule/kg in any medium.
gray (Gy)	SI unit of absorbed dose.
rem	Conventional unit for dose equivalent. The dose equivalent in rem is numerically equal to the absorbed dose in rad multiplied by the quality factor.
roentgen (R)	A unit of x ray and gamma ray exposure. It is measured by the amount of ionization in air produced by x ray and gamma radiation. One R equals 2.58×10^{-4} coulomb per kg of air.
sievert (Sv)	The SI unit of dose equivalent. It is equal to the dose in grays times a quality factor; 1 Sv equals 100 rem.
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 the effectiveness of the absorbed dose on a common scale for all ionizing radiation.

Table 6-2. Scientific Units

Prefix (symbol)	Power of 10	Decimal Equivalent
atto	10^{-18}	0.000000000000000001
femto (f)	10^{-15}	0.000000000000001
pico (p)	10^{-12}	0.000000000001
nano (n)	10^{-9}	0.000000001
micro (μ)	10^{-6}	0.000001
milli (m)	10^{-3}	0.001
centi (c)	10^{-2}	0.01
deci (d)	10^{-1}	0.1
kilo (k)	10^{3}	1,000
mega (M)	10^{6}	1,000,000
giga (G)	10^{9}	1,000,000,000
tera (T)	10^{12}	1,000,000,000,000
peta (P)	10^{15}	1,000,000,000,000,000
exa (E)	10^{18}	1,000,000,000,000,000,000

11-year cycles. Cosmic rays bombard the periphery of the earth's atmosphere at a rate of $2x10^{18}$ particles per second, at a density of about 4 rays/cm^2-sec, and at an energy flux of 2,000 MeV/cm^2•sec. These rays, referred to as "primary cosmic rays," are deflected and slowed by particles in the earth's atmosphere, creating "secondary cosmic rays" that often reach and even penetrate the earth's surface. The interaction of cosmic rays with the atmosphere leads to the production of several cosmogenic radionuclides, notably carbon-14 (^{14}C), tritium (^{3}H) and beryllium-7 (^{7}Be). Because of the shielding effect of the atmosphere and the earth's geomagnetic fields, which tend to deflect charged cosmic ray particles towards the magnetic poles, the cosmic ray dose rate increases with altitude and latitude. The average annual dose from cosmic radiation in the United States is 29 mrem (0.29 mSv), but this value doubles for every 6,000-foot (1,828 meters) increase in altitude. Thus, the dose from cosmic rays received in Denver, Colorado, and Leadville, Colorado (altitudes of 1,600 m and 3,200 m, respectively), is approximately two and four times that received at sea level, respectively (Eisenbud 1987; Korff 1964; NASA 1995; Shapiro 1990; UNSCEAR 1993). At altitudes of 30,000 to 40,000 feet (9144 to 12192 meters), where most jet aircraft fly, the cosmic ray dose rate is about 1 mrem per hour (0.01 mSv/hr).

6.3 TERRESTRIAL RADIATION EXPOSURE

Cosmic radiation contributes approximately the same amount of background radiation as terrestrial radiation (8%), which is emitted by naturally occurring radioactive materials found in the earth's crust, such as ^{40}K, uranium and its progeny, and thorium and its progeny (see Figure 6-1). Uranium, for example, is found in all types of soil and rock at concentrations ranging from 0.003 ppm in meteorites to 120 ppm in phosphate rock from Florida. Exposure to radioactive materials in the soil and earthen products occurs continuously since we are surrounded by these sources. The radiation dose varies tremendously and is affected by such factors as geographic location, concentration of natural radioactive materials in the soil and building materials, and the types of materials used in building structures.

Some communities situated on soil with high concentrations of granite or mineral sand receive doses many times the average. Examples include coastal areas in Espiritos Santos and Rio de Janeiro in Brazil; Kerala, on the southwest coast of India; and the Guangdong province in China. In Brazil, the black sand beaches are composed of monazite, a rare earth mineral containing 9% radioactive thorium. External radiation dose rates from these sands may be as high as 5 mrem/hr (0.05 mSv/hr); permanent residents experience an average annual dose equivalent of approximately 500 mrem (5 mSv). In Kerala, on the

west coast of India, residents receive 1,300–1,500 mrem (13–15 mSv) annually, due to the presence of monazite sand. Some dose rates are as high as 3,000 mrem/yr (Eisenbud and Gesell 1997).

Apart from radiation exposures due to living in close proximity to the earth's crust, people are also exposed to additional radiation when earth crust products (oil, coal, coal ash, minerals) are extracted, refined, and used. The naturally occurring radioactive materials in these products are concentrated into what is called technologically enhanced naturally-occurring radioactive materials (TENORM). In general, the hazards of exposure to TENORM during the extraction and processing of earth materials are relatively small compared to the hazards of exposure to other chemicals. As a result, radiation exposure from these sources, with the exception of uranium mining, milling, and processing, is not routinely monitored (Eisenbud 1987; UNSCEAR 1993). The radiation hazards associated with the mining of coal, oil, natural gas, phosphate rock products, and sand are discussed below.

Radon exposure makes up the largest fraction of total radiation dose and contributes to both internal and external radiation exposures. The following subsections discuss various radioactive materials primarily associated with external radiation exposures from various terrestrial activities. Radon is inherent in these terrestrial sources, as well, and is discussed because of its association, but with the understanding that it is a major internal radiation exposure source.

6.3.1 Coal Production

Exposure to radionuclides occurs during the mining and use of coal and coal ash. The methods of coal usage vary considerably among countries; on average worldwide, about 40% of coal is burned in electric power stations, 10% in dwellings, and 50% in other industries. Based on samples from 15 countries, the average concentrations of ^{40}K, ^{238}U, and ^{232}Th in coal are 50, 20, and 20 Bq/kg (1.35, 0.54, and 0.54 nCi/kg), respectively. These concentrations may vary considerably, depending upon the mine location. For example, concentrations of these radionuclides in China are 104, 36, and 30 Bq/kg (2.81, 0.97, and 0.81 nCi/kg), respectively. Coal mine exhaust typically contains radon; the estimated annual per person dose from radon in coal mine dust is 0.1–2 nSv. The average annual per person doses of radiation from coal-fired power plants and from domestic cooking with coal are about 0.2 mrem (2 μSv) and 0.04–0.8 mrem (0.4–8 μSv), respectively.

About 280 million tons of coal ash are produced by power plants each year. Potential uses for the ash include fertilizers and building materials for roads and dwellings. Most U.S. power plants recover fly ash exhaust using scrubbers, electrostatic precipitators, or bag houses. The radioactive content of coal tends to concentrate in the ash, resulting in 5- to 10-fold increases in the concentration of lead-210 (^{210}Pb) and polonium-210 (^{210}Po) as compared to unburned coal. When fly ash is used in building materials, the degree of external exposure to radiation and the inhalation of radon gas increases directly with the amount of ash incorporated into these materials, and, for radon, the porosity of the materials. The average annual exposure associated with living in concrete and wooden houses is 7 mrem (70 μSv) and 3 mrem (30 μSv), respectively. An EPA report published in 1979 estimated that the exposure to radioactive materials emitted from all 250 coal-fired power plants resulted in an additional 1.5 cancers per year (Eisenbud 1987; EPA 1979 as cited by Eisenbud; UNSCEAR 1982, 1988).

6.3.2 Crude Oil and Natural Gas Production

About $3x10^{12}$ kg of crude oil and 10^{12} m^3 of natural gas are produced worldwide annually. Oil-fired power plants use about 15% of all oil. Gas-fired power plants are estimated to use about 15% of all gas. Radon is present in natural gas; concentrations of radon in gas at well heads average approximately 40 pCi/L (1.5 Bq/L). The processing and blending of liquefied petroleum gas (LPG) tends to enhance radon concentrations, and the long-lived radon daughters (^{210}Pb and ^{210}Po) tend to accumulate on LPG processing machinery, resulting in low level exposure to maintenance workers. The annual per person doses from crude oil and gas are estimated to be 0.001 mrem (10 nSv) and 0.0001 mrem (1 nSv), respectively. The estimated doses are small and result from inhalation of radioactive particles and radon gas (Eisenbud 1987; UNSCEAR 1993).

6.3.3 Phosphate Rock Products

Phosphate rock, the precursor of all phosphorous products including fertilizer, is mined at a rate of 130 million tons per year worldwide. The worldwide use of fertilizer, estimated to be 30 million tons, constitutes the greatest source of ^{40}K and ^{226}Ra mobility. In the United States, the application rate for fertilizers ranges from 30 kg of phosphate per hectare (barley) to 150 kg/hectare (potatoes and tobacco) for commercial agricultural application, and possibly less for residential applications. Concentrations of ^{40}K and ^{232}Th in phosphate rock are similar to those in soil (a few grams per hundred grams of soil and a few grams per million grams of soil, respectively). Levels of ^{238}U and its transformation products are

much higher in phosphate rock than in soil. Concentrations of ^{238}U in phosphate deposits are typically about 1,500 Bq/kg (40.5 nCi/kg). The practice of using phosphate fertilizers has resulted in uranium concentrations in food at levels up to 8 ng/g (0.005 pCi/g). Exposure to the general public occurs near areas of mining and processing through waste effluent. Several end-products of phosphate processing, phosphogypsum and calcium silicate, are used for fertilizer, for back-fill and road-base material, in additives to concrete, in mine reclamation, and in the recovery of sulphur. Phosphogypsum is also used as a substitute for natural gypsum in the manufacture of cement, wallboard and plaster. The primary radioactive material in phosphogypsum is ^{226}Ra, which is found at concentrations of 900 Bq/kg (24.3 nCi/kg).

Exposure to phosphate-borne radioactivity also occurs as a result of discharges into surface waters. The primary pathway of exposure to radioactivity in humans is through the consumption of fish and shellfish. Elevated concentrations of radon have been detected in structures built over reclaimed phosphate mines, and over unmined mineral deposits. Maximum annual individual doses near phosphate facilities range from 4 mrem (40 μSv) in the Netherlands to 600 mrem (6 mSv) in the United States. The average annual per person dose of ^{40}K derived from fertilizers is approximately 0.2 mrem (2 μSv); while the average per person dose from potassium in the body is about 20 mrem (0.2 mSv) per year, maximum annual individual doses, from consumption of seafood, have been estimated at 15 mrem (150 μSv), with ^{210}Po as the main contributor. The annual per person radiation dose from ^{226}Ra-laden phosphogypsum in building materials is estimated to be about 1 mrem (0.01 mSv) (Eisenbud 1987; Shapiro 1990; UNSCEAR 1982, 1988, 1993). The use and disposal of phosphogypsum is regulated by the EPA, and these regulations are intended to ensure that the public is not exposed to unsafe levels of radionuclides from this material.

6.3.4 Sand

Mineral sands, defined as sands with a specific gravity of more than 2.9, originate from eroded rock. These sands are mined in Australia, Bangladesh, Indonesia, Malaysia, Thailand, and Vietnam. The heavy mineral is extracted from the sand and is processed into, among other items, paint pigment, titanium metals, catalysts, and structural materials. The sand itself is used as abrasive material for sandblasting. The principal radioactive components are ^{232}Th and ^{238}U. Exposure is mainly external through minerals spilled at the processing plants. Although information on exposures is scant, annual levels are estimated to be in the low μSv range (UNSCEAR 1993).

6.3.5 Hot Springs and Caves

Geothermal energy, produced in Iceland, Italy, Japan, New Zealand, Russia, and the United States, is produced from steam or water from high-temperature areas within the earth's crust. Mineral springs and spas, which are found in South America, Europe, Japan, and the United States, are also clustered around these high-temperature areas of the earth's crust. The primary radionuclides in this source are those of the uranium transformation chain. Of these, ^{226}Ra and ^{222}Rn are considered to be the most important to public health.

The diffusion of radon from ordinary rock and soils and from radon-rich water can cause notably elevated radon concentrations in tunnels, caves, and spas. In Bad Gastein, Austria, approximately 5 million gallons of mineral water are distributed to hotels and spas daily, allowing the release of about 58 Ci (2 Mbq) of radon per year into the environment. In comparison with levels in outdoor air, the concentrations of radon and its transformation products in confined air spaces such as mines and caves are elevated. The average annual per person radiation dose from this source is estimated to be 0.0001 mrem (1 nSv); however, the doses received by those intentionally spending time in these environs (e.g., tourists, workers, miners) are much greater than this amount (Eisenbud 1987; IARC 1988; UNSCEAR 1993).

6.4 NATURAL INTERNAL EXPOSURE

Natural internal radionuclides contribute an estimated 11% to the average population radiation dose. Radioactive materials enter the body by inhalation, ingestion, or dermal absorption. Although radioactive materials may also enter the body through punctures (either wounds or injections), this route of exposure will not be addressed in this toxicological profile.

The effects induced by internally deposited nuclides or external radiation are classified as either "acute" (early-occurring effects of radiation, which appear within days or weeks after exposure) or "latent" (chronic or late-occurring effects of radiation, which appear months or years after exposure). Acute effects are not expected for natural sources of radiation because they are not capable of producing high dose rates in a short period of time. However, they may cause latent effects. The most common latent radiation effect is an increased probability of certain types of cancer. More information on the health effects of ionizing radiation can be found in Chapter 3 of this toxicological profile.

6.4.1 Inhalation

The sources of inhaled radioactive materials include debris from atmospheric nuclear testing; nuclear reactor and medical gaseous waste; radioactive materials manufacturing; diagnostic medical radionuclide use; coal- and gas-burning power plants; airborne soil; and naturally emanating gases. The radionuclides (and their average concentrations) commonly found in the atmosphere include: ^{222}Rn and ^{220}Rn (270 pCi/m^3 [10 MBq/m^3] each); ^{210}Pb (0.01 pCi/m^3); ^{210}Po (0.001 pCi/m^3); ^{238}U (12×10^{-5} pCi/m^3); ^{232}Th (3×10^{-5} pCi/m^3); ^{230}Th; (4.5×10^{-5} pCi/m^3); and ^{228}Th (3×10^{-5} pCi/m^3), ^{14}C and ^{3}H. In addition, smokers are exposed to radiation from the radionuclide ^{210}Po, which is found in tobacco; the resulting dose to the bronchial epithelium can be as high as 20 mrem (0.2 mSv) per year (NCRP 1984; Shapiro 1990; UNSCEAR 1993).

The largest dose of radiation from natural sources comes from the inhalation of ^{222}Rn and ^{220}Rn (thoron) gases. These colorless and odorless gases, which are in the uranium and thorium transformation chains, respectively, are continuously released from the soil. Worldwide, the total emanation rate of radon is estimated to be 50 Ci/sec (2 TBq/sec); the total atmospheric content is estimated to be 25 MCi (1 EBq). The main factors controlling the rate of radon release and subsequent exposure are: ground porosity, ground cover, temperature, meteorological conditions, and the type of construction and ventilation properties of dwellings. The rate of radon emanation from soil is thought to increase with diminished atmospheric pressure and to decrease during periods of, or in areas of, elevated moisture, while the atmospheric concentration of radon tends to increase during temperature inversions and as the humidity decreases.

The health hazards of radon exposure were first recognized in the 1930s when radium miners in Scheenburg, Germany, and Joachimstal, Czechoslovakia, were found to have a high incidence of lung cancer. Over half of all miner deaths were attributed to lung cancer, and most of the miners were less than 50 years of age when they died. In the general U.S. population, the EPA estimated that radon exposure accounts for approximately 10% (17,000) of all lung cancers, while smoking accounts for approximately 85% (144,500) of all lung cancers. The average annual effective dose equivalent from radon is about 200 mrem (2 mSv), but individual doses may be much higher. It is estimated that 1–3% of all homes have radon levels in excess of 8 pCi/L, which is twice the EPA recommended residential limit of 4 pCi/L. Approximately 50,000 to 100,000 homes in the U.S. have radon concentrations exceeding 20 pCi/L, which results in exposures equal to or exceeding the limit for occupational exposure. The ^{220}Rn doses are considerably lower than those of ^{222}Rn, due to its short half-life (55 sec for ^{220}Rn versus 3.8 days for

^{222}Rn). Both ^{220}Rn and ^{222}Rn have several short-lived progeny in their transformation chains (see Table 6-3), and radiation from these daughter products constitutes the hazard from radon. Thus, in assessing the effects associated with radon exposure, one must consider the simultaneous and cumulative effect of the entire radon series (BEIR V 1990; Eisenbud 1987; LBL 1993; NCI 1996; Shapiro 1990; UNSCEAR 1993).

Table 6-3. Radioactive Properties of ^{222}Radon and its Daughter Products

		Radiation energies (MeV)		
Radionuclide	Half-life	α	β	γ
^{222}Radon	3.8 days	5.49	—	—
^{218}Polonium	3.1 minutes	6.00	—	—
^{214}Lead	26.8 minutes	—	0.67 0.73	0.30 0.35
^{214}Bismuth	19.9 minutes	—	1.51 1.54 3.27	0.61 1.12 1.76
^{214}Polonium	164 μseconds	7.60	—	0.8
^{210}Lead	22.3 years	—	0.016 0.06	0.05
^{210}Bismuth	5 days	—	1.16	—
^{210}Polonium	138 days	5.31	—	—
^{206}Lead	No half-life; stable element			

Source: adapted from Schleien 1992 (includes radiations over 10% intensity)

Coal mine exhaust and the combustion products from the use of coal and oil typically contain radon and daughter products, which contribute doses of 0.001 mrem (10 nSv) or less. The average annual per person doses from radiation from coal- and oil-fired power plants are about 0.2 mrem (2 μSv) and 0.001 mrem (10 nSv), respectively. The average annual per person dose from radiation from domestic cooking and heating with coal is about 0.04–0.8 mrem (0.4–8 μSv); this dose originates primarily from radon and its daughter products (UNSCEAR 1993).

Several radioactive by-products of the nuclear power industry may be inhaled and result in internal exposure. During uranium fuel fabrication, uranium hexafluoride gas is enriched to increase the percentage of ^{235}U and then converted into uranium oxide or metal. Depending upon the type of reactor

fuel or nuclear weapons material being produced, uranium must be enriched to a minimum of 3% ^{235}U for fuel and 93.5% for nuclear weapons. Emissions from fabrication facilities usually consist of the long-lived isotopes ^{234}U, ^{235}U, and ^{238}U, and the short-lived isotopes ^{234}Th, and protactinium-234m (^{234m}Pa). The major route of exposure from this source is inhalation. More information about uranium is available in the ATSDR *Toxicological Profile for Uranium* (ATSDR 1999).

6.4.2 Ingestion

The sources of radionuclides that contribute to radiation exposure by ingestion include nuclear weapons testing, the accidental or intentional release of radioactivity from nuclear reactors, the release of medical or experimental radionuclides into sanitary sewers, and naturally occurring radionuclides (which normally represent the source of highest oral dose). For most radionuclides present at waste sites containing low levels of radioactive nuclides, oral exposure is not a major route of exposure. There is a small probability of radionuclide ingestion because of the potential for surface water and groundwater contamination and uptake by plants and animals following erosion of ground cover from a contaminated site.

Among the naturally occurring radionuclides, uranium, ^{40}K, and ^{226}Ra are found in soils and fertilizers; as a result, they are incorporated into foods consumed by animals and humans. The practice of using phosphate fertilizers has resulted in uranium concentrations in food at levels up to 8 ng/g, resulting in an estimated average annual intake of uranium from dietary sources of 10 Bq; as a result, the average skeletal content of uranium is estimated to be 25 μg, which is equivalent to approximately 17 pCi (Eisenbud 1987; UNSCEAR 1993).

The most important radionuclides that are ingested are ^{40}K, ^{226}Ra, and the transformation products of ^{226}Ra. However, wherever it is found, all potassium is radioactive because its natural isotope, ^{40}K, is radioactive. The body content of potassium is under strict homeostatic control and is maintained at a relatively constant level of about 140 g/70 kg. This amount of potassium contains approximately 0.1 μCi (4,000 Bq) of ^{40}K. Because the body controls the potassium balance, environmental variations have little effect on the ^{40}K content in the body (Eisenbud 1987; Shapiro 1990). This natural ^{40}K delivers a dose of 20 mrem/year (0.2 mSv/year) to the gonads and other soft tissues and 15 mrem/year (0.15 mSv/year) to bone.

FDA has developed guidelines for radionuclide levels in food for individuals from 3 months to adult that are summarized in Chapter 7 (Regulations), Table 7-4, FDA Derived Intervention Levels (FDA 1998).

6.4.3 Dermal

For the purposes of this profile, dermal exposure to radionuclides refers to exposures from a radionuclide placed in direct contact with skin surface. Dermal exposure is typically a minor route of internal and external exposure. In general, depending on the specific physical properties of the radionuclide that may reside on the skin, the percutaneous absorption of radionuclides from particles is negligible, especially if the skin is thoroughly washed immediately after exposure. The long-term biological effects of dermally absorbed radionuclides are limited to the level of the epidermis and dermis (and its vasculature). More soluble forms of the radionuclides may result in a small percentage of the nuclide being absorbed if it is not removed from the skin's surface, for example tritium, as tritiated water or vapor, is readily absorbed into the body through the skin. Generally, the skin is an effective barrier against absorption of radionuclides (except for tritiated water) into the body. The dermal exposure pathway is, therefore, a minor route of exposure at low-level radioactive waste sites.

6.5 X RAY AND NUCLEAR MEDICINE EXPOSURES

Radioactive materials and other sources of ionizing radiation are widely used in the diagnosis and treatment of some diseases in human and veterinary medicine (NCRP 1989a; 1996). They represent 15% of the average population dose, 11% for x rays and 4% for nuclear medicine. In 1989, the estimated number of x ray machines used in the US was 109,000 for medical diagnosis, 143,000 for dental diagnosis, and 1,300 for therapy: 3 million diagnostic examinations were made which produced a collective US dose of 92,000 man•Sv (9,200,000 man-rem). Typical effective dose equivalents for various procedures are 0.14 mSv (14 mrem) for a chest x ray, 1.0 mSv (100 mrem) for mammography, and 7.2 mSv (720 mrem) for an upper GI tract evaluation. Due to the usefulness of nuclear medicine, radioactive drugs and diagnostic compounds have become significant contributors to internal radiation dose from man-made sources today. The average U.S. nuclear medicine examination gives an effective dose equivalent of 5 mSv (500 mrem) with individual prodedured delivering 2.5 mSv (250 mrem) for a thyroid uptake, 6.3 mSv (630 mrem) for a bone scan, and 14 mSv (1,400 mrem) for a cardiovascular screen. Each year in the US, the collective effective dose from nuclear medicine procedures is 32,000 man•Sv (3,200,000 man-rem). Therapeutic doses are much larger to the individual but many fewer individuals are exposed. After many millions of diagnostic radionuclide procedures, we have found no increase in cancers from these procedures.

The common sources of radiation exposure associated with radiotherapy and diagnosis include x rays, thallium-201 (^{201}Tl), technetium-99m (^{99m}Tc), ^{125}I, and ^{131}I. More exposures are related to diagnosis than to therapy, and the average number of treatments per person increases as the level of health care improves. Also, the average dose per individual treatment tends to decrease as techniques and equipment improve. Overall, x ray treatments deliver a higher average per person dose in industrialized nations (average of 0.3–2.2 mSv) than in countries with less developed health care (average exposure 0.02–0.2 mSv). On an individual basis, the average dose increases with age, from 52 mrem/year in adolescents to 151 mrem/year in persons over 65 years of age. Exposures are usually lower for examinations of the extremities and skull and higher for examination of the gastrointestinal (GI) tract. In the United States, the average annual dose to the bone marrow from this source increased from 83 mrem in 1964 to 103 mrem in 1970. A person receiving a full set of dental x rays would add approximately 40 mrem to his or her annual dose. On the other hand, the average annual dose per patient from the diagnostic use of radionuclides is lower in industrialized nations, largely because of greater use of ^{99m}Tc. This radionuclide is preferred over ^{131}I because its shorter half-life (6 hours versus 8 days) gives a much lower patient dose. There is currently no radioiodine in the atmosphere due to atmospheric testing because of the 8-day half-life of ^{131}I. The shorter half-life and higher cost of ^{99m}Tc make it more available in developed than in developing nations, where ^{131}I has frequent use. While the average dose (per individual) in patients undergoing radiotherapy is much greater than in patients undergoing diagnosis, the exposure group is much smaller, resulting in a lower overall population-at-risk. Unfortunately, serious exposures resulting from failures of equipment, procedures, or personnel errors (usually a result of not following procedures) sometimes occur, with several hundred failures out of several hundred million procedures per year worldwide.

There are several emerging trends in diagnostic nuclear medicine. Some of these trends include: the introduction of radiolabeled monoclonal antibodies for imaging and treatment; the emergence of new compounds used in positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies; and the use of computed x ray tomography (CAT scans). Radiolabeled monoclonal antibodies have proven useful in the localization of tumors and metastases. Common radionuclides associated with these antibodies include indium-111 (^{111}In), ^{131}I, and ^{99m}Tc. SPECT is used for tumor localization, brain and cardiac studies, and bone or abdominal imaging. PET, which uses nuclides such as ^{11}C and ^{18}F, can gather anatomical and physiological information that would otherwise be difficult to collect. Whole-body imaging using radiolabeled compounds (e.g., anticancer drugs) is becoming a common PET application (DOE 1996; Eisenbud 1987; Shapiro 1990; UNSCEAR 1993).

The use of radiopharmaceuticals has stabilized in industrialized countries but is increasing in developing countries. Long-lived radionuclides are used more frequently in developing countries, while industrialized countries tend to use short-lived radionuclides. This results in increased exposures per examination among developing country patients compared to those of industrialized nations. For example, a typical thyroid scintigraphy with ^{99m}Tc can give an effective dose of less than 0.1 rem (1 mSv), while the same procedure using ^{131}I gives 10 rem (100 mSv); however, ^{99m}Tc is less readily available in developing countries. Although the average per patient dose equivalent is lower in developed (2–5 mSv [200-500 mrem]) than in less developed countries (20 mSv [2,000 mrem]), an apparently larger fraction of individuals in developed nations receive nuclear medicine treatment, so the average per capita annual dose from radiopharmaceuticals in developed countries (0.07 mSv [7 mrem]) is an order of magnitude more than that of developing nations (0.004 mSv [4mrem]) (UNSCEAR 1993).

Radionuclides are frequently produced and used in industry, medicine, and research. The number of users and frequency of radionuclide use are both steadily increasing. The number of establishments in Japan that generate and/or use radionuclides has increased from 100 in 1960 to 5,000 in 1990. The public may be exposed to radionuclides from these sources as a result of routine use or from being near someone who has recently received a nuclear medicine procedure, as well as improper handling, use, or disposal. In Japan, the usage of ^{14}C, ^{125}I, ^{3}H, and ^{131}I has been estimated to be 5.2, 6.1, 14, and 34 GBq (0.14, 0.16, 0.38, and 0.92 Ci) per million persons, respectively. In contrast, the production of ^{14}C in the United States and Britain has been estimated to be 30 and 55 GBq (0.81 and 1.49 Ci) per million, respectively. The annual global production and usage of ^{14}C has been estimated to be 30 GBq (810 mCi) per million persons, or a total of 0.05 PBq (1.5 kCi). The total amount of ^{131}I produced in Sweden for medical purposes was estimated to be 0.9 TBq (110 GBq [2.97 Ci] per million) in 1986, while the amount of ^{131}I discharged from Australian hospitals in 1988 and 1989 was estimated to be 2.9 TBq (190 GBq [5.13 Ci] per million) (UNSCEAR 1993). Information about some radionuclides used for medical applications is shown in Table 6-4.

^{3}H and noble gases are released to the air, while ^{14}C release is through airborne and fluid effluents. The isotopes ^{131}I and ^{125}I are primarily released through liquid effluent. The annual collective dose from medical and radiopharmaceutical wastes to local populations is thought to be in the range of 10,000 man•rem (100 man•Sv). This level of exposure is relatively unimportant compared to that from other sources (Eisenbud 1987; UNSCEAR 1993).

Table 6-4. Some Radiopharmaceuticals Used in Medicine

Radionuclide	Preparation	Use	Properties
^{99m}Tc Albumin	Reduce pertechnetate ^{99m}Tc in the presence of human albumin, ascorbic acid, $FeCl_2$, and $SnCl_2$.	Primarily used for lung imaging. Also used for imaging of coronary, urogenital, liver, gastrointestinal, lymphatic, and peripheral circulation.	The biological clearance half-life from the lungs of 14 to 15 hours.
^{111}In Albumin	Incubate ^{111}In with human albumin in phosphate at pH 3; adjust pH to 11 and heat.	Primarily used for lung imaging. Also used for imaging of coronary, urogenital, liver, gastrointestinal, lymphatic, and peripheral circulation.	The biological clearance half-life from the lungs of 14 to 15 hours.
^{113m}In Albumin	Incubate ^{113m}In with human albumin in phosphate at pH 3; adjust pH to 11 and heat.	Primarily used for lung imaging. Also used for imaging of coronary, urogenital, liver, gastrointestinal, lymphatic, and peripheral circulation.	The biological clearance half-life from the lungs of 14 to 15 hours.
^{203}Pb Albumin	Incubate ionic ^{203}Pb with human albumin at pH 10 with heat.	Primarily used for lung imaging. Also used for imaging of coronary, urogenital, liver, gastrointestinal, lymphatic, and peripheral circulation.	The biological clearance half-life from the lungs of 14 to 15 hours.
^{51}Cr Albumin	Incubate $^{51}CrCl_3$ with human albumin	Detection and quantitation of gastrointestinal protein loss and placental localization	Cr (III) has strong affinity for plasma proteins without affecting (binding to) red blood cells.
^{125}I Albumin	Mild iodination of human albumin at 10 EC in slightly alkaline medium	Diagnostic aid in determining total blood and plasma volumes	Longer shelf life than ^{131}I; emits no beta radiation (all gamma emissions); lower doses needed to obtain greater resolution compared to ^{131}I
^{131}I Albumin	Mild iodination of human albumin at 10 EC in slightly alkaline medium	Diagnostic aid in determining total blood and plasma volumes, circulation times, or cardiac output.	May cause sensitization.
^{131}I Albumin, aggregated	Mild iodination of human albumin at 10 EC in slightly alkaline medium	Diagnostic study of the lungs, especially the diagnosis of pulmonary embolisms.	Aggregates block a small percentage (<0.5%) of the fine capillaries. Disintegrating aggregates are cleared by phagocytic Kupffer cells in the liver. Thyroid uptake may be blocked by prior administration of Lugol's solution.
^{197}Hg Chlormerodrin	Reflux allylurea with ^{197}Hg mercuric acetate in methanol; add aqueous sodium chloride	Diagnostic aid in scanning the brain for lesions. Also used for scanning kidneys for anatomical and functional abnormalities.	Rapidly cleared by the kidneys. Provides smaller radiation dose compared to ^{131}I albumin. A high tumor:background ratio is obtained within 4 hours, allowing quicker scans with greater resolution.

Table 6-4. Some Radiopharmaceuticals Used in Medicine (continued)

Radionuclide	Preparation	Use	Properties
^{203}Hg Chlormerodrin	Reflux allylurea with ^{203}Hg mercuric acetate in methanol; add aqueous sodium chloride	Diagnostic aid in scanning the brain for lesions. Also used for scanning kidneys for anatomical and functional abnormalities.	Rapidly cleared by the kidneys. Provides smaller radiation dose compared to ^{131}I albumin. A high tumor:background ratio is obtained within 4 hours, allowing quicker scans with greater resolution.
^{32}P Chromic phosphate	React $Na_2H^{32}PO_4$ with chromic nitrate in a saline-carboxymethylcellulose vehicle.	A neoplastic suppressant that provides palliative treatment of pleural and peritoneal effusions.	Emits virtually no gamma radiation; delivers 10-fold greater radiation dose per millicurie compared to ^{198}Au. Because it remains *in situ* after injection, it may be injected directly into a malignancy.
^{60}Co	Neutron bombardment of ^{59}Co	Replaced radium in various therapeutic areas.	The gamma radiation matches that of radium very closely.
^{192}Ir	Neutron bombardment of ^{191}Ir	Replaced radium in various therapeutic areas. May be enclosed in nylon mesh for interstitial use.	Provides softer (i.e., less penetrating) radiation compared to radium.
^{57}Co Cyanocobalamin	Vitamin B_{12} in which a portion of the molecule contains ^{57}Co.	Diagnostic aid in studying the absorption and deposition of vitamin B_{12}, especially the diagnosis of pernicious anemia.	
^{60}Co Cyanocobalamin	Vitamin B_{12} in which a portion of the molecule contains ^{60}Co.	Diagnostic aid in studying the absorption and deposition of vitamin B_{12}, especially the diagnosis of pernicious anemia.	Although the half-life is 5.24 years, ^{60}Co cyanocobalamin may decompose in storage; thus, frequent radiochemical analysis may be required.
Exametazime	^{99m}TcO is incorporated into the exametazine molecule.	An adjunct in detecting regional cerebral perfusion in stroke; leukocyte labeling.	Is rapidly cleared from the blood. Maximum brain uptake (3.5-7.0%) is reached within 1 minute of injection. Must be used within 30 minutes of reconstitution due to conversion of lipophilic complex to second lipophilic complex that will not cross the blood-brain barrier.
^{113}In Ferric hydroxide	^{113}In is stirred with FeCl3 while titrated with 0.5 N NaOH to a pH of 11 to 12. While stirring, a 20% gelatin is added to attain a pH of 7.6 to 8.5 while heating in a boiling waterbath; preparation is then autoclaved.	A diagnostic aid in lung imaging.	Particles are in the 20 to 50 μm range.

Table 6-4. Some Radiopharmaceuticals Used in Medicine (continued)

Radionuclide	Preparation	Use	Properties
^{59}Fe Ferrous Citrate	^{59}Fe complexed with citrate; neutron bombardment of ^{58}Fe.	A diagnostic aid in studying the kinetics of iron metabolism.	It may be administered directly into the bloodstream where it reacts with the metal-binding globulin.
^{99m}Tc Ferrous hydroxide	Add ^{99m}Tc to a vial containing ferrous sulfate; the hydroxide is precipitated with 0.1N NaOH at a pH of 7.5 to 10.7. Gelatin is added to stabilize the particles; final pH should be 7.1 to 8.3.	A diagnostic aid in pulmonary scintigraphy.	Most of the particles are in the 11 to 13 μm range; virtually all particles fall in the 3 to 50 μm range;.
^{125}I Fibrinogen	^{125}I in the form of I_2, ICl or I^- is combined with fibrinogen and is oxidized by chloramine-T, electrolytically or enzymatically. Unreacted iodine is removed by the addition of sodium thiosulfate.	A diagnostic aid in the localization of deep vein thrombosis. Other applications include detection of renal transplant rejection, tumors, and the study of fibrinogen turnover.	Accumulates in clots, the radiation is easily detected at the external surface of the affected limb.
^{67}Ga Gallium citrate	^{67}Ga is produced by proton irradiation of ^{67}Zn-enriched ZnO_2	Used in the diagnosis of lesions of the lung, breast, maxillary sinuses and liver. A positive ^{67}Ga uptake is potentially indicative of malignancies such as lymphomas, bronchogenic carcinoma, and Hodgkin's disease. Also useful for placental localization and diagnosis of pancreatitis and disk disc-space infection.	Concentrates in tumors of soft tissues and bone. The half-life of the isotope is 78 hours; the biological half-life of the citrate compound is 53 days.
^{111}In Indium chlorides	A cadmium target is bombarded with deuterons. The ^{111}In is then etched from the target with HCl, carrier Fe^{3+} is added, and the mixture is precipitated with NH_4OH. The precipitate is dissolved in HCl and the ferric iron is removed by extraction with isopropyl ether.	^{111}In has been used as a tag for a variety of compounds such as transferrin, EDTA and DTPA (used in cisternography), bleoycin (used for tumor localization), platelets (detection of coronary thrombi), lymphocytes (monitoring cardiac antirejection therapy), and leukocytes (diagnosis of upper-abdominal infections).	Indium normally exists in aqueous solution as a trivalent cation. In aqueous solution InCl exists as a mixture of hydrated chlorides.
^{111}In Oxyquinoline		Used to label various blood components such as neutrophils, platelets and lymphocytes; cardiac imaging (labeled platelets); localization of infectious and inflammatory processes (labeled leukocytes).	

Table 6-4. Some Radiopharmaceuticals Used in Medicine (continued)

Radionuclide	Preparation	Use	Properties
^{113m}In Indium Chloride	^{113m}In is formed by the radioactive transformation of ^{113}Sn. ^{113m}In is separated from ^{113}Sn using sterile, pyrogen-free dilute HCl.	Used in blood-pool studies, including visualization of aneurysms, and placental scintigraphy; also used for bone, liver, lung, brain, and renal imaging.	Indium normally exists in aqueous solution as a trivalent cation. In aqueous solution InCl exists as a mixture of hydrated chlorides. Urinary excretion is low, resulting in low urinary bladder activity.
^{113m}In Indium hydroxide	^{113m}In Indium chloride is adjusted to a pH of 4 or more, whereupon the indium is converted to the insoluble hydroxide. The particle size and stability are controlled by heating and the addition of a stabilizer (gelatin, mannitol, etc.).	Used in liver, spleen and bone marrow scintigraphy.	
^{125}I or ^{131}I Insulin	Prepared by mild iodination with high-specific-activity radioactive iodine followed by purification via dialysis, ion-exchange or other process.	Used for *in vitro* assay of circulating insulin; study of *in vivo* insulin kinetics	Longer shelf life than ^{131}I; emits no beta radiation (all gamma emissions); lower doses needed for correct resolution compared to ^{131}I
^{123}I or ^{131}I Na Iodohippurate	Iodobenzyl chloride is condensed with glycine with the aid of a dehydrochlorinating agent. The resulting *o*-iodohippuric acid is reacted with NaOH.	Used in the detection of renal malfunction.	Excreted almost exclusively by the kidneys.
^{81m}Kr gas	A transformation product of ^{81}Rb, which is produced by alpha bombardment of ^{79}Br.	Used for lung function, ventilation, and perfusion. Also used in radiocardiology.	
^{123I} Iofetamine Hydrochloride		Used in assessing regional cerebral blood flow.	Crosses the intact blood-brain barrier. Concentrates in metabolically active brain cells. Binding by relatively nonspecific high-capacity binding sites results in brain retention.
^{125}I or ^{131}I Liothyronine	Synthetic liothyronine is exchanged with ^{131}I. The mixture is then purified by column or strip paper chromatography.	Used for *in vitro* evaluation of thyroid function.	^{125} I binds to thyroxine-binding proteins. Due to the high specific activity, this compound may not be taken internally as radiation damage can occur easily. This may be prevented in part by the use of propylene glycol (50%) as a solvent. The materials should be refrigerated or frozen and should be used within 2 weeks.

Table 6-4. Some Radiopharmaceuticals Used in Medicine (continued)

Radionuclide	Preparation	Use	Properties
^{125}I or ^{131}I Levothyroxine	Obtained by synthesis, with the I-tag in the 3'-position.	Used to study the endogenous metabolism of endogenous thyroxine; to measure thyroxine-binding protein capacity.	Binds to thyroxine-binding proteins.
^{111}In Pentetate Indium Disodium	Cyclotron-produced indium chlorides mixed with pentetic acid at low pH (#3.5) to form an indium-DTPA chelate. A trisodium salt of the complex is formed by increasing the pH to 7.0–7.5.	Used as a diagnostic aid for studies of cardiac output, glomerular filtration evaluation; used for cisternography and renal scintigraphy.	Shelf-life is limited by the half-life of ^{111}In (67.5 hours).
^{113m}In Pentetate Indium Trisodium	Pentetic acid containing some ferric ion and HCl is mixed with ^{113m}In. The resulting chelate is stabilized by increasing the pH to 7.0–7.5, resulting in the formation of a trisodium salt.	Used as a diagnostic aid for studies of glomerular filtration; also used for brain scanning and kidney imaging, and cisternography of spinal fluid circulation.	
^{169}Yb Pentetate Ytterbium Trisodium	Buffered, lyophilized pentetic acid is mixed with ^{169}Yb.	Used as a diagnostic aid for brain scanning and kidney imaging, and cisternographic diagnosis of CSF rhinorrhea.	May be administered orally or intravenously.
^{42}K Potassium Chloride	By neutron bombardment of natural potassium.	Used for tumor localization and studies of renal blood flow measuring total exchangeable potassium.	Suitable for intravenous administration.
^{43}K Potassium Chloride	By alpha bombardment of a natural argon target.	Used as a diagnostic aid for heart imaging.	
^{131}I Rose Bengal Sodium	Prepared by thermal condensation of tetrachlorophthalic anhydride with 2,4-diiodoresorcinol. The resulting phthalein is reacted with NaOH, and the purified product is labeled by isotope exchange	A diagnostic aid for liver function; especially useful for differential diagnosis of hepatobiliary disease.	Accumulates in the polygonal cells of the liver and is excreted via the biliary system. If liver function is impaired, it is excreted via the kidneys.
^{75}Se Seleno-methionine	Extracted from yeast grown on sulfur-free medium to which trace amounts of radiolabeled sodium selenite have been added. Selenomethionine is separated from separated from the yeast proteins.	Used for scintigraphy of the pancreas and parathyroid glands; also used to visualize the parotid and prostate glands.	Incorporated into newly-formed proteins. Blood levels decline to a minimum value at 20 to 45 minutes after IV injection; blood levels then rise to about 3/4 that seen at 2 minutes postinjection.
^{22}Na Sodium Chloride	By deuteron bombardment of ^{24}Mg	Used for determination of circulation times, sodium space, and total exchangeable sodium.	The usual required tracer dose is well within tolerated levels. Emits positrons which are easily detected by coincidence counting.

Table 6-4. Some Radiopharmaceuticals Used in Medicine (continued)

Radionuclide	Preparation	Use	Properties
^{51}Cr Sodium Chromate	By neutron bombardment of enriched ^{50}Cr.	Used as a biological tracer to measure red-cell volume, red-cell survival time, and whole-blood volume. Also used to detect blood cell loss due to hemolytic anemia or GI bleeding.	Requires 15–60 minutes to diffuse into red cells; binds to globin molecules. Has no deleterious effect on erythrocytes.
^{18}F Sodium Fluoride	By neutron bombardment of enriched ^{6}Li in the form of lithium carbonate. Contamination with ^{3}H must be removed prior to use.	Useful for bone imaging, especially areas of altered osteogenic activity.	
^{123}I Sodium Iodide	By proton bombardment of enriched ^{124}Te or by deuteron bombardment of enriched ^{122}Te or by transformation of ^{123}Xe.	For diagnostic procedures in thyroid function studies; for organ imaging including the thyroid, liver, lung, and brain.	Short half-life (13.2 hours) and radiation characteristics result in a smaller radiation dose compared to other iodine isotopes.
^{125}I Sodium Iodide	By neutron bombardment of xenon gas.	For diagnostic procedures in thyroid function studies; for organ imaging including the thyroid, liver, and brain; treatment of deep-seated non-resectable tumors.	For organ imaging, dose to patient may be decreased with better delineation of organ and clearer resolution than ^{131}I.
^{131}I Sodium Iodide	By neutron bombardment of enriched ^{131}Te or as a byproduct of uranium fission.	For diagnostic procedures in thyroid function studies; a neoplastic suppressant.	
^{99m}Tc Sodium Pertechnetate	Produced by the elution of sodium pertechnetate through a generator containing ^{99}Mo which decays to ^{99m}Tc.	Used in the detection and localization of cranial lesions, thyroid and salivary gland imaging, placenta localization, and blood-pool imaging.	^{99m}Tc has an ideal half-life which is long enough for diagnostic procedures but is short enough to minimize radiation doses to the patient. Also, it lacks a beta radiation component. Pertechnetate is readily absorbed by the thyroid; this can be reduced by preinfusion of potassium perchlorate.
^{32}P Sodium Phosphate	By neutron bombardment of elemental sulfur in an atomic reactor. ^{32}P is then separated by leaching with NaOH.	A neoplastic and polycythemic suppressant; a diagnostic aid for the localization of certain ocular tumors.	
^{85}Sr Strontium	By neutron bombardment of a strontium salt enriched in ^{85}Sr.	A diagnostic aid for scanning bones and bony structures to detect and define lesions and to study bone growth and abnormal formations.	Has a long half-life (64 days), resulting in high bone doses.
^{99m}Tc Albumin	Albumin is tagged with a reduced form of the pertechnetate. The pertechnetate may be reduced by one of several methods.	Diagnostic aid in determining total blood and plasma volumes, circulation times, or cardiac output.	See earlier comment on ^{99m}Tc.

Table 6-4. Some Radiopharmaceuticals Used in Medicine (continued)

Radionuclide	Preparation	Use	Properties
^{99m}Tc Albumin, Aggregated	Denatured human albumin is tagged with a reduced form of the pertechnetate. The pertechnetate may be reduced by one of several methods.	Diagnostic aid in study of the lungs. Primary use is for diagnosing pulmonary embolism. Also useful for static blood-pool imaging, angiography, dynamic function tests and visualization of placental tissues.	See earlier comment on ^{99m}Tc. ^{99m}Tc is preferred over ^{131}I as the radioactive tag because of the smaller delivered dose.
^{99m}Tc Etidronate or ^{99m}Tc Oxidronate	Acetic acid is treated with PCl_3; the disodium salt is formed when a solution of etidronic acid is adjusted to a pH of 8.5. Stannous chloride and sometimes a stabilizer such as sodium ascorbate are added. Freshly eluted ^{99m}Tc is added.	Useful for bone imaging.	See earlier comment on ^{99m}Tc. This compound is superior to ^{18}F bone scans and to roentgen studies and is frequently more sensitive in detecting metastases to the bone.
^{99m}Tc Iminodiacetic Acid (IDA)	Usually provided in kit form, the compound is reconstituted and tagged by adding sterile ^{99m}Tc sodium pertechnetate.	Useful for hepatobiliary imaging.	See earlier comment on ^{99m}Tc.
^{99m}Tc Ferpentate	Usually in kit form, the compound is made by adding a solution of ^{99m}Tc sodium pertechnetate; the pH is adjusted with sodium hydroxide and a solution of pentetic acid is added. The chelate is formed by gentle mixing.	Useful for kidney imaging.	See earlier comment on ^{99m}Tc.
^{99m}Tc Pentetate	Prepared by adding sterile ^{99m}Tc pertechnetate saline solution to an aliquot of buffered stock solution of DTPA containing stannous chloride as a reducing agent. Instant DTPA ^{99m}Tc kits are available.	Useful for brain and kidney visualization, for vascular dynamic studies for measurement of glomerular filtration and for lung ventilation studies.	See earlier comment on ^{99m}Tc. Does not concentrate in any organ. DTPA is uniformly distributed throughout the extracellular space and is rapidly cleared by the kidneys without retention.
^{99m}Tc Pyrophosphate	Sodium pyrophosphate, mixed with stannous tin, are combined with a solution of ^{99m}Tc sodium pertechnetate. Kits are available commercially.	Used as a skeletal imaging agent; used to demonstrate areas of altered osteogenesis; also used as a cardiac imaging agent, as an adjunct in the diagnosis of myocardial infarction.	See earlier comment on ^{99m}Tc. The pyrophosphate compound has been found to concentrate in muscle tissue, especially contused muscle tissue. myocardium.
^{99m}Tc Sestamibi	Usually in kit form, the compound is reconstituted and tagged with sterile ^{99m}Tc sodium pertechnetate.	Used as a myocardial perfusion agent in the evaluation of ischemic heart disease and distinguishing and locating abnormal myocardium.	Accumulates in viable myocardial tissue.

Table 6-4. Some Radiopharmaceuticals Used in Medicine (continued)

Radionuclide	Preparation	Use	Properties
^{99m}Tc Succimer	Usually in kit form, the compound is reconstituted and tagged with sterile ^{99m}Tc sodium pertechnetate.	Used in renal cortical imaging.	Use within 30 minutes of formulation.
^{99m}Tc Sulfur Colloid	A colloidal suspension of sulfur labeled with ^{99m}Tc.	Used as a diagnostic aid for liver, spleen, and bone marrow scanning. Also used in detection of intrapulmonary and lower GI bleeding, as well as visualization of the lungs by inhalation of the colloid.	See earlier comment on ^{99m}Tc. Colloids are phagocytized by the liver. The plasma clearance is rapid (approximately 2.5 min). At least 80% of dose accumulates in the liver.
^{99m} Tc Tebroxime		Used for myocardial perfusion imaging for distinguishing normal versus abnormal myocardium.	Use within 6 hours of reconstitution.
^{99m}Tc Gluceptate	Freshly eluted ^{99m}Tc sodium pertechnetate is added to sodium glucoheptonate in combination with stannous chloride.	Useful as a renal imaging agent; possibly useful for localization of brain, lung, and gallbladder lesions.	See earlier comment on ^{99m}Tc. Optimal results are obtained 1–2 hours after administration.
^{99m}Tc Sodium Methylene Diphosphonate	Sodium methylene diphosphonate, available in kit form, is mixed reconstituted with ^{99m}Tc sodium pertechnetate.	Useful for skeletal imaging.	See earlier comment on ^{99m}Tc. When administered by IV, compound concentrates in areas of altered osteogenesis.
^{99m}Tc Mertiatide	Usually provided in kit form, the compound is reconstituted and tagged by adding sterile ^{99m} Tc mertiatide.	Useful as a renal imaging agent; provides information on renal function, split function, renal angiograms and renogram curves for whole kidney & renal cortex.	Is reversibly bound to serum protein and is excreted rapidly by kidneys and cleared by the blood.
^{99m}Tc Sodium Phosphates	Polyphosphate polymer, available in kit form mixed with stannous chloride, is mixed with ^{99m}Tc pertechnetate.	Useful for bone and renal imaging.	See earlier comment on ^{99m}Tc.
^{99m}Tc Sodium Phytate	Sodium phytate, available in kit form mixed with stannous chloride, is reconstituted with ^{99m}Tc pertechnetate.	Useful for liver and spleen imaging	See earlier comment on ^{99m}Tc. Cleared rapidly from the blood by the reticuloendothelial system. Over 80% of compound localizes in the liver and spleen within 30 minutes of an iv injection. The addition of ionic calcium to the ^{99m}Tc stannous phytate mixture enhances splenic uptake.
^{99m}Tc Tetracycline	Tetracycline, available in kit form, is reconstituted with stannous chloride and ^{99m}Tc pertechnetate.	For imaging kidneys and gall bladder; myocardial imaging is possible with larger doses.	See earlier comment on ^{99m}Tc. The compound localizes in the gall bladder.

Table 6-4. Some Radiopharmaceuticals Used in Medicine (continued)

Radionuclide	Preparation	Use	Properties
^{201}Tl Thallium Chloride	Thallium target material is bombarded with protons to produce ^{201}Pb. The unused thallium material is removed by ion exchange, and the remaining ^{201}Pb subsequently decays to ^{201}Tl.	Used for myocardial perfusion imaging for the localization of myocardial ischemia and infarction; used as an adjunct to angiography. Also useful for thyroid imaging, particularly the detection of goiter and thyroid carcinoma.	Thallium mimics potassium ions and is taken up by the cells of the heart; decreased cell vitality is indicated by decreased thallium uptake. Rapidly disappears from the blood.
^{15}O Water	Prepared by labeling with a cyclotron-generated radionuclide.	Used in blood-flow imaging using positron emission tomography scanning.	
^{127}Xe Xenon gas	Produced by proton bombardment of cesium-133 with ^{127}Xe.	As a gas, used for lung imaging to detect alveolar block-age; also used for mapping cerebral blood flow. Dissolved in saline used as a tracer for measurement of regional blood flow.	The biological half-life of the gas is approximately 15 minutes.
^{133}Xe Xenon	A product of nuclear fission; also formed by neutron activation of ^{132}Xe.	As a gas, used for lung imaging to detect alveolar blockage; also used for mapping cerebral blood flow. Dissolved in saline used as a tracer for measurement of regional blood flow.	The biological half-life of the gas is approximately 15 minutes.

Source: Remington 1985; Remington and Gennaro 1995

6.6 EXPOSURE FROM CONSUMER PRODUCTS

Consumer products contribute an estimated 3% to the average population radiation dose. Several consumer products, used both within the home and in many public areas, emit minuscule amounts of radiation. Among these are ionization-type smoke detectors, television sets, and liquid propane gas (LPG) appliances. The first smoke detectors contained radium (approximately 20 μCi [0.7 MBq]), but now contain americium-241 (^{241}Am), which is more economical and produces much less radiation dose. While present-day detectors contain 0.5–1.0 μCi (0.02-0.04 MBq) of ^{241}Am, the original units contained approximately 80 μCi (3 MBq). In the 1980s, annual sales of smoke detectors approached 12 million, representing approximately 8.5 Ci (300 GBq) of ^{241}Am. Smoke detectors contain a small ionization chamber in which the air between two electrodes is ionized by the source radionuclide. This ionization allows the flow of current across the gap between the electrodes. When the flow is stopped by smoke particles, the interruption in current flow is interpreted by the detector to indicate the presence of smoke. Television sets accelerate electrons that bombard the screen; in the process, low-energy x rays are emitted. The total annual dose associated with watching a color television has been estimated to be 2–3 mrad per year (0.02-0.03 mGy/yr). Radon is found in LPG, which may be used in water heaters,

stoves, and fireplaces; it has been estimated that exposure to radon in homes using natural gas results in an average annual dose of approximately 5 mrem (0.05 mSv) in the United States.

Among consumer products of the past are items that contained radium, such as medicines, tonics, luminous paints, and ceramic glazes. After its discovery in the early part of the 20th century, radium was used for many years in the treatment of rheumatism (arthritis) and mental disorders; oral solutions contained ^{226}Ra and ^{228}Ra at concentrations up to 2 µCi/60 mL, while ampules for intravenous administration contained 5–100 µg ^{226}Ra and ^{228}Ra. Radium was also used to produce luminescent paints that were applied to wristwatches, clocks, static eliminators, fire alarms, electron tubes, and military and educational products. During the peak years of production, approximately 3 million radium-laden timepieces were sold annually in the United States. The radium content of a man's wristwatch ranged from 0.01 to 0.36 µCi (370-13,000 Bq), resulting in potential gonadal doses of 0.5–6 mrem/year (0.005—0.06 mSv/yr). Radium has been replaced with ^{3}H and prometium-147 (^{147}Pm), and watch cases are sufficiently thick to absorb the beta emissions from these radionuclides. Uranium has been used as a coloring agent for ceramic glazes, resulting in doses to the hands of up to 20 mrad/hour (0.02 mGy/hr). The dose from ceramics produced since 1944 is thought to be five-fold less than that from earlier pieces. For more than 40 years, ^{224}Ra has been used in Europe to treat the symptoms of tuberculosis and ankylosing spondylitis. Although its use in children was curtailed in the 1950s, ^{224}Ra has been used for treating the pain associated with ankylosing spondylitis. In two studies of patients treated with ^{224}Ra, average calculated skeletal doses ranged from 0.65–4.2 Gy (65–420 rad) (Eisenbud 1987; Harley 1996; Harvard Medical School 1996; NCRP 1993).

6.7 EXPOSURE FROM OTHER SOURCES

Other sources contribute less than 1% to the average population radiation dose. This radiation exposure may result from several anthropogenic sources, including the radioactive debris still remaining from atmospheric and underground detonation of nuclear weapons, electrical energy production, radiopharmaceuticals, and radionuclide production and use (Shapiro 1990; UNSCEAR 1993).

6.7.1 Exposure from the Nuclear Fuel Cycle

The nuclear fuel cycle contributes around 0.1% to the average population radiation dose and refers to the mining, milling and enrichment of uranium; fabrication of fuel elements; the production of electricity; and the recycling, transportation, and waste storage/disposal of radioactive materials used in nuclear weapons or reactor-grade nuclear fuel. The steps involved in the uranium fuel cycle are depicted in Figure 6-2 and described in the Toxicological Profile for Uranium (ATSDR 1999b). The primary radionuclide components of nuclear weapons and reactors include ^{239}Pu, ^{235}U, ^{238}U, and ^{3}H. Radionuclides associated with uranium mining and milling include ^{235}U, ^{238}U, and their natural decay chain radionuclides, such as ^{226}Ra, ^{234}Th, ^{234m}Pa, ^{230}Th, and ^{222}Rn, while those associated with power production and subsequent waste disposal include (but are not limited to) ^{60}Co, ^{3}H, ^{14}C, ^{129}I, ^{131}I, ^{134}Cs, and ^{137}Cs. Noble gas radionuclides of Kr, Xe, and Zr are only associated with operational reactor releases. The various steps within this cycle provide multiple opportunities for the exposure of humans to these materials.

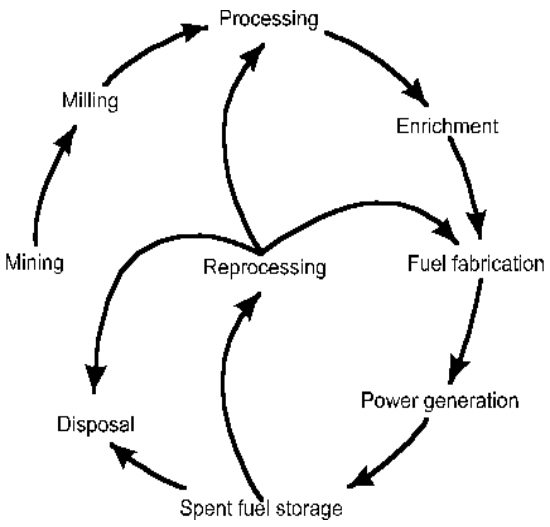


Figure 6-2. Schematic of the Nuclear Fuel Cycle

Mining and milling. Uranium ore typically contains uranium at concentrations ranging from a tenth of a percent to a few percent; thus, millions of tons of ore are mined and processed annually to meet the needs of nuclear power plants for uranium fuel. Radon is the predominant radionuclide released from uranium mines. Radon containing air is discharged from mines at a rate of approximately 0.5–20 μCi/min/1,000 ft^3; these are point releases whose concentrations dilute quickly with distance from the release shaft and, thus, pose no additional health risk to the general public. Incomplete extraction of uranium during milling results in uranium concentrations in mill tailings of 0.001–0.01%. The presence of radon precursors (^{226}Ra and ^{230}Th) in mill tailings presents a potential long-term source for atmospheric radon. The rate of radon emanation varies with meteorological factors such as barometric pressure and humidity. The rate of soil and mill tailings migration depends primarily on wind and water erosion of the site (Eisenbud 1987; UNSCEAR 1993).

Enrichment and fuel fabrication. In both nuclear weapons and nuclear fuel production, after being mined and milled, uranium must be converted to uranium hexafluoride gas, which is then enriched and converted to uranium oxide or metal. If enrichment is carried to about 90%, the uranium may be used to make nuclear weapons or to fuel naval warships; alternatively, the uranium may be enriched by only a small percentage for use in civilian nuclear energy facilities. Metallic uranium is capable of reacting with both air and water exothermically; because of this reactivity, the more stable uranium oxide is the most commonly used fuel in reactors. While this form is more stable, it has poor thermal conductivity, necessitating the use of small-diameter fuel rods. The fuel is in the form of high melting point ceramic pellets, about 0.5 inches in diameter and 1 inch long, in which UO_2-enriched to 3–4% ^{235}U is dispersed. These pellets are stacked end to end in zirconium alloy or stainless steel tubes about 12 feet long (called cladding) and then sealed to retain the fission products that are produced during operation. These fuel filled tubes are then assembled in groups of 8 x 8 to 17 x 17 arrays into fuel rod assemblies. About 500 of these assemblies make up the core of a nuclear power reactor. For a frame of reference, a single pellet contains the energy equivalent of about one ton of coal or 3 barrels of oil. Emissions from fabrication facilities usually consist of the long-lived isotopes ^{234}U, ^{235}U, and ^{238}U, and the short-lived nuclides ^{234}Th and ^{234m}Pa; however, the relative value of the refined and enriched uranium and the high level of accountability for uranium stock preclude any long-term or widespread loss of material. The major route of exposure from this source is inhalation (Eisenbud 1987; UNSCEAR 1993). More information about the toxicological properties of uranium can be found in the *Toxicological Profile for Uranium* (ATSDR 1999b).

Power generation. Power production from nuclear plants has increased steadily since the industry's birth in the 1950s. During the years between 1970 and 1989, the number of nuclear reactors worldwide increased from 77 to 426, and total nuclear power generation increased from 9 to 212 gigawatts per year. In 1996, nuclear power plants produced 17% and 19.4% of the world's and U. S. electrical energy, respectively (DOE 1997c). The annual worldwide production of uranium from 1979 to 1989 ranged from 19,000 to 44,000 tons; from 1985 to 1990, the annual production was approximately 50,000 tons. USNRC regulations require that all the component parts of the nuclear fuel cycle be designed and operated to limit the annual dose to a member of the public from the total nuclear fuel cycle to a maximum of 25 mrem (0.25 mSv). Various regulations identified in Chapter 7 of this profile are designed to limit human exposure to radiation and radioactive materials. Guidance documents, such as the ANSI air sampling standard (ANSI 1999), are available to aid in establishing monitoring programs for assessing discharges from nuclear facilities. During the energy production phase, radioactive contamination of the coolant occurs through small defects in the protective cladding surrounding the fuel

pellets, through fission of "tramp" uranium contamination on the outside surface of the fuel rods and through neutron activation of contaminants in the cooling medium.

In general, the levels of radionuclide emissions from reactors are not typically detectable, except at points close to effluent discharges; because of this, estimates of radionuclide discharge levels must be modeled. Based on such models, the total collective dose due to reactor discharges through 1989 was estimated to be 370,000 man•rem (3,700 man•Sv) over a 45-year period. This may be compared to the collective dose to the U.S. public from the natural radioactive potassium within everyone's body, which is about 5,000,000 man•rem (50,000 man•Sv) each year . A 1981 U.S. Nuclear Regulatory Commission (USNRC) study of the doses received by 98 million people living within 80 km of 48 nuclear facilities concluded, on the basis of a zero threshold model, that 0.02 excess fatal cancers per year, or 1 every 50 years, could be attributed to exposures from nuclear facilities (USNRC 1981). A study of the cancer rates in populations surrounding 62 U.S. nuclear facilities, performed by the National Cancer Institute (NCI) in 1990, found no evidence of a relationship between proximity to a nuclear facility and the occurrence of cancer (Eisenbud 1987; NCI 1990; UNSCEAR 1993).

Weapons production. There is little public information regarding the amount of radioactive materials produced for use as weapons. The atmospheric content of krypton-85 (^{85}Kr), a by-product of plutonium extraction, has been used to estimate the plutonium stockpiles in both the United States and Russia. After adjusting for production and release of ^{85}Kr from nuclear reactors, it is estimated from the atmospheric content of ^{85}Kr that plutonium stockpiles in both the United States and Russia is about 100 tons each. United Nations estimates from 1981 and 1990 state that nuclear arsenals are comprised of 40,000 weapons with a combined explosive power of 13,000 Mt. Tritium, which has a half-life of 12.32 years, must be continually produced to replace aging stockpiles. It is estimated that an annual production of 3 kg is sufficient to replace that lost by transformation in the United States. By inference, this would indicate a total U.S. stockpile of 55 kg and a world stockpile of about 110 kg (UNSCEAR 1993).

The dose from nuclear weapons research, development, and production is less than 1% of the dose from atmospheric testing. Variations in local exposure from former weapons plants have been reported. In the United States, the Hanford nuclear weapons facility has released a significant amount of radioactive material into the atmosphere and the Columbia River from its plutonium production and reprocessing plants. The majority of the radioactive material (^{131}I) was released between 1944 and 1946 (18 PBq; 486 kCi), although additional releases are known to have occurred from 1947 to 1956 (2 PBq; 54kCi). A

recent study reconstructed the radiation doses to individuals who were exposed to the ^{131}I released from the Hanford site, medically determined their thyroid health, and found that the Hanford releases had not caused thyroid problems. The thyroid radiation doses to the 3,193 participants averaged 0.186 Gy (18.6 rad) and ranged from 0–2.842 Gy (0–284.2 rad). Health impacts to the thyroid which have been related to radiation exposure in other studies include thyroid cancer, benign thyroid nodules, hypothyroidism, and autoimmune thyroiditis. The study assessed these conditions and concluded that the occurrence of these diseases in the population were not related to the Hanford releases' radiation dose to the thyroid (CDC 1999).

The Chelyabinsk-40 center, located near Kyshtym in the Soviet Union, was the first nuclear weapons processing facility in Russia. A uranium-graphite-moderated reactor and a fuel reprocessing plant were opened in 1948. Due to poor waste handling and the storage of radioactive wastes in the open, significant liquid releases (100 PBq; 2.7MCi) to the Techa River occurred from 1949 to 1956, with the majority of the releases (95%) occurring from March 1950 to November 1951. The main nuclides released included ^{89}Sr, ^{137}Cs, ^{95}Zr, ^{95}Nb, and ruthenium and rare-earth nuclides. The population along the Techa River was exposed to both external and internal doses of radiation; a total of 20 settlements (7,500 people) were eventually evacuated. The average doses to persons living in the village of Metlino, 7 km downstream from the plant, were estimated to be as much as 140 rad (1.4 Gy) (UNSCEAR 1993).

Fuel reprocessing. Fuel reprocessing allows the recovery of uranium and plutonium from the irradiated fuel pellets. Less than 10% of the nuclear fuel is consumed in a spent fuel rod. The radionuclides most commonly associated with reprocessing waste are: ^{3}H, ^{14}C, ^{85}Kr, ^{129}I, ^{131}I, ^{134}Cs, ^{137}Cs and transuranium nuclides. At present, reprocessing is carried out in only a few countries, and only a small portion of the total fuel inventory is being reprocessed (4% from 1985 to 1990). The remainder is retrievably stored (UNSCEAR 1993).

The reprocessing of nuclear fuel has been performed almost exclusively at government-owned facilities designed to meet military needs. Only 1 operable reprocessing facility exists in the U.S. As with nuclear reactors, the facility and the equipment used have been designed with numerous safeguards to prevent criticality and to ensure containment of radioactive material in the event of a non-nuclear explosion or system failure. The estimated collective dose due to reprocessing to date is estimated to be 460,000 man•rem (4,600 man•Sv); the main radionuclide constituents (>90%) of these releases have been ^{137}Cs and ^{106}Ru. Releases of gaseous ^{85}Kr and ^{3}H from reprocessing facilities have also been reported. The main pathways of exposure are consumption of locally caught fish and shellfish, external (whole-body) irradiation from intertidal areas, and external (dermal) irradiation of fishermen handling pots and nets.

Annual individual doses were estimated for critical populations living near three foreign reprocessing plants (Sellafield, England; Cap de la Hage, France; and Tokai-Mura, Japan) for which records of radioactive effluent exist. For the critical population living near Sellafield, annual individual doses from ingestion were estimated to be approximately 350 mrem (3.5 mSv) during the early 1980s and declined to approximately 20 mrem (0.2 mSv) by 1986. The estimated doses in the same group due to external irradiation were estimated to be about 100 mrem (1 mSv) in the early 1980s and 30 mrem (0.3 mSv) by 1986. In contrast, annual individual doses for critical populations living near the Cap de la Hage and Tokai-Mura reprocessing plants were approximately 25 mrem (0.25 mSv) and 0.1 mrem (1 μSv) (Eisenbud 1987; UNSCEAR 1993). A nuclear criticality accident occurred at the Tokai-Mura, Japan uranium reprocessing plant on September 30, 1999 with acute exposures to workers and general population (UPI 1999).

Waste disposal. Solid wastes derived from reactor operations and from the handling, processing, and disposal of spent fuel are classified as low-, intermediate-, or high-level wastes. While low- and intermediate-level wastes had been packaged and placed into shallow burial sites, high-level waste disposal strategies have only recently been implemented. Some low-level wastes were packaged and disposed at sea from 1946 to 1982. Currently, some high level waste is being vitrified (mixed with hot liquid glass), solidified inside double-walled stainless steel containers, and prepared for long-term retrievable storage. Exposure to uncontained buried wastes is thought to occur throught groundwater migration from leakage at the burial site. The major radionuclide found in reactor waste is ^{14}C (UNSCEAR 1993).

6.7.2 Japanese Atomic Bomb Exposure

A large human cohort (86,572 people who survived the detonation of two atomic bombs in Japan in 1945 and whose radiation doses are reasonably well known) are being studied for the effects of external exposure to ionizing radiation. The Japanese survivors are not the largest cohort; some medically exposed populations are larger. However, the Japanese survivors are probably the most important because of the length of follow-up

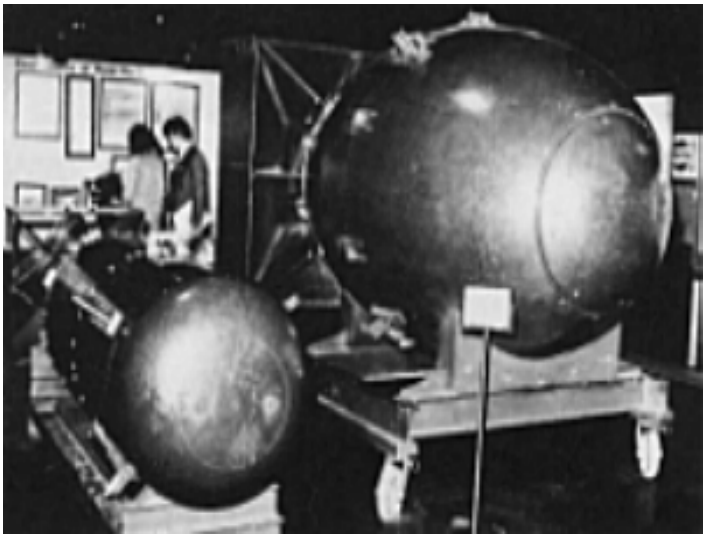


Figure 6-3. Replicas of the "Little Boy" and "Fat Man" Bombs Dropped on Hiroshima and Nagasaki (adapted from A-Bomb WWW Museum, http://www.csi.ad.jp/ABOMB).

and the wide range of doses received. The first atomic bomb was detonated on July 16, 1945, in Alamogordo, New Mexico. The U.S. military, in an effort to bring a swifter end to World War II and to avoid a costly ground invasion of Japan, which could claim more U.S. and Japanese lives, detonated a ^{235}U atomic bomb, nicknamed "Little Boy," (see Figure 6-3) over the city of Hiroshima, Japan, on August 6, 1945. Three days later, an atomic bomb using ^{239}Pu, nicknamed "Fat Man," was detonated over the city of Nagasaki, Japan.

The uranium used in the "Little Boy" bomb was enriched to >80% ^{235}U. (Natural uranium contains 0.7% ^{235}U, and reactor fuel is enriched to 3–4% ^{235}U). The uranium bomb design of Little Boy used a standard explosion trigger, called the "gun" method, because it was originally made using a gun barrel. In this configuration, a sub-critical uranium mass, referred to as the "bullet," was propelled inside the gun barrel toward a second sub-critical portion of the uranium mass (called the "target"), which was located at the end of the gun barrel. The target contained slightly less than the amount of uranium needed to achieve critical mass (the amount necessary to create a chain reaction). The instant the two subcritical pieces of uranium came together, super-criticality was attained, and an explosion with a force equivalent to 15,000 tons (15 kt) of trinitrotoluene (TNT) occurred (Roesch 1987). In the case of Little Boy, the bullet was a cylindrical stack of nine ^{235}U wafers about 10 cm wide and 16 cm long, containing 40% of the bomb's total ^{235}U mass (25.6 kg). The target was a hollow cylinder 16 cm long and wide; it weighed 38.4 kg and was composed of two separate rings that were inserted into the bomb separately to prevent reaching critical mass during assembly. The complete Little Boy weapon was 10.5 feet long, 28–29 inches in diameter, and reportedly weighed between 8,900 and 9,700 pounds. The firing mechanism was so simple and was considered so failproof that it was not tested prior to its use over Hiroshima. The gun-type firing mechanism was, however, an unsafe weapon design, in that once the firing mechanism was loaded with high explosive, anything that ignited it would cause a nuclear explosion. Also, a crash or even an accidental drop of the bomb could have driven the bullet into the target, potentially resulting in a nuclear explosion. No other weapon of this design was ever tested, and although several Little Boy units were built, none ever entered the U.S. nuclear arsenal.

The plutonium bomb, Fat Man, was dramatically different from the Little Boy design. The gun-type firing mechanism could not be used to unite two pieces of plutonium fast enough to achieve a nuclear blast; impurities in the plutonium would have caused premature detonation. Fat Man contained a ball of subcritical plutonium (plutonium core), which was surrounded with high explosives. The high explosives were cast into spheres, called lenses, and were wired so they would all fire at the same instant. The instantaneous pressure from all sides compressed the plutonium core in on itself, causing it to reach critical mass and density, and create a nuclear blast. The combat configuration for the Fat Man bomb

consisted of the implosion device encapsulated in a steel armor egg. Fat Man was 5 feet in diameter, 12 feet in length, and weighed 10,300 pounds (American Airpower Heritage Museum 1996; Sublette 1996). The explosion of Fat Man at Nagasaki was equivalent to 21,000 tons (21 kt) of TNT (Roesch 1987).

In Hiroshima and Nagasaki, a total of 64,000 people within 1 km of the hypocenter (the point on the ground directly below where the bomb exploded in the air) died on the first day. The total numbers of acute deaths from the explosions were 90,000–140,000 in Hiroshima and 60,000–80,000 in Nagasaki. For bombs the size (approximate yield of 15 kilotons) and type of Little Boy, the energy released within the first minute after detonation was in the forms of thermal radiation (35%), blast wave (50%), and ionizing radiation (15%); most casualties (including fatalities) resulted from the heat and blast. Two-thirds of those who died during the first day were burned. People close enough to suffer from radiation illness were also well within the lethal zones from blast and heat; thus, the proportion of survivors experiencing radiation illness (30%) was much smaller than the expected proportion based solely on exposure to radiation. People within 1–2 km of the hypocenter who initially survived the blast and received several hundred rad (several grays) of radiation, suffered the ill effects of acute radiation syndrome. It is estimated that all persons whose bodies received a dose of 600 rad (6 Gy) and half of those whose radiation doses were 450 rad (4.5 Gy) died shortly thereafter, as a direct result of radiation exposure. Of those who survived the immediate radiation illness effects, a portion would suffer from the latent effects of radiation-induced cancer (the excess cancer death rate among the exposed population is on the order of 5% greater than that of an unexposed population). It is estimated that approximately 500 survivors have died of radiation induced cancers since 1945. Given the estimated altitudes at which Little Boy and Fat Man detonated (1,900±50 ft. and 1,650±33 ft., respectively), little or no soil was carried up into the fireball, so the fallout produced came mainly from the detonation itself. Of that, very little radioactive material was deposited on the ground in the vicinity of ground zero; the majority was carried high into the atmosphere by heat convection. A small amount of fallout did occur in areas close to the cities due to rainfall that occurred shortly after the explosions; the affected areas were to the west and northwest of Hiroshima and a few miles east of Nagasaki. Fatality rates in the Hiroshima and Nagasaki attacks were 1–2 orders of magnitude greater than rates from conventional bombings because of the nearly instantaneous destruction of buildings that occurred without warning, and because survivors were so incapacitated that they could not escape the rapidly ensuing fire storms. Approximately one-third of all Japanese bombing fatalities occurred in these two cities (Masse 1996; Sublette 1995, 1996; Uranium Information Center 1995; Zajtchak 1989).

6.7.3 Exposure from Nuclear Weapons Testing

Nuclear weapons testing is conducted to assess design efficiency and magnitude of resulting damage. Nuclear explosions world wide were carried out above ground from 1945 to 1980, with the periods of greatest activity occurring from 1952 to 1958, and from 1961 to 1962. A total of 520 tests with an estimated total equivalent energy of 545 megatons (Mt) of TNT was performed, resulting in the release of 220 PBq (6 MCi) of radioactive material. The first U.S. testing of nuclear weapons after World War II was performed in the Marshall Islands in the Pacific Ocean from 1946 to 1948. The Soviet Union conducted its first weapons test in 1948. In the 1950s, as the frequency of weapons testing escalated, so did public concerns over radioactive fallout. In the fall of 1958, the United States, Britain, and Russia, declared a moratorium on weapons testing; however, Russia broke the agreement in 1961, and another rapid escalation in testing ensued. In 1963, the United States, Britain, and Russia, signed the Limited Test Ban Treaty, which prohibited atmospheric testing. Although these three countries have remained faithful to the treaty, other countries such as France, China, India, and Pakistan have since conducted weapons testing (Eisenbud 1987; PBS 1999; UNSCEAR 1993).

The energy from nuclear weapons devices is generated by one or both of the following reactions: (1) the fission of ^{235}U or ^{239}Pu in a chain reaction and (2) the fusion of the hydrogen isotopes deuterium and tritium. Fission-type weapons accounted for 217 Mt of the total test yield, while fusion-type weapons accounted for 328 Mt. Many radionuclides are produced by U and Pu fission. Fusion reactions produce helium and result in the neutron activation of the surrounding substance. The most notable neutron activation product is ^{14}C, which is formed from the neutron bombardment of atmospheric nitrogen. Unused weapons material is also liberated after detonation due to premature loss of critical mass (Radnet 1996; UNSCEAR 1993).

The most important radionuclides associated with nuclear weapons testing exposures are ^{14}C; ^{137}Cs; zirconium-95 (^{95}Zr); niobium-95 (^{95}Nb); ^{90}Sr; ruthenium-106 (^{106}Ru); manganese-54 (^{54}Mn); ^{144}Ce; ^{131}I; and ^{3}H. This is in addition to the large amounts of ^{14}C and ^{3}H in the biosphere's carbon and hydrogen inventories which are produced by the interaction of cosmic rays with atmospheric gases.

The disposition of ingested strontium-90 (^{90}Sr) has been studied extensively due to its abundance (15 MCi of that introduced into the atmosphere as a result of nuclear weapons testing fell to the earth by January 1970), its long half-life (28 years), and its tendency to localize in bones. Metabolically, Sr follows the pathways of calcium (Ca); however, the body discriminates against Sr in favor of Ca.

Because of this parallel mechanism, Sr concentrations are often expressed as activity of Sr per gram of Ca. In 1965, bone levels of ^{90}Sr in 1- to 4-year-old Norwegian children averaged 11.8 pCi/g Ca. In New York City, bone levels of ^{90}Sr in 1- to 2-year-olds varied from 7 pCi/g Ca in 1965 to 1.6 pCi/g Ca in 1975. In 5- to 19-year-olds, bone levels varied from 3 pCi/g Ca during 1956–1968 to 1.4 pCi/g Ca in 1975 (Shapiro 1990). In an effort to quantify exposure resulting from nuclear testing, ^{90}Sr deposition has been monitored worldwide at 50 to 200 stations in cooperation with the Environmental Measurements Laboratory (EML), and by a network of 26 stations organized by the United Kingdom Atomic Energy Authority. These data are compiled into a report called Environmental Radiation Data (ERD), which is distributed quarterly by the Office of Radiation and Indoor Air's National Air and Radiation Environmental Laboratory (NAREL). The report contains data from the Environmental Radiation Ambient Monitoring System (ERAMS). ERAMS was established in 1973 by the EPA to provide air, surface and drinking water, and milk samples from which environmental radiation levels are derived. These samples are collected from locations that provide adequate population coverage and function to monitor fallout from nuclear devices and other radioactive contamination from the environment. Samples are subjected to analysis for gross alpha and beta emissions; gamma analyses for fission products; and more specific analysis for uranium plutonium, strontium, iodine, radium, and tritium (EPA 1997).

Zirconium-95 (^{95}Zr) deposition has been monitored as an indicator of exposure to short-lived radionuclides. Monitoring levels of ^{3}H and ^{14}C is more difficult due to the rapid recycling of these elements in a biosphere that contains large cosmogenically produced amounts of these same radionuclides. Interhemispheric transfer is limited due to prevailing trade winds and the scavenging effect of precipitation in the tropics. The best estimate of the average total per person dose, for persons in the northern and southern hemispheres, for all 22 major radionuclides resulting from nuclear testing is 440 and 310 mrem (4.4 and 3.1 mSv), respectively. Worldwide, the average total cumulative dose is 370 mrem (3.7 mSv). However, as noted below, extreme variations in local exposures due to testing have been noted (UNSCEAR 1993).

Approximately 23 billion Ci of ^{131}I have been introduced into the atmosphere as a result of nuclear weapons testing. In October 1961, the air concentration of ^{131}I in the United States averaged 3.8 pCi/m^3. This was estimated to result in an annual dose of 24 mrad to a 1-year-old child. In 1962, the concentration of ^{131}I in milk in the United States averaged 32 pCi/L. Although about two-thirds of orally administered ^{131}I is excreted in the urine within the first 24 hours, the remainder concentrates in the thyroid. It has been estimated that an infant receiving milk from cows that grazed on forage contaminated with 1 µCi ^{131}I/m^2 could receive a dose to the thyroid of 30 rad (Shapiro 1990; UNSCEAR 1993). In addition, studies of pregnant women who died suddenly of non-radiation-induced causes (e.g., car

accidents) found that fetal tissue concentrations of ^{131}I were 30% greater than those in maternal tissues (Shapiro 1990). Due to the short 8-day half-life of ^{131}I, there is no ^{131}I remaining in the atmosphere or in food from nuclear weapons testing.

Plutonium (Pu) has been introduced into the atmosphere from sources such as weapons testing (>5,000 kg [>320 kCi]) and the vaporization of energy power packs from a Russian satellite (20 kg [0.27 TBq] of ^{239}Pu) and U.S. satellites (1 kg [17 kCi] of ^{238}Pu) that burned up upon re-entry. Air activity of Pu, monitored in New York, peaked in 1963 at a concentration of 1.7 fCi/m^3. The cumulative inhalation intake from 1954 to 1975 averaged 43 pCi per person. For comparison, the EPA's annual limit on intake (ALI) for ^{239}Pu for occupational exposure is 2,000 pCi. Cumulative individual tissue doses (through the year 2000) due to inhalation are predicted to be: lungs, 1.6 mrad; liver, 1.7 mrad; and bone lining cells, 1.5 mrad (Shapiro 1990).

Radioactive debris from nuclear explosions falls into three categories: large particles, which fall out close to the explosion site within hours of the explosion; smaller particles, which penetrate the troposphere, behave like aerosols, and may not fall out for days; and the smallest particles, which penetrate the stratosphere, distribute worldwide, and fall out over many months or years. The greatest portion of fallout from nuclear weapons testing was injected into the stratosphere (78%), while 10% and 12% were injected into the troposphere and in the locality of the test, respectively. As of 1993, the total cumulative worldwide collective dose due to fallout was estimated to be $7x10^6$ man•Sv. The collective dose will continue to climb, mainly due to long-lived ^{14}C (Eisenbud 1987; UNSCEAR 1993).

Airborne radioactive materials, both naturally occurring and fallout-derived, usually attach to dust particles; the potential for inhalation of radionuclides bound to particles, and the respective threat this poses to animal and human health, varies considerably. In regions downwind of nuclear weapons test sites or nuclear weapons production facilities, or areas with abnormally high concentrations of naturally occurring radionuclides (e.g., New York state or Denver, Colorado), the potential for inhalation of particulate-bound radionuclides increases. Although most inhaled radioactive particles are eliminated from the lungs by normal clearing mechanisms, some of the particles remain in the lungs for extended periods. Others are carried to lymph nodes by scavenger cells (Eisenbud 1987; Shapiro 1990).

Radiation dose from atmospheric testing is attributed to external exposure to radionuclides on the earth's surface, internal exposure from inhalation of gases or particulate matter, and ingestion of contaminated foods and water. Approximately 80% of the radiation dose from nuclear testing is estimated to be

delivered through ingestion, with 16% and 4% of the dose delivered through external exposure and inhalation, respectively. Radioactive particles resulting from fallout can contaminate food supplies directly by foliar deposition, or indirectly by entry into the soil and subsequent incorporation into plants, although this delayed incorporation through root uptake accounts for a small portion of that ingested. Surface waters can be contaminated through soil runoff or direct contamination from the atmosphere. The degree of radionuclide incorporation into plants through root uptake varies considerably among radionuclides. For example, ^{137}Cs and radium bind tightly to clay or organic minerals upon entering the soil and are not amenable to root uptake; thus, foliar deposition is the primary route for oral exposure to ^{137}Cs. Likewise, ^{131}I poses little threat through root uptake due to its short half-life (8 days). The concentrations of radionuclides in food vary considerably across food types. The concentration of ^{226}Ra ranges from 0.15 pCi/kg in cow's milk to 2,000 pCi/kg in Brazil nuts. Concentrations of ^{137}Cs range from 20 pCi/kg in cow's milk to 5,000 pCi/kg in beef. More important than concentrations in foods is the rate of intake and absorption of a radionuclide. Individual intake varies considerably; for a given radionuclide and locality, intake may vary as much as 500-fold. Likewise, the extent of absorption varies among the various nuclides, from almost completely in the case of ^{40}K, ^{137}Cs, and ^{131}I, to very poorly (0.003%) in the case of Pu radionuclides. Many alpha emitters, such as ^{226}Ra, are taken up and retained in the bone, resulting in sustained alpha irradiation of the bone-forming cells and bone surface lining cells (Eisenbud 1987; McClellan 1982; Shapiro 1990).

The primary radionuclides of concern are ^{90}Sr, ^{137}Cs, and ^{131}I. Within the first year, 45% of ^{137}Cs is transferred to the food chain (through milk, grain and meat). ^{90}Sr enters the food chain primarily through milk and grain products. Exposure to ^{14}C and ^{3}H is through ingestion and inhalation; however, the contribution of ^{14}C and ^{3}H by ingestion is trivial. The dose rate from naturally occurring ^{14}C is about 1 mrem per year. At its peak effect, the dose rate from ^{14}C due to weapons testing also was about 1 mrem per year, and is now decreasing. The dose from the tritium due to weapons is considered to be even less. At the peak, the additional ^{3}H contributed less than 0.1 mrem per year (UNSCEAR 1993). The radiation dose from ^{131}I occurs largely during the first 2 months following detonation, due to its short 8-day half-life, and the primary exposure route is via the pasture-cow's milk ingestion pathway.

In addition to exposures from inhalation and ingestion, radiation exposure also occurs externally from particles deposited on the ground. Since the debris spends more time on the ground than in the air, the radiation dose from earthbound particles ranges from 100 to 1,000,000 times that from airborne particles (UNSCEAR 1993).

6.7.3.1 Atmospheric Testing

Atmospheric testing refers to the detonation of nuclear bombs above the earth's surface.

Nevada Test Site Fallout. A total of 100 surface or near-surface tests with a total explosive yield of about 1 Mt were performed at the Nevada test site between 1951 and 1962. The population around the site at this time was approximately 180,000 persons. Within this population, thyroid doses in children may have been as high as 100 rad (1 Gy). The collective dose received by this population was approximately 50,000 man•rem (500 man•Sv); 90% of this dose was delivered between 1953 and 1957. The dust from these tests also drifted over the United States, producing bands of exposure to radioactive material. Deposition of fallout varied considerably because of meteorological conditions. For example, the greatest (non-local) fallout levels from one of the Nevada test explosions occurred in New York State, some 2,000 miles away, due to rainfall. The cumulative dose from gamma radiation in New York, approximately 100 mrad (1 mGy), exceeded the doses received by any remote U.S. location for all of 1953 (Eisenbud 1987; UNSCEAR 1993).

Bikini Atoll Fallout. Operation Crossroads was a series of nuclear weapons tests that began in the Marshall Islands, a group of atolls in the Pacific, on July 1, 1946. Prior to testing, the inhabitants of the Bikini Island Atoll were evacuated. The second test in this series, designated "Baker," was a 21-kiloton bomb that was detonated underwater. This resulted in contamination of ships staged nearby and the atoll itself. Local soil contamination prevented the return of the Bikini native population until 1969. Although the island was still contaminated in 1969, it was thought that dietary restrictions and the importation of foods would allow safe habitation. However, body burdens of plutonium began to increase in the natives, resulting in their re-evacuation in 1978.

During Operation Castle, another series of nuclear tests, the second test, "Bravo," resulted in significant fallout and contamination of humans. Abrupt changes in wind direction after the 15-Mt detonation on March 1, 1954, resulted in the inadvertent exposure of residents of the Rongelap and Utirik islands, which lie 210 and 570 km to the east of Bikini, as well as exposure of a group of 23 Japanese fishermen whose boat was caught in the fallout approximately 80 miles downwind. Since the device was mounted on a barge situated in shallow water, a considerable amount of coral was incorporated into the fireball. The fishermen reported that the fallout particles resembled snow and that deposits of fallout on the boat were of sufficient depth to allow one to see footprints. Because they were unaware of the circumstances, the fishermen took no precautionary measures to minimize exposure; they remained on the contaminated boat

until returning to port some 13 days later. Within 1–2 days after exposure to the fallout, the fishermen began to experience itching and burning sensations on exposed skin. By the third day, skin lesions and epilation began to develop; the skin lesions became ulcerous in about 70% of the fishermen. Lesions were less severe in those who had worn protective clothing such as hats (ACHRE 1995; Eisenbud 1987). A more detailed description is available (Simon and Vetter 1997).

Within 78 hours of the explosion, 82 and 159 persons were evacuated from Rongelap and Utirik, respectively. However, as with the fishermen, the island inhabitants took no precautionary measures to minimize exposure to radioactive fallout. Within 1–2 days after exposure to fallout, itching and burning sensations on exposed skin were experienced by the natives of Rongelap, but not those of Utirik. Skin lesions and epilation occurred within 21 days of exposure, becoming ulcerous in about 25% of the Rongelaps; lesions were less severe in those who had worn protective clothing or bathed during the period prior to evacuation. The island of Utirik was not heavily contaminated, and its residents were allowed to return within a few months; however, the Rongelap residents were not allowed to return to their island until 1957, and they were monitored annually by U.S. medical teams thereafter. Despite the monitoring, fears among the island residents that exposure-related health problems were occurring prompted a second evacuation, initiated by the residents, in 1985. External doses, ranging from 10 to 190 rad (0.1 to 1.9 Sv), were mostly from short-lived radionuclides. Mean thyroid doses to adults, 9-year-olds, and 1-year-olds, were 1,300, 2,200, and 5,200 rad (13, 22, and 52 Gy), respectively. Maximum thyroid doses to these groups were 4,200, 8,200, and 20,000 rad (42, 82, and 200 Gy), respectively (ACHRE 1995; Eisenbud 1987; NAS 1994; UNSCEAR 1993).

Average gamma dose rates 3 feet above ground level on Rongelap island, estimated from a survey performed in July 1956, were 0.2–0.5 mR/hr (mean of 0.4 mR/hr) (DOE 1994b). Environmental samples collected in 1964 showed ^{239}Pu concentrations of 11 pCi/g (0.4 Bq/g) in a soil sample collected at a depth of 0.5–1.0 inch. A more extensive survey that included 14 of the atoll islands was performed in April and May of 1967. External radiation, as well as the radioactive content of food, vegetation, and soil, was measured. On the islands closest to the detonations, the major contributor to the external gamma radiation field was ^{60}Co, which was associated with neutron activation of scrap metal; the major contributor to the external gamma radiation field on distant islands was ^{137}Cs. Additional samples were collected during the U.S. cleanup operations in 1969. ^{239}Pu concentrations on Bikini Island ranged from 1.3 to 190 pCi/g (0.1–7 Bq/g). ^{239}Pu concentrations on Eneu Island ranged from 0.5 to <3 pCi/g (0.02–<0.1 Bq/g) (DOE 1970). Measurements of gamma radiation exposure performed in June 1975 showed highly variable exposure rates on Bikini island (10–20 μR/hr at the shore versus 30–100 μR/hr in

the interior), while exposure rates on Eneu island were relatively constant (<10 μR/hr) over the entire island. Thirty-year cumulative doses were estimated to be 0.057 and 0.027 Sv (5.7 and 2.7 rem) for those living on Bikini Island (interior portions) and Eneu Island, respectively (USERD 1975). Water samples collected from Eneu Island in 1975 showed ^{90}Sr and ^{137}Cs at concentrations that would lead to a combined 30-year whole-body and skeletal dose of 25 mrem (0.25 mSv). Sampling of cistern water on Bikini Island during the same period revealed ^{90}Sr concentrations, which would lead to a 30-year skeletal dose of 9.1 mrem (0.09 mSv), and ^{137}Cs at concentrations that would lead to a 30-year whole-body dose of 1.9 mrem (0.02 mSv) (DOE 1975). Whole-body counting of Bikini Island residents in 1974, 1977, and 1978 showed that the major contributor to whole body doses was ^{137}Cs. The average body burden for ^{137}Cs increased 10-fold between 1974 and 1977 and by 72% between 1977 and 1978. Nine persons had body burdens exceeding the federal standards for non-occupational dose in that year (0.5 rem/year [0.005 Sv/yr]); the highest body burdens were approximately twice the permissible levels (DOE 1978).

Semipalatinsk Test Site Fallout (Russia). Approximately 10,000 people living near the Semipalatinsk test site in the Kazakh region of Russia were exposed to radioactive materials from atmospheric testing between the years of 1949 and 1962. Underground testing, which typically retains the radioactive material underground, was conducted between 1964 and 1989. The collective doses to this population from external and internal radiation were estimated to be 260,000 and 200,000 man•rem (2,600 and 2,000 man•Sv), respectively (UNSCEAR 1993).

Australian Test Site Fallout (United Kingdom). The United Kingdom performed a total of 12 nuclear tests at 3 sites in Australia with total explosive yields at each site of 100, 16, and 60 kilotons, respectively. The collective dose delivered to the Australian population was estimated to be 70,000 man•rem (700 man•Sv). In addition, several hundred smaller experiments were performed, resulting in the contamination of hundreds of square kilometers with a total of 24 kg of ^{239}Pu. Potential annual exposures to individuals in these areas, assuming continuous habitation, is estimated to range up to several rem (several hundredths of a Sv) (UNSCEAR 1993).

Lop Nor Test Site Fallout (People's Republic of China). China has performed more than 40 nuclear weapons tests. Approximately 23 tests were atmospheric; the last atmospheric test was performed on October 16, 1980 and the fallout was measured worldwide. The remaining tests have been performed underground; the most recent underground test occurred on August 17, 1995. All Chinese nuclear testing occurs at the Lop Nor site, located in the Xinjian region in northwest China. China has not allowed independent assessments of the ecological or health impacts of its testing program; however, increased

mortality rates due to fallout of radioactive materials have been reported by a political advocacy group in neighboring eastern Turkestan (Eastern Turkestan Information Bulletin 1996). Both the data and the claims are unsubstantiated.

6.7.3.2 Underground Testing

Underground testing refers to the detonation of nuclear bombs below the earth's surface. About 1,400 underground nuclear tests have been performed worldwide, with a total explosive yield of 90 Mt. The frequency of underground testing increased dramatically after the 1963 signing of the Limited Test Ban Treaty, which banned atmospheric testing. The nature of underground tests typically causes all the radioactive material produced to be retained underground. However, some radioactive material can be released if the blast penetrates the surface or if inadvertent leaks occur due to ground structure damage or the gradual diffusion of gases. Of the 500 underground tests performed at the Nevada test site, only 32 led to off-site contamination. The total activity of ^{131}I inadvertently released was about 5 PBq (135 kCi), which is about five orders of magnitude lower than that released during atmospheric testing. Based on calculations of theoretical yields, it is estimated that the total release of noble gases from underground testing resulted in a population dose of 500 man•rem (5 man•Sv). Of the noble gases, ^{133}Xe is the predominant radionuclide. It is estimated that the total dose from ^{3}H resulting from underground testing is 0.1 man•rem (0.001 man•Sv) (UNSCEAR 1993).

In addition to military-sponsored nuclear explosions, a series of about 100 test detonations was carried out during the 1960s for the purpose of developing peaceful applications for nuclear explosives, such as building flood prevention reservoirs and interoceanic canals similar to the Panama canal (designated as Project Plowshare). As the benefits were far outweighed by the issues of contamination, the project was subsequently terminated. Of these tests, six were performed at the Nevada test site. The estimated collective dose delivered to the surrounding population (180,000 persons) from one of these tests (Sedan; 104 kt explosion) was estimated to be 300 man•rem (3 man•Sv). As a result of the Schooner cratering experiment carried out in the United States in 1968, tungsten-181 (^{181}Tu) generated from the neutron shield was detected as far away as Europe. The estimated collective dose from this explosion to the population living in the 40º–50º latitude band of the northern hemisphere was estimated to be 2,000 man•rem (20 man•Sv) (UNSCEAR 1993).

6.7.4 Occupational Exposure

Occupational exposure to radiation occurs when workers handle radioactive materials or are exposed to radiation sources (e.g., x rays and radioactive sources). The history of occupational exposure to radioactivity is as old as its use. In the period between the discovery of x rays and the early 1930s, more than 100 radiologists died of skin cancer, anemia, and leukemia, largely because they knew very little about the hazards of radiation and how to protect themselves adequately from it. The frequencies of anemia and noncancerous skin damage were also elevated. The concept of a "tolerance dose" was developed early, based initially upon the levels of exposure that resulted in erythema. Originally, limits of 5 R/month or 0.2 R/day were established, and these limits were successively lowered as the body of knowledge concerning radiation health effects grew. The current limits are 5 rem/year (0.05 Sv/year) total effective dose equivalent; 50 rem/year (0.5 Sv/year) for the sum of deep-dose equivalent (from external radiation) and committed dose equivalent (from internal radionuclides) to any individual organ or tissue other than the lens of the eye; 15 rem/year (0.15 Sv/year) shallow dose equivalent to the skin or to any extremity. While most exposure is external, internal exposure occurrs in several occupations, such as radium dial painters, powerplant workers, uranium miners, radiopharmaceutical manufacturers, and nuclear medicine support staff.

In the early 1900s, it was discovered that radium, when mixed with zinc sulfide causes the zinc sulfide to glow. This discovery spurred the development of radioluminescent paints, which consists of a mixture of finely powdered radium salt and zinc sulfide crystals in an appropriate volatile vehicle. This paint was used in the manufacture of dial faces, wristwatches, static eliminators, emergency exit signs, electron tubes, and educational products. In 1924, bone damage that looked like phosphorus poisoning was observed in radium dial painters employed at a northern New Jersey plant, and later it was determined to be bone cancer caused by radium. It was determined that the young women were inadvertently ingesting radium due to the practice of lip-pointing the brush tips when painting fine numerals. A group of 24 dial painters ingested approximately 900–1,300 μCi (33–48 MBq) radium during the course of their careers, which resulted in the formation of bone cancers (see Chapter 3 of this toxicological profile) (Eisenbud 1987; Shapiro 1990; UNSCEAR 1993).

Exposure to airborne uranium ore dust occurs in uranium miners and millers, while exposure to airborne elemental uranium or uranium salts occurs in uranium processors. Uranium ore contains other radionuclides including ^{226}Ra, ^{222}Rn, ^{220}Rn, ^{218}Po, ^{214}Po, and ^{210}Po. Radon diffuses from the rock into the mine air, where the radon progeny become attached to particles of dust or moisture and are inhaled into the

lungs. In the 1800s, silver and uranium miners in Europe were dying of a mysterious malady; the illness was diagnosed as intrathoracic malignancy (lung cancer) in 1879. At that time, it was estimated that the life expectancy of these miners was 20 years after entering the occupation. Death rates from lung cancer in these miners were much higher than expected; as early as 1942, the deaths were attributed to radon exposure. It has been estimated that as much as 40% of all lung cancers in miners may be due to exposure to radon and its progeny (Archer et al. 1973a; Gottlieb and Husen 1982; Lubin et al. 1969, 1995; Samet et al. 1984, 1986). Although radon and its transformation products have been implicated as causative agents in miners with lung cancer, it is difficult to isolate the cancer risk that may be specific to the miners' exposure because they were concurrently exposed to other suspected or known carcinogens such as tobacco smoke, silica and other dusts, and diesel engine exhaust fumes (ACHRE 1995; Auerbach et al. 1978; Band et al. 1980; Lundin et al. 1969; Saccomanno et al. 1971, 1976, 1986; Whittemore and McMillan 1983).

A study of 16 male Navajo uranium miners who developed lung cancer between February 1965 and May 1979 found that the mean cumulative radon exposure was 1,140 working level months (WLM) (Gottlieb and Husen 1982). The working level is a measure of airborne concentration of radon progeny. The WLM is a measure of total exposure. It is the product of the concentration, in WL's and the exposure time, in months (1 working month = 170 hrs). One WLM corresponds to an alpha dose to the tracheobronchial epithelium of approximately 1 rad (0.01 Gy). An excess of lung cancer deaths was also found in uranium miners who had worked underground for at least 1 year in the Grants mineral belt area of New Mexico. Mean exposures in these studies ranged from 2.6 to 42 WLM from 1954 to 1966 and from 0.3 to 21.8 WLM from 1967 to 1982 (Acquavella et al. 1985; Samet et al. 1986). A National Institutes of Health study (NIH 1994) summarized cumulative WLM for several mining cohorts and Colorado miners had the highest average WLM of 807 (follow-up period 1950–1987). Exposed New Mexico miners had an average WLM estimate of 110 and non- U.S. miners ranged from an average WLM of 7 to 370. It should be noted that, in several of these studies, exposure to dust and cigarette smoke was also found to be related in varying degrees to the incidence of cancer.

With the discovery of fission and the development of particle accelerators (Cockcroft-Walton, Van de Graaff generator, cyclotron), numerous new radionuclides and new elements could be readily produced. The number of users and frequency of radionuclide use are both steadily increasing.

Other professions in which workers receive elevated radiation doses include: commercial airline personnel (pilots and flight attendants), military pilots, astronauts, industrial and nuclear power plant workers, radiographers, and dental and medical personnel. A person flying cross-country receives about

5 mrem (0.05 mSv) per flight due to the increased levels of cosmic radiation associated with the increase in elevation; it has been estimated that pilots and flight attendants receive an annual dose that is approximately 160 mrem (1.6 mSv) higher than that of the average population. Astronauts are exposed to intense radiation emanating from solar flares, the earth's radiation belts, and ambient cosmic radiation. The average radiation doses for crews of the Apollo missions (5–12 days/mission) were 0.16–1.14 rad (0.0016–0.0114 Gy); the average doses for the Skylab missions, which lasted 20–90 days, were 1.6–7.7 rad (0.016–0.77 Gy). These high doses of radiation require attention if people begin living in the environments of outer space (space stations, interplanetary travel, etc.). The processing and blending of LPG tends to enhance radon concentrations, and the long-lived radon daughters (^{210}Pb and ^{210}Po) tend to accumulate inside LPG processing machinery, resulting in a possible risk of exposure to maintenance workers. A nuclear power plant worker averages 300 mrem (3 mSv) additional dose per year, resulting in doses about 80% higher than the average population (DOE 1996; Eisenbud 1987).

6.8 ADEQUACY OF THE DATABASE

The database is considered to be adequate for use as the basis for radiation safety standards.

6.9 CONCLUSIONS

The issue of radiation exposure is a matter of interest to the general public; however, radiation exposure is inevitable as it is a natural part of the environment. Indeed, radioactive materials have always existed around and even within us. While the risk of exposure to radiation from man-made sources exists, with the exception of locally high exposures, the average individual dose received from man-made radiation is small compared to that received from natural sources. When assessing the risks associated with a radiation exposure, one must weigh the potential benefits (e.g., gain in quality of life related to medical diagnoses and treatments) against the potential detriments (acute radiation sickness, cancer risk) associated with the exposure. Conversely, in situations presenting minimal risks of exposure to radiation and radioactive materials, one may also compare the potential risks associated with the use of alternatives. For example, in the case of nuclear power versus power from fossil fuels, one may want to weigh the risk of exposure to coal dust, radioactive materials, combustion products , and waste materials associated with coal power versus the risk of radiation exposure from nuclear power production and waste disposal. The regulations concerning radiation exposure limitations are based upon the studies and recommendations of numerous scientific organizations to ensure the health of occupational workers and the public.

7. REGULATIONS

Because of the potential for ionizing radiation to cause deterministic (acute radiation syndrome, cataracts) and nondeterministic (cancer) health effects in exposed individuals, safe dose guidelines and regulations have been established for both external radiation exposure and radionuclides in air and water by a number of international and national agencies. International and national regulations and guidelines pertinent to human exposure to ionizing radiation are summarized in Table 7-1. Those that protect against deterministic effects are based on identified acute thresholds doses for those effects, with a reduction to protect sensitive populations and provide safety margins that account for uncertainties. Those that protect against nondeterministic effects use the observed frequencies with which those effects occur at high doses, account for uncertainties that may exist, and assume a linear dose-effect relationship to calculate the doses at which the effects would be presumed to occur at some acceptable frequency, such as the range of 10^{-4} to 10^{-6} which EPA often considers. This proportionality assumes a linear no threshold (LNT) dose effect curve. During the last decade, there have been reductions in LNT-based public radiation dose limits and site cleanup levels that have increased the scope and cost of medical, occupational, and environmental radiation protection efforts. Some recent studies found a reduction in health effects when the dose was delivered at lower dose rates, indicating a potential application to future protection guidelines and regulations.

An MRL of 0.004 mSv (0.4 rem) has been derived for acute-duration external exposure (14 days or less), based on the developmental studies of Schull et al. (1988) and the IQ studies of Burt (1966).

An MRL of 0.001 Sv/yr (0.1 rem/yr) above background has been derived for chronic-duration external exposure (365 days or more) to radiation based on information that identified radiation doses that have not been reported to have detrimental effects on humans (BEIR V 1990).

The health effects of radiation have been recognized since early in the twentieth century, and by 1928 the International X-Ray and Radium Protection Committee (now the International Commission on Radiological Protection [ICRP]) was established. In the United States, a year later, the Advisory Committee on X Ray and Radiation Protection, now called the National Council on Radiation Protection and Measurements (NCRP), was formed. The NCRP was chartered in 1964 by the U.S. Congress to: (1) disseminate information of public interest and recommend radiation levels to protect the public, (2) support cooperation among organizations concerned with radiation protection, (3) develop basic concepts

about radiation protection, and (4) cooperate with the ICRP and the International Commission on Radiation Units and Measurements. Even though the NCRP is a nongovernmental organization, it provides recommendations that guide the establishment of federal radiation policies, agency requirements, and statutory laws. Through the governmental agencies that rely on NCRP recommendations, the work of this organization has a significant impact on the many activities in the United States involving the use of radiation and radioactive materials.

In the United States, the Environmental Protection Agency (EPA) sets radiation safety policy and basic safety standard. The execution of this policy is assigned to the various regulatory agencies, including the EPA itself, for application to the specific activities that they regulate. The U.S. Nuclear Regulatory Commission (USNRC), an independent government agency, regulates commercial nuclear power reactors; research/test/training reactors; fuel cycle facilities; and the transport, storage and disposal of nuclear materials and waste (USNRC 1997b). The EPA is responsible for protecting the public and the environment and for clean up of radioactively contaminated sites (EPA 1997). The Mine Safety and Health Administration (Department of Labor) is responsible for protecting miners from exposure to radon and its daughters and gamma rays in underground or surface mines (MSHA 1997). The Food and Drug Administration (FDA) develops standards for equipment that emits ionizing radiation, such as radiographic and fluoroscopic equipment (FDA 1997), radioactive material concentrations in food (FDA 1998), and medical devices used in radiation therapy (FDA 1997).

A mammogram device, for example, uses low-dose x rays to produce a radiographic image of breast tissue. Unfortunately, mammograms are among the most difficult radiographic images to read. To reduce the chance of false negative and false positive diagnoses, the image must be of high quality (FDA 1997). Senate hearings on breast cancer held in 1992 found a wide range of problems with mammography practices in the United States. In response to these issues and to the growing incidence of breast cancer and its associated mortality rate, the U.S. Congress enacted the Mammography Quality Standards Act (MQSA). The enactment of the MQSA in 1992 was a statutory means of certifying and inspecting mammography facilities. Regulations established by the FDA to implement the MQSA ensured that only facilities accredited by an approved accreditation body and certified by the Secretary of Health and Human Services would lawfully continue to operate after October 1, 1994. In order to meet the October deadline, however, the MQSA needed to be amended and the process for issuing standards for facilities and the standards to be met by the accrediting bodies needed to be shortened. The

amendments gave the FDA the authority to issue interim regulations, which were published on December 21, 1993 (FDA 1997, 1999a, 1999b). Final regulations for the MQSA, published on October 28, 1997, mandated that facilities would incorporate new requirements into their programs by April 28, 1999, the effective date for most of the regulations. Regulations concerning equipment will become effective on October 28, 2002 (FDA 1999b). Except for the Department of Veterans Affairs, all mammography facilities that produce, process, or interpret mammograms must meet the requirements of the MQSA. In order to keep the basic safeguards in place beyond the year 2000, the Mammography Quality Standards Reauthorization Act of 1998 was passed by Congress on October 9, 1998 (U.S. Congress 1998). The FDA recently announced the availability of its guidance document, *Compliance Guidance: The Mammography Standards Act Final Regulations Document #1*, which is intended to assist mammography facilities in meeting the MQSA final regulations (FDA 1999a).

The FDA recently updated its guidance document that presents recommended action levels for radionuclides in foods, both domestic and imported (FDA 1998). These derived intervention levels (DILs) are estimated levels in food that could lead to individuals receiving a radiation equivalent dose equal to the FDA protection action guide (PAG) that is set as the more limiting of either 0.5 rem (5 mSv) for committed effective dose or 5 rem (50 mSv) committed dose equivalent to any individual tissue or organ. Table 7-4 presents the most restrictive food DILs.

Transport of radioactive materials is regulated by the Department of Transportation (DOT) in conjunction with the USNRC. Coordinating government emergency response to accidents involving radioactive materials is the responsibility of the Federal Emergency Management Administration (FEMA).

National regulations governing the occupational exposure to ionizing radiation include USNRC regulations (10CFR20), EPA standards for uranium and thorium mills (40 CFR 192), Occupational Safety and Health Administration (OSHA) standards for ionizing radiation (29 CFR 1910.1096), the Department of Energy (DOE) standards for occupational radiation protection (10 CFR 835), and MSHA's radon and gamma ray standards (60 FR 33719). National regulations concerning general population exposure to radiation have been developed by the EPA and USNRC based on the dose limit recommendations of the ICRP (ICRP 1997) and the NCRP (NCRP 1993).

Currently there are 29 "NRC Agreement States." An agreement state is any state that has entered into an agreement with the USNRC under Section 274 of the Atomic Energy Act of 1954, as amended. The USNRC relinquishes to these states the majority of its regulatory authority over source, by-product, and special nuclear material in quantities not sufficient to form a critical mass. However, the regulation of nuclear reactors is under USNRC jurisdiction. In the remaining states, USNRC still handles all of the inspection, enforcement, and licensing responsibilities. States can regulate exposure to workers from electronic sources, as well as from naturally occurring and accelerator-produced radioactive materials. State regulations for ^{226}Ra and strontium isotopes are listed in Tables 7-2 and 7-3, respectively.

The basic philosophy of radiation safety is to minimize unnecessary radiation exposure. The specific objectives of radiation safety guidance as stated by NCRP are (1) to prevent the occurrence of severe radiation-induced deterministic (nonstochastic) disease, and (2) to limit the risk of the nondeterministic (stochastic) effects (fatal cancer, and genetic effects) to a reasonable level compared with nonradiation risks and in relation to societal needs, benefits gained, and economic factors. In addition to regulations that set upper limits on radiation dose, the concept of ALARA (As Low As Reasonably Achievable) was introduced to ensure that work place endeavors resulting in exposures to radiation provide sufficient benefits which offset any potential detriment they cause (ACGIH 1998). The goal is not to eliminate all radiation exposure, which would not be possible, but instead to strive for an appropriate balance between protection of public health and reasonable costs (economic, social, etc.) while maintaining desirable dose limits. The American Conference of Governmental Industrial Hygienists (ACGIH) has adopted the occupational exposure guidance of the ICRP (ACGIH 1998). The values used by ACGIH as guidelines for exposure to radiation are given in Table 7-1.

The USNRC has set dose limits for individual members of the public of 0.1 rem/year, 5 rem/year for occupationally exposed workers, and 0.5 rem (0.005 Sv) during the gestation period to the fetus of a pregnant worker (USNRC 1996). More specific information on regulations pertaining to ionizing radiation exposure can be found in the references listed in Table 7-1 of this profile.

Table 7-1. Regulations and Guidelines Applicable to Ionizing Radiation

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
a. Occupational			
ICRP	Whole Body	10 rem/5 years[a] not to exceed 5 rem/year	ICRP 1991
	Equivalent Dose to Lens of Eye	15 rem/year	
	Equivalent Dose to Skin, Hands and Feet	50 rem/year	
	Annual Limits of Intake	$\frac{2\ \text{rem}}{E\ (50)\ \text{Bq}^{-1}}$	
b. General Population			
ICRP	Effective dose limit and, if needed, higher values provided that the annual average over 5 years does not exceed this limit	0.1 rem/year	ICRP 1991
	Equivalent dose limit		
	lens of eye	1.5 rem/year	
	skin, hands and feet	5 rem/year	
	woman's abdomen	0.2 rem	
NATIONAL			
Regulations:			
a. Air			
DOE	Derived Air Concentrations	Yes	63 FR 59662 (10 CFR 835.209) DOE 1998
EPA	Hazardous Air Pollutant; radionuclides (including radon)	Yes	CAA Amendments, Title III, Section 112 (b) U.S. Congress 1990
	National Emissions Standards for Radon Emissions from Underground Uranium mines—effective dose equivalent for the public	10 mrem/year	40 CFR 61, Subpart B EPA 1989a
	National Emission Standards for Emissions of Radionuclides Other Than Radon from Department of Energy Facilities	Yes	40 CFR 61, Subpart H EPA 1989d
	National Emissions Standards for radionuclide Emissions from Facilities Licensed by the Nuclear Regulatory commission and Federal Facility not Covered by Subpart H	Yes	40 CFR 61, Subpart I EPA 1996a
	National Emission Standards for Radionuclide Emissions from Elemental Phosphorus Plants	2 Ci/year[b]	40 CFR 61, Subpart K EPA 1991
	National Emissions Standards for Radon Emissions from Phosphogypsum Stacks—inactive stacks	20 pCi/m^2	40 CFR 61, Subpart R EPA 1992
	National Emission Standards for Radon Emissions from the Disposal of Uranium Mill Tailings—Radon-222 emissions to the ambient air from non-operational piles	20 pCi/m^2-s of radon	40 CFR 61, Subpart T EPA 1994

Table 7-1. Regulations and Guidelines Applicable to Ionizing Radiation (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Test Methods		40 CFR 61, Appendix B
	Test method for measuring radionuclide emissions from stationary sources	Method 114	EPA 1996b
	Monitoring for radon-222 emissions	Method 115	
	Methods for Estimating Radionuclide Emissions	Yes	40 CFR 61, Appendix D EPA 1989c
	Compliance Procedures Methods for Determining compliance with [40 CFR 61], Subpart I	Yes	40 CFR 61, Appendix E EPA 1989b
OSHA	Toxic and Hazardous Substances—ionizing radiation	Yes	29 CFR 1910.1096 OSHA 1996a
	Safety and Health Regulations for Construction	Yes	29 CFR 1926.53 OSHA 1996b
b. Water:			
EPA	Maximum Contaminant Levels for Radium-266, Radium-228, and Gross Alpha Particle Radioactivity in Community Water Systems		40 CFR 141.15 EPA 1976a
	Combined radium-266, and radium-228	5 pCi/L	
	Gross alpha particle activity; including radium-226, but excluding radon and uranium	15 pCi/L	
	MCL for beta particles and photon activity	0.004 rem/year	40 CFR 141.16 EPA 1976b
	Average Annual Concentrations Assumed to Produce Total Body or Organ Dose of 4 mrem/yr		
	Tritium (total body)	20,000 pCi/L	
	Strontium-90 (bone marrow)	8 pCi/L	
	Monitoring frequency for radioactivity in community water systems	Yes	40 CFR 141.26 EPA 1976c
	National Primary Drinking Water Regulations; Analytical Methods for Radionuclides (final rule and proposed rule)	Yes	62 FR 10168 (40 CFR 141.25) EPA 1997
	Class V Injection Wells Underground Injection Control Regulations, revisions; proposed rule	Yes	63 FR 40586 (40 CFR 144, 145, and 146) EPA 1998b
c. Other: Occupational			
DOE	Exposure Limits for General Employees		63 FR 59662 DOE 1998 and 10 CFR 835 DOE 1993
	Total effective dose	5 rem/year (0.05 Sv)[c]	
	Deep dose equivalent plus Committed dose to any organ or tissue other than lens of the eye	50 rem/year (0.5 Sv)	
	Eye lens dose equivalent	15 rem/year (0.15 Sv)	

Table 7-1. Regulations and Guidelines Applicable to Ionizing Radiation (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Shallow dose equivalent to skin or other extremity	50 rem/year	
	Planned Special Exposures	Yes	
	Limits for the embryo/fetus	0.5 rem (conception to birth)	
	Limit for minors (total effective dose equivalent)	0.1 rem (0.001 sievert) per year	
	Limit for members of the public in a controlled area (total effective dose equivalent)	0.01 rem per year	
	Requirements for Individual Monitoring	Yes	
DOT	General Requirements for Shipments and Packaging—Class 7 (Radioactive Material)		49 CFR 173, Subpart I DOT 1997
	Scope and definitions	Yes	
	Packaging design requirements	Yes	
	Table of activity limits	Yes	
	Requirements for determining A_1 and A_2 values for radionuclides and for the listing of radionuclides on shipping papers and labels	Yes[d]	
	Table of A_1 and A_2 values	Yes	
	Radiation level limitations external surface radiation level not to be exceeded under conditions normally incident to transportation	2 mSv/hour (200 mrem/hour) and the transport Index (TI) is less than 10	
	-packages exceeding the radiation level limit		
	transport by exclusive use shipment	Yes	
	conditional maximum radiation level	10 mSv/hour (1000 mrem/hour)	
	Outer surfaces of vehicle including top and underside	2 mSv/hour (200 mrem/hour)	
	Any point 2 meters (6.6 feet) from the outer lateral surfaces, excluding top and underside	0.1 mSv/hour (10 mrem/hour)	
	Any normally occupied space except carriers operating under the provisions of a state or federally regulated radiation protection program and wearing radiation dosimetry devices	0.02 mSv/hour (2 mrem/hour)	63 FR 48568 (49 CFR 173) DOT 1998

Table 7-1. Regulations and Guidelines Applicable to Ionizing Radiation (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
FDA	Radiation Protection Program Requirements		63 FR 48566 (49 CFR 172, et al.)
	Hazardous materials table, special provisions, hazardous materials communications, emergency response information and training requirements (49 CFR 172, Subpart I)	Removed	DOT 1998
	Carriage by rail (49 CFR 174.705)	Removed	
	Carriage by aircraft (49 CFR 175.706)	Removed	
	Carriage by vessel (49 CFR 176.703)	Removed	
	Carriage by public highway (49 CFR 177.827)	Removed	
	Carriage by Public Highway		49 CFR 177.842
	Requirements for class 7 (radioactive material)	Yes	DOT 1995
	Total transport index number	50	
	Irradiation in the Production, Processing and Handling of Animal Feed and Pet Food		
	Ionizing radiation for treatment of laboratory animal diets		21 CFR 579.22 FDA 1993a
	-energy source	Gamma rays from sealed units of the radionuclides cobalt-60 or cesium-137	
	-limit for electrons generated	Not to exceed 10 million electron volts	
	-single treatment for microbial disinfection of bagged complete diets for laboratory animals (mice, rats, hamsters, rabbits, and guinea pigs)	Absorbed dose not to exceed 50 kGy (5 Mrad)	
	Ionizing radiation for the treatment of poultry feed and poultry feed ingredients		21 CFR 579.40 FDA 1995
	-energy source	Gamma rays from sealed units of cobalt-60	
	-single treatment poultry feed or feed ingredients that do not contain drugs for rendering them salmonella negative	2.0 kGy (0.2 Mrad) minimum dose; 25 kGy (2.5 Mrad) maximum dose	

Table 7-1. Regulations and Guidelines Applicable to Ionizing Radiation (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Performance Standards For Ionizing Radiation Emitting Products		
	Cold-cathode gas discharge tubes	Yes	21 CFR 1020.20 FDA 1973b
	Diagnostic X-ray systems and their major components	Yes	21 CFR 1020.30 FDA 1994a
	Radiographic equipment	Yes	21 CFR 1020.31 FDA 1993b
	Fluoroscopic equipment	Yes	21 CFR 1020.32 FDA 1994b
	Computed tomography (CT) equipment	Yes	21 CFR 1020.33 FDA 1991
	Cabinet X-ray systems	Yes	21 CFR 1020.40 FDA 1974
MSHA	Radon daughters, Monitoring required 1/3 months Monitoring required 1/week Uranium Mines; monitoring monthly	 >0.1 WL >0.3 WL 0.1 WL	MSHA 1997
	Gamma Radiation Dosimeters for All Employees and Records of Cumulative Individual Exposure	>0.002 roentgens/hr	
NRC	Limits for Adults Total effective dose	 5 rem/year	10 CFR 20, Subpart C USNRC 1991
	Effective deep dose equivalent plus committed dose to any organ or tissue other than lens of the eye	50 rem/year	
	Eye lens dose equivalent	15 rem/year	
	Skin or other extremity; shallow dose	50 rem/year	
	Dose Limit for Minors	10% of annual dose limit for adult workers	
	Dose Limit to an Embryo/fetus [of pregnant female]	0.5 rem	
	Annual Limits On Intake (ALIs) and Derived Air Concentration (DACs) of Radionuclide for Occupational Exposure	Yes	10 CFR 20, Appendix B USNRC 1993
	Quantities of Licensed Material Requiring Labeling	Yes	10 CFR 20, Appendix C USNRC 1995
	Physical Protection for Spent Nuclear Fuel and High-level Radioactive Material	Yes	63 FR 29655 USNRC 1998
d. Other : General Population			
EPA	Hazardous Waste Injection Restrictions Waste specific prohibitions, newly listed and identified waste -radioactive wastes mixed with newly identified D004-D011 waste	Effective May 26, 2000	63 FR 28556 (40 CFR 148.18) EPA 1998a

Table 7-1. Regulations and Guidelines Applicable to Ionizing Radiation (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Environmental Standards for Uranium Fuel Cycle: Standards for Normal Operation		40 CFR 190, Subpart B EPA 1977
	Annual dose not to exceed:		
	-whole body	≤ 25 mrem	
	-thyroid	≤ 75 mrem	
	-any other organ	≤ 25 mrem	
	Total quantity of radioactive materials entering the general environment		
	-krypton-85		
	-iodine-129	50,000 Ci	
	-plutonium-239 combined with other alpha-emitting transuranic radionuclides with half-lives greater than one year	5 mCi 0.5 mCi	
	Environmental Radiation Protection Standards for Management and Disposal of Spent Nuclear Fuel, High-level and Transuranic Radioactive Wastes		40 CFR 191 EPA 1993a
	Environmental standards for management and storage— applicability and definitions	Yes	
	-whole body	25 mrem	
	-thyroid	75 mrem	
	-other critical organs	25 mrem	
	Environmental standards for disposal— applicability, definitions, containment and individual protection requirements	Yes	
	-release limits for containment requirements	Per 1000 MTHM[e]	
	Americium-241 or -243	100	
	Carbon-14	100	
	Cesium-135 or-137	1,000	
	Iodine-129	100	
	Neptunium-237	100	
	Plutonium-239, -240, or -242	100	
	Radium-226	100	
	Strontium-90	1,000	
	Technetium-99	10,000	
	Thorium-230 or -232	10	
	Tin-126	1,000	
	Uranium-233, -234, -235, -236, or -238	100	
	Any other alpha-emitting radionuclide with a half-life greater than 20 years	100	
	Any other radionuclide with a half-life greater than 20 years that does not emit alpha particles	1,000	

Table 7-1. Regulations and Guidelines Applicable to Ionizing Radiation (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Environmental Standards for Ground-water Protection		
	-applicability and definitions	Yes	
	-disposal standards; levels of radioactivity in any underground drinking water source	Not to exceed limits specified in 40 CFR 141	
	Land Disposal Restrictions, Effective dates of surface disposed wastes —mixed radioactive/newly identified waste codes D003-D011	May 26, 2000	63 FR 28556 (40 CFR 268, App. VII) EPA 1998a
	F035; mixed with radioactive waste	May 12, 1999	
	Treatment Standards; radioactive high level wastes (nonwastewaters) generated during the reprocessing of fuel rods—Hazardous waste codes D002, D004-D011	HLVIT[f]	
	Standards for Control of Residual Radioactive Material from Inactive Uranium Processing Sites	Yes	40 CFR 192, Subpart A EPA 1995a
	Definitions	Yes	
	Standards (for control of residual radioactive materials and their listed constituents)	Yes	
	Maximum concentration of constituents for ground-water protection	30 pCi/L	
	Standards for Cleanup of Land and building Contaminated with Residual Radioactive Materials from Inactive Uranium Processing Sites	Yes	40 CFR 192, Subpart B EPA 1995b
	Guidance for Implementation	Yes	40 CFR 192, Subpart C EPA 1995c
	Additional Listed Constituents (replacement list of constituents for screening purposes)	Combined ^{234}U and ^{238}U	
	Standards for Management of Uranium Byproduct Materials Pursuant to Section 84 of the Atomic Energy Act of 1954, as Amended	Yes	40 CFR 192, Subpart D EPA 1993b
	Standards (for application during processing operations and prior to the endo of the closure period—concentration limits	5 pCi/L	

Table 7-1. Regulations and Guidelines Applicable to Ionizing Radiation (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Standards for Management of Thorium Byproduct Materials Pursuant to Section 84 of the Atomic Energy Act of 1954, as Amended	Yes	40 CFR 192, Subpart E EPA 1993c
FDA	Irradiation in the Production, Processing and Handling of Food		
	Sources of radiation used for inspection of food, inspection of packaged food and for controlling food processing	Yes	21 CFR 179.21 FDA 1996a
	General provisions for food irradiation		21 CFR 179.25 FDA 1986
	Ionizing radiation for the treatment of food		21 CFR 179.26 FDA 1997
	-energy source	gamma rays from seal units of radionuclides ^{60}Co or ^{137}Cs	
	-limit for electrons generated	10 million electron volts	
	-limit for X-rays	5 million electron volts	
	-control of *Trichinella spiralis* in pork carcasses of fresh	0.3 kGy to 1 kGy (30 to 100 krad)	
	-growth and maturation inhibition of fresh food	Not to exceed 1 kGy (100 krad)	
	-disinfestation of arthropod pests in food	Not to exceed 1 kGy (100 krad)	
	-microbial disinfection of dry or dehydrated enzyme preparations (including immobilized enzymes)	Not to exceed 10 kGy (1 Mrad)	
	-microbial disinfection of selected dry or dehydrated aromatic vegetables substances when used as ingredients in small amounts solely for flavoring or aroma	Not to exceed 30 kGy (3 Mrad)	
	-control of food-borne pathogens in fresh or frozen, uncooked poultry products	Not to exceed 30 kGy (3 Mrad); packaging shall not exclude oxygen	
	-sterilization of frozen, packaged meats used solely in the National Aeronautics and Space Administration space flight program	Minimum dose 44 kGy (4.4 Mrad)	

Table 7-1. Regulations and Guidelines Applicable to Ionizing Radiation (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	-control of food-borne pathogens in and for extension of shelf-life of refrigerated or frozen, uncooked meat, meat byproducts or meat food products	Not to exceed 4.5 kGy (450 krad) maximum for refrigerated products; not to exceed 7.0 kGy (700 krad) maximum for frozen products	
	Radio-frequency radiation for the heating of food, including microwave frequencies	Yes	21 CFR 179.30 FDA 1977a
	Ultraviolet radiation for the processing and treatment of food	Yes	21 CFR 179.39 FDA 1977b
	Pulsed light for the treatment of food -radiation sources	xenon flashlamps; emitting broad band radiation of 200 to 1,000 nanometers	21 CFR 179.41 FDA 1996b
	-pulse duration	2 milliseconds	
	-total cumulative treatment for control surface microorganisms	12 Joules/cm^2	
	Packaging materials for use during the irradiation of prepackaged foods	Yes	21 CFR 179.45 FDA 1996c
	Performance Standards for Ionizing Radiation Emitting Products Television receivers	Yes	21 CFR 1020.10 FDA 1973a
NRC	Radiation Dose Limits For Individual Members of the Public Total effective dose equivalent to individual	0.1 rem/year	10 CFR 20.1301 USNRC 1997b
	Dose from external sources	0.002 rem/hour	
	Effluent Concentrations and Concentrations for Releases to Sewerage	Yes	10 CFR 20, Appendix B USNRC 1993
USDA	Hawaiian Fruits and Vegetables	Yes	7 CFR 318.13 to .13-4f USDA 1997
Guidelines:			
a, Water	MCLG for beta particles and photon activity	none	EPA 1998c
	MCLG for gross alpha particle activity	none	
	MCLG for ^{226}Rn and ^{228}Rn combined	none	
ACGIH	Effective Dose Any single year Averaged over 5 years; per year	 50 mSv (5 rem) 20 mSv (2 rem)	

Table 7-1. Regulations and Guidelines Applicable to Ionizing Radiation (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
b. Other: Occupational			
	Annual Equivalent Dose		ACGIH 1998
	Lens of the eye	150 mSv (15 rem)	
	Skin	500 mSv (50 rem	
	Hands and feet	500 mSv (50 rem)	
	Embryo-Fetus exposures once pregnancy is known		
	Monthly equivalent dose[g]	0.5 mSv (0.05 rem)	
	Dose to surface of women's abdomen (lower trunk); for the remainder of the pregnancy	2 mSv (0.2 rem)	
	Intake of radionuclide	1/20 of annual limit on intake (ALI)	
	Radon Daughters	4 working level months (WLM)	
DOT	General public	2 mrem/hr	DOT 1996
	Cumulative dose, individual	100 mrem/week 500 mrem/year	
EPA[h]	Effective dose equivalent		EPA 1987
	Adult	5 rem/year	Fed Reg Part II
	Lens of the eye	15 rem/year	
	All other organs	50 rem/year	
	Juvenile workers(<18 years old)	0.5 rem/year	
	Pregnant workers	0.5 rem/gestation period	
	Effective dose equivalent limit (stochastic limits)	5 rem/year not to exceed 1 rem x age of individual	NCRP 1993
	Equivalent dose limit (nonstochastic limits)		
	Skin, hands, and feet	5 rem/year	
	Lens of the eyes	15 rem/year	
	All other organs	50 rem/year	
	Guidance: Cumulative exposure	1 rem x age in years	
	Annual Reference Levels of Intake (ARLI)	2 rem /yr (20 mSv/yr)[i]	
c. Other: General Population			
FDA	Accidental Radioactive Contamination of Human Food and Animal Feeds: Recommendations for State and Local Agencies	Yes	FDA 1998
	Protective action guides for tissue or organ; ingestion pathway		
	Committed effective dose equivalent	5 mSv (0.5 rem)	
	Committed dose equivalent	50 mSv (5 rem)	

Table 7-1. Regulations and Guidelines Applicable to Ionizing Radiation (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
NCRP[h]	Effective dose equivalent limit		NCRP 1993
	Continuous or frequent exposure	0.1 rem/year	
	Infrequent exposure	0.5 rem/year	
	Lens of the eye, skin, and extremities	5 rem/year	
	Embryo-fetus	0.05 rem/month	
	Remedial action recommended		NCRP 1987
	Effective dose equivalent[j]	>0.5 rem/year	
	Exposure to radon and its decay products	>2 WLM/year	
	Education and Training Exposures		
	Effective dose equivalent limit	0.1 rem/year	
	Dose equivalent limit in a month	0.05 rem	
	Negligible Individual Risk Level		
	Effective dose equivalent per source or practice	0.01 rem/year	
STATE			
Regulations and Guidelines: Public Protection			
a. Virginia	Acceptable ambient air concentrations Radionuclides	8.00 $\mu g/m^3$ (24 hours)	NATICH 1992

[a] Rem means the unit of dose equivalent from ionizing radiation to the total body or any internal organ or organ system. A "millirem (mrem)" is 1/1000 of a rem.
[b] Curie (CI) means the quantity of radioactive material producing 37 billion nuclear transformations per second; 1 millicurie [mCi] = 0.001 Ci, 1 picocurie [pCi] = 10^{-12} Ci).
[c] Unless otherwise specified, the radiological unit Sievert (Sv) is provided in the DOE regulations parenthetically and is not authorized for use in the documents required for record keeping. The quantities used in the records must be clearly indicated in special units of curie, rad, or rem, including multiples and subdivisions of these units. 10 mSv = 1 rem.
[d] A_1 means the maximum activity of special form Class 7 (radioactive) material permitted in a Type A package. A^2 means the maximum activity of class 7 material, other than special form, low specific activity material or surface contaminated objects permitted in a Type A package. See 49 CFR 173.403 for more detailed definitions.
[e] Values represent cumulative releases to the accessible environment for 10,000 years after disposal.
[f] HLVIT means vitrification of high level mixed radioactive wastes in units in compliance with all applicable radioactive protection.
[g] Sum of internal and external exposure but excluding doses from natural sources as recommended by the NCRP.
[h] Sum of external and internal exposures.
[I] The ARLI is the occupational, annual intake of radionuclides in Bq, averaged over 5 years, that equal a 50-year committed effective dose equivalent of 20 mSv.
[J] Including background but excluding internal exposures.

ACGIH = American Conference of Governmental Industrial Hygienists; CAA = Clean Air Act; DOE = Department of Energy; DOT = Department of Transportation; EPA = Environmental Protection Agency; ICRP = International Commission on Radiological Protection; kGy = KiloGray; krad = Kilorad; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; MSHA = Mine Safety Health Administration; Mrad = Megarad; mSv = Millisievert; MTHM = Metric Tons of Heavy Metal; NATICH = National Air Toxics Information Clearing House; NCRP = National Council on Radiation Protection; NRC = Nuclear Regulatory Commission (USNRC); OSHA = Occupational Safety and Health Administration; WL = working level; WLM = working level month

Table 7-2. Regulations and Guidelines Applicable to ^{226}Ra

Agency	Description	Information	References
STATE			
a. Regulations:			
	Water Quality Criteria: Human Health		CELDs 1994
AK	Drinking water	5 pCi/L	
AL	Drinking water	5 pCi/L	
AZ	Drinking water	5 pCi/L	
CA	Drinking water	5 pCi/L	
CO	Drinking water	5 pCi/L combined	
CT	Drinking water	5 pCi/L	
DE	Drinking water	5 pCi/L	
FL	Drinking water	5 pCi/L combined	
GA	Drinking water	5 pCi/L	
HI	Drinking water	5 pCi/L	
IA	Drinking water	5 pCi/L	
IN	Drinking water	5 pCi/L	
KY	Drinking water/waste management	5 pCi/L	
MD	Drinking water	5 pCi/L	
ME	Drinking water	5 pCi/L	
MT	Drinking water	5 pCi/L	
NC	Drinking water	5 pCi/L	
ND	Drinking water	5 pCi/L	
NE	Drinking water	5 pCi/L	
NH	Drinking water	5 pCi/L combined	
NM	Drinking water	5 pCi/L	
NY	Drinking water	3 pCi/L	
PR	Drinking water	3 pCi/L	
OH	Drinking water	5 pCi/L	
OK	Drinking water	5 pCi/L	
RI	Drinking water	5 pCi/L	
SC	Drinking water	5 pCi/L	
SD	Drinking water	5 pCi/L	
TN	Drinking water	5 pCi/L	
TX	Drinking water	5 pCi/L	
VA	Drinking water	5 pCi/L	
UT	Drinking water	5 pCi/L	

Table 7-2. Regulations and Guidelines Applicable to ^{226}Ra (continued)

Agency	Description	Information	References
STATE (cont.)			
WA	Drinking water	3 pCi/L	
WV	Drinking water	5 pCi/L	
WY	Drinking water	3 pCi/L combined	
	Water Quality Criteria: Aquatic Life		CELDs 1994
IA	Raw water sources for potable water	5 pCi/L	
MT		None	
NC		5 pCi/L	
ND		5 pCi/L	
NH		5 pCi/L	
PR		3 pCi/L	
WV		5 pCi/L	
WY		5 pCi/L	
	Water Quality Criteria: Agriculture		CELDs 1994
AZ	Private Agriculture	5 pCi/L	
ND	Irrigation	5 pCi/L	
WY	Not specified	5 pCi/L	
	Water Quality Criteria: Recreational		CELDs 1994
ND	Recreational (boating, fishing)	5 pCi/L	
NH	Recreational	3 pCi/L	
WY	Not specified	5 pCi/L	
	Water Quality - Monitoring		CELDs 1994
CA	Drinking water	5 pCi/L	
FL	Drinking water	5 pCi/L	
IA	Drinking water	1 pCi/L	
ID	Drinking water	5 pCi/L	
IL	Drinking water	5 pCi/L	
IN	Drinking water	3 pCi/L	
MA	Drinking water	5 pCi/L	
MD	Drinking water	1 pCi/L	
MI	Drinking water	3 pCi/L	
MO	Drinking water	5 pCi/L	
MT	Drinking water	Yes	
NC	Drinking water	5 pCi/L	
ND	Drinking water	5 pCi/L	

Table 7-2. Regulations and Guidelines Applicable to ^{226}Ra (continued)

Agency	Description	Information	References
STATE (cont.)			
NM	Drinking water	1 pCi/L	
NY	Drinking water	5 pCi/L	
OH	Drinking water	5 pCi/L	
PR	Drinking water	5 pCi/L	
RI	Drinking water	5 pCi/L	
SC	Drinking water	5 pCi/L	
SD	Drinking water	5 pCi/L	
TN	Drinking water	1 pCi/L	
TX	Drinking water	5 pCi/L	
VA	Drinking water	5 pCi/L	
UT	Drinking water	5 pCi/L	
WA	Drinking water	5 pCi/L	
WI	Drinking water	5 pCi/L	
WV	Drinking water	5 pCi/L	
	Groundwater Quality Standards		CELDs 1994
NE	Groundwater	5 pCi/L	
NC	Drinking, potable mineral water	5 pCi/L	
NY	Not specified	3 pCi/L	
PR	Not specified	3 pCi/L	
TN	Not specified	5 pCi/L	
VA	Not specified	5 pCi/L	
WY	Not specified	5 pCi/L	
	Groundwater Monitoring Parameters		CELDs 1994
CA	Hazardous waste facilities	Yes	
CO	Hazardous waste facilities	5 pCi/L	
IN	Public supply	3 pCi/L	
NC	Public supply	5 pCi/L	
NJ	Hazardous waste facilities	5 pCi/L	
NM	Public supply	1 pCi/L	
NY	Hazardous facility	5 pCi/L	
SC	Hazardous waste	5 pCi/L	
TN	Not specified	5 pCi/L	
WI	Hazardous waste	5 pCi/L	

CELDS = Comprehensive Environmental Legislative Database

Table 7-3. Regulations and Guidelines Applicable to Strontium Isotopes

Agency	Description	Information	References
STATE			
a. Regulations:			
	Water Quality Criteria - Human Health		CELDs 1994
AZ	Agricultural, public, aquatic	8 pCi/L	
AL	Drinking water	8 pCi/L	
CA	Drinking water	8 pCi/L	
CO	Drinking water	2 pCi/L	
CT	Drinking water - standard	8 pCi/L	
DE	Drinking water - standard and monitoring	8 pCi/L	
FL	Drinking water	8 pCi/L	
GA	Drinking water	Yes	
HI	Drinking water	8 pCi/L	
IA	Drinking water	8 pCi/L	
ID	Drinking water	8 pCi/L	
IL	Drinking water	8 pCi/L	
IN	Drinking water	8 pCi/L	
	Surface Water Quality Standards		CELDs 1994
CO		8 pCi/L	
	Water Quality Monitoring		CELDs 1994
AL	Drinking water	Yes	
AZ	Drinking water	Yes	
CA	Drinking water	8 pCi/L	
CO	Drinking water	2 pCi/L	
DE	Drinking water	8 pCi/L	
GA	Drinking water	Yes	
HI	Drinking water	Yes	
IA	Drinking water	Yes	
ID	Drinking water	Yes	
IL	Drinking water	8 pCi/L	
IN	Drinking water	Yes	
	Groundwater Quality Standards		CELDs 1994
CO	Groundwater - Public	8 pCi/L	
IN	Groundwater - Drinking	10 pCi/L	

CELDS = Comprehensive Environmental Legislative Database

Table 7-4. FDA Derived Intervention Levels[a] (Bq/kg)

Radionuclide	Age of individual at time of ingestion					
	3 months	1 year	5 years	10 years	15 years	Adult
^{90}Sr	308	362	616	389	160	465
^{131}I	196	167	722	1200	1690	2420
^{134}Cs	1600	2190	1940	1530	958	930
^{137}Cs	2000	2990	2810	2180	1370	1360
Cs group[b]	1800	2590	2380	1880	1160	1150
^{103}Ru	6770	8410	12200	16400	25000	28400
^{106}Ru	449	621	935	1340	2080	2360
^{238}Pu	2.5	21	17	14	12	10
^{239}Pu	2.2	18	14	13	10	9.8
^{241}Am	2.0	17	13	11	9.1	8.8
Pu+Am group[c]	2.2	19	15	13	9.6	9.3

[a] Derived Intervention Levels (DIL) presented are food concentrations whose consumption would deliver a committed effective dose equivalent equal to the most limiting of the protective action guides (PAGs) developed by FDA

[b] Computed as: (DIL for ^{134}Cs + DIL for ^{137}Cs)/2

[c] Computed as: (DIL for ^{238}Pu + DIL for ^{239}Pu + DIL for ^{241}Am)/3

Source: FDA 1998

8. LEVELS OF SIGNIFICANT EXPOSURE TO RADIATION AND RADIOACTIVE MATERIAL

To help public health professionals and others address the needs of those who are exposed to radiation and radioactive material, the information in this section on ionizing radiation is organized first by route of exposure—inhalation, oral, dermal and external; and then by health effect—death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. The systemic effects are subdivided into respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, and body weight effects.

The data for the observed effects from radiation and radioactive material are presented in the following tables. These tables are not meant to be exhaustive reviews of all of the literature that reports biological effects resulting from exposure to ionizing radiation. It does, however, provide health care professionals, persons exposed (or potentially exposed) to radiation in their occupations, and the general public an overview of the types of effects observed in each category. The tables report no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs), which reflect the actual radiation doses (or concentration of radioactive material) used in the studies. LOAELS have been further 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 radiation sickness 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 radiation doses at which major health effects may 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.

A range of radiological units were used in the studies and these are reported in Tables 8-1 to 8-4. In these studies, some authors reported units of absorbed dose (rad, Gy) or dose equivalent (rem, Sv), while other authors reported effects in terms of units of concentration, transformations (disintegrations) or activity

(μCi/kg or Bq/kg, etc). Conversions between units is possible when given specific information about the exposed animal, organ weights, and the nuclide; however, the specific information required to perform those conversions was, in many cases, not complete or not reported at all. Many of the activities reported in Ci or Bq could not be converted into absorbed dose (rad, Gy) or dose equivalent (rem, Sv) to determine a dose-response relationship. Since these conversions were not practical, the unit information (rad, Gy, rem, Si) with the corresponding NOAEL or LOAEL are listed first under each heading (death, respiratory, gastrointestinal, etc). This information is then immediately followed by the studies that examined end points in terms of concentration or activity (μCi/kg or Bq/kg) for each organ system route of exposure. This provides the reader an opportunity to more clearly observe any dose-response effects resulting from exposure to ionizing radiation, both from an absorbed dose (rad, Gy) aspect as well as from a radionuclide activity (Ci, Bq) perspective.

The significance of the exposure levels shown in Tables 8-1 to 8-4 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. Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of ionizing radiation are also indicated in Tables 8-1 through 8-4.

Estimates of exposure levels posing minimal risk to humans may be of interest to health professionals and citizens alike. Estimates of the acute radiation dose and chronic radiation dose rate that pose minimal risk to humans (Minimal Risk Levels or MRLs) have been made for ionizing radiation. 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 as well as for external exposure. Appropriate methodology does not exist to develop chemical MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are always associated with these techniques. 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.

MRLs have been derived for radiation effects. During the evaluation process, ATSDR examined many factors, including (1) which specific studies would lend themselves to be most suitable for deriving an MRL, and (2) what health effect(s) an MRL should be based upon (cataract formation, reduction in IQ, etc.).

The tables showing Levels of Significant Exposure (LSE) to Radiation and Radioactive Material consist of the following information:

(1) Route of Exposure One of the first considerations when reviewing the toxicity of ionizing radiation using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist, four tables are presented in the document by the four principal routes of exposure, i.e., inhalation, oral, dermal, and external (Levels of Significant Exposure to Radiation and Radioactive Material tables 8-1, 8-2, 8-3 and 8-4, respectively). Not all studies will have data on each route of exposure.

(2) Health Effect The major categories of health effects included in Levels of Significant Exposure to Radiation and Radioactive Material tables 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 table.

(3) Species The test species, whether animal or human, are identified in this column.

(4) Duration/ Frequency of Administration 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.

(5) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. Other systems considered separately in these tables are immunological/lymphoreticular, neurological, reproductive, developmental, genotoxic, and cancer. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems.

(6) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied.

(7) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been arbitrarily 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 endpoint used to quantify the adverse effect accompanies the LOAEL.

(8) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects.

(9) Chemical Form The nuclide, the chemical form (chloride, oxide, etc.) and the type of emission (alpha or beta particle and gamma ray) is indicated in this column.

(10) Reference The complete reference citation is given in chapter 10 of the profile.

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
					Less serious	Serious		
	Death							
1	Rat (Fischer- 344)	20 min				71 rad M	(decr. median survival time in fibrotic vs non-fibrotic rats)	Lundgren et al. 1991 Alpha Particles [239]PuO2
2	Rat (Fischer- 344)	20 min				340 rad F	(decr. median survival time in fibrotic vs non-fibrotic rats)	Lundgren et al. 1991 Alpha Particles [239]PuO2
3	Dog (Beagle)	3-46 min				8,400 rad	(21/33 dogs died-7.5 to 163 d post-exposure)	Hobbs et al. 1972 Beta Particles [90]Y
4	Dog (Beagle)	once				8700 rad	(3/4 died)	Benjamin et al. 1976 Beta Particles [90]Y
5	Dog (Beagle)	once				10,000 rad	(16/16 dogs died 12 to 163 d post exp)	McClellan et al. 1970 Beta Particles [90]Y
6	Dog (Beagle)	<70 min				15,000 rad	(40/96 died <3 yrs post exposure)	Boecker et al. 1988 Beta Particles [91]Y
7	Dog (Beagle)	once				27,000 rad	(14/16 died or were sacrificed due to severe condition within 5 yrs post exposure)	Benjamin et al. 1978 Beta-Gamma Particles [144]Ce

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
					Less serious	Serious		
8	Dog (Beagle)	once				39,000 rad	(1/4 died)	Benjamin et al. 1976 Beta Particles [90]Sr
9	Dog (Beagle)	once				42,000 rad	(2/4 died)	Benjamin et al. 1976 Beta Particles [144]Ce
10	Dog (Beagle)	once				48,000 rad	(9/9 dogs died 143- 410 d post exposure)	McClellan et al. 1970 Beta Particles [144]Ce
11	Monkey (Rhesus)	once				270 nCiM	(5/5 animals died 430- 4334 d after exposure)	Hahn et al. 1987 Alpha Particles [239]PuO2
12	Monkey (Cynomol- gus)	once				1.08 uCiM	(3/12 died)	Brooks et al. 1992 Alpha Particles [239]Pu
13	Mouse (CFW)	10-20 min				21 uCiM	(survival 12% of controls, with median survival of 66 d)	Lundgren et al. 1981 Beta Particles [90]Y
14	Rat (Fischer- 344)	1x/2 mo 1 yr (7x)				32.4 uCi	(29.3-31.9% shortened life span)	Hahn and Lundgren 1992 Beta Particles [144]CeO2

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
					Less serious	Serious		
15	Dog (Beagle)	once				320 uCi	(5 dogs died, 93- 279 d post exposure)	McClellan et al. 1970 Beta Particles [144]Ce
16	Dog (Beagle)	once				320 uCi	(5 dogs died, 93- 279 d post exposure)	McClellan et al. 1970 Beta Particles [144]Ce
17	Dog (Beagle)	once				0.26 uCi/kg	(death in 8/24 dogs over 1125- 2143 d post-exposure)	Hahn et al. 1981 Alpha Particles [238]PuO2
18	Dog (Beagle)	once				0.97 uCi/kg	(51/72 died)	Benjamin et al. 1979 Beta Particles [90]SrCl2
19	Dog (Beagle)	once				1.7 uCi/kg	(27/72 died at 585+ d)	McClellan et al. 1973 Beta Particles [90]SrCl2
20	Dog (Beagle)	once				2.6 uCi/kg	(43/55 died)	Benjamin et al. 1979 Beta Particles [144]CeCl3
21	Dog (Beagle)	once				14 uCi/kg	(21/46 died)	Benjamin et al. 1979 Beta Particles [91]YCl3

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
					Less serious	Serious		
22	Dog (Beagle)	2-22 min				45.9 uCi/kg	(death in 6/66 animals within 32 d)	Gillett et al. 1987a Beta Particles [90]SrCl2
23	Dog (Beagle)	once				74 uCi/kg	(6/72 dogs died at 18-31 d)	McClellan et al. 1973 Beta Particles [90]SrCl2
24	Dog (Beagle)	<70 min				NS	(58/96 died >3 yrs post exposure)	Boecker et al. 1988 Beta Particles [91]Y
	Systemic							
25	Hamster (Syrian)	1-45 min	Resp			40 radM	(radiation pneumonitis in 8%)	Lundgren et al. 1983 Alpha Particles [239]PuO2
26	Hamster (Syrian)	1 yr 7x/yr 1-45 min/x	Resp			220 radM	(radiation pneumonitis in 40% and bronchiolar epithelial hyperplasia in 35%)	Lundgren et al. 1983 Alpha Particles [239]PuO2
27	Dog (Beagle)	once	Resp			3700 rad	(severe radiation pneumonitis and pulmonary fibrosis in 7/144)	Hahn et al. 1981 Alpha Particles [238]PuO2
28	Dog (Beagle)	once	Resp			8700 rad	(pneumonitis, fibrosis, inflammation in 3/4 dogs)	Benjamin et al. 1976 Beta Particles [90]Y

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL				Reference Chemical Form
					Less serious		Serious		
29	Dog (Beagle)	once	Resp				27,000 rad	(pneumonitis and pulmonary fibrosis)	Benjamin et al. 1978 Beta-Gamma Particles [144]Ce
30	Dog (Beagle)	once	Resp				39,000 rad	(dyspnea and cyanosis; pneumonitis and fibrosis in 1/4 dogs)	Benjamin et al. 1976 Beta Particles [90]Sr
31	Dog (Beagle)	once	Resp				42,000 rad	(pneumonitis, fibrosis, inflammation in 2/4 dogs)	Benjamin et al. 1976 Beta Particles [144]Ce
32	Dog (Beagle)	once	Resp		230 rad	(decr. lung capacity & compliance, & incr. respiratory frequency & minute volume)			Muggenburg et al. 1988 Alpha Particles [239]PuO2
33	Rat (Fischer- 344)	20 min	Resp		240 rad	(decr. functional residual capacity and incr. percentage of forced vital capacity, mild septal fibrosis, small focal scars, decr. in lung volume, incr. in connective tissue)			Lundgren et al. 1991 Alpha Particles [239]PuO2
34	Dog (Beagle)	3-46 min	Resp		8,400 rad	(incr. resp. rate, pulmonary & pleural fibrosis, metaplastic and/or hyperplastic lesions in terminal bronchiolar and alveolar regions)			Hobbs et al. 1972 Beta Particles [90]Y

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
					Less serious	Serious		
35	Monkey (Rhesus)	once	Resp			270 nCi M	(pulmonary fibrosis)	Hahn et al. 1987 Alpha Particles [239]PuO2
36	Monkey (Rhesus)	once	Resp			1000 nCi M	(radiation pneumonitis and pulmonary fibrosis)	LaBauve et al. 1980 Alpha Particles [239]PuO2
37	Monkey (Rhesus)	once	Resp	210 nCi M				Hahn et al. 1987 Alpha Particles [239]PuO2
38	Monkey (Cynomol- gus)	once	Resp			0.27 uCi M	(2/2 fibrosis, 1/2 pneumonitis)	Brooks et al. 1992 Alpha Particles [239]Pu
39	Mouse (C57BL/6J)	once	Resp			4.8 uCi F	(92%, 34%, and 59% radiation pneumonitis in 70-, 260-, and 450-day old mice)	Lundgren et al. 1980a Beta Particles [144]CeO2
40	Mouse (CFW)	10-20 min	Resp			21uCi M	(radiation pneumonitis in 75-100% of mice)	Lundgren et al. 1981 Beta Particles [90]Y
41	Dog (Beagle)	28-53 min	Resp			24,000 uCi	(radiation pneumonitis in 6/7 dogs)	Hahn et al. 1975 Beta Particles [90]Y

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL				Reference Chemical Form
					Less serious		Serious		
42	Monkey (Cynomol- gus)	once	Resp	0.108 M uCi					Brooks et al. 1992 Alpha Particles [239]Pu
43	Mouse (C57BL/6J)	once	Resp	1.1 uCi F					Lundgren et al. 1980a Beta Particles [144]CeO2
44	Dog (Beagle)	once	Resp				2.6 uCi/kg	(3/55 radiation pneumonitis, pulmonary fibrosis)	Benjamin et al. 1979 Beta Particles [144]CeCl3
45	Dog (Beagle)	<1 hr	Resp				33 uCi/kg	(radiation pneumonitis)	Hahn et al. 1976 Beta Particles [144]Ce
46	Dog (Beagle)	3-46 min	Cardio		8,400 rad	(ECG changes in 5/12 and hemorrhagic areas near ventricular junction in right atria of 7/12 dogs dying 64-92 d post exposure)			Hobbs et al. 1972 Beta Particles [90]Y
47	Dog (Beagle)	once	Cardio	3200 rad					Muggenburg et al. 1988 Alpha Particles [239]PuO2
48	Dog (Beagle)	28-53 min	Gastro				3200 rads	(colon lesion, ulcerative and atrophic foci in 1/2 dogs)	Hahn et al. 1975 Beta Particles [90]Y

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL				Reference Chemical Form
					Less serious		Serious		
49	Dog (Beagle)	28-53 min	Gastro		32,000 uCi	(colitis in 2/7 dogs)			Hahn et al. 1975 Beta Particles [90]Y
50	Dog (Beagle)	2-22 min	Gastro		45.9 uCi/kg	(diarrhea)			Gillett et al. 1987a Beta Particles [90]SrCl2
51	Dog (Beagle)	3-46 min	Hemato				8,400 rad	(lymphopenia)	Hobbs et al. 1972 Beta Particles [90]Y
52	Dog (Beagle)	3-46 min	Hemato		8,400 rad	(suppression of bone marrow in deaths up to 31d, repopulation of marrow in later deaths			Hobbs et al. 1972 Beta Particles [90]Y
53	Monkey (Cynomol- gus)	once	Hemato	1.08 uCi M					Brooks et al. 1992 Alpha Particles [239]Pu
54	Dog (Beagle)	once	Hemato				0.97 uCi/kg	(bone marrow aplasia)	Benjamin et al. 1979 Beta Particles [90]SrCl2
55	Dog (Beagle)	once	Hemato				2.6-360 uCi/kg	(9/55 bone marrow aplasia)	Benjamin et al. 1979 Beta Particles [144]CeCl3

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL				Reference Chemical Form
					Less serious		Serious		
56	Dog (Beagle)	once	Hemato				14 uCi/kg	(11/46 bone marrow aplasia)	Benjamin et al. 1979 Beta Particles [91]YCl3
57	Dog (Beagle)	2-22 min	Hemato				45.9 uCi/kg	(bone marrow hypoplasia)	Gillett et al. 1987a Beta Particles [90]SrCl2
58	Dog (Beagle)	2-22 min	Hemato		9.99 uCi/kg	(decreased platelet counts)			Gillett et al. 1987a Beta Particles [90]SrCl2
59	Hamster (Syrian)	1 yr 7x/yr 1-45 min/x	Hepatic				3900 rad M	(degenerative liver lesions in 40%)	Lundgren et al. 1983 Alpha Particles [239]PuO2
60	Dog (Beagle)	3-46 min	Hepatic		8,400 rad	(moderate or marked centrilobular hepatic congestion in deaths >38d, no necrosis)			Hobbs et al. 1972 Beta Particles [90]Y
61	Dog (Beagle)	once	Hepatic				2.6-360 uCi/kg	(3/55 hepatic degeneration)	Benjamin et al. 1979 Beta Particles [144]CeCl3
62	Dog (Beagle)	3-46 min	Dermal		8,400 rad	(alopecia, atrophy and loss of hair follicles in 4/33 dogs)			Hobbs et al. 1972 Beta Particles [90]Y

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL				Reference Chemical Form
					Less serious		Serious		
63	Dog (Beagle)	28-53 min	Dermal		?	(nasal dermatitis in 4/7 dogs)			Hahn et al. 1975 Beta Particles [90]Y
64	Dog (Beagle)	3-46 min	Bd Wt		8,400 rad	(anorexia and progressive weight loss)			Hobbs et al. 1972 Beta Particles [90]Y
65	Dog (Beagle)	2-22 min	Metab		45.9 uCi/kg	(fever)			Gillett et al. 1987a Beta Particles [90]SrCl2
	Immunological/Lymphoreticular								
66	Dog (Beagle)	once					1400 rad	(fibrosis, atrophy, or hyperplasia in lymph nodes)	Galvin et al. 1989 Alpha Particles [239]PuO2
67	Dog (Beagle)	once					27,000 rad	(60% decr. in lymphocyte count)	Benjamin et al. 1978 Beta-Gamma Particles [144]Ce
68	Dog (Beagle)	once					39,000 rad	(lymphopenia and decr. in lymphocyte function)	Benjamin et al. 1976 Beta Particles [90]Sr
69	Dog (Beagle)	once					42,000 rad	(lymphopenia and decr. in lymphocyte function)	Benjamin et al. 1976 Beta Particles [144]Ce

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL				Reference Chemical Form
					Less serious		Serious		
70	Dog (Beagle)	once			520 rad	(decr. response of lymphocytes to PHA in middle aged dogs)			Davila et al. 1992 Alpha Particles [239]PuO2
71	Dog (Beagle)	once			740 rad	(decr. response of lymphocytes to Con A and PHA in aged tumor bearing dogs)			Davila et al. 1992 Alpha Particles [239]PuO2
72	Dog (Beagle)	once			1400 rad	(incr. IgG in lung; neutrophils six-fold higher in lungs)			Galvin et al. 1989 Alpha Particles [239]PuO2
73	Dog (Beagle)	3-46 min			8,400 rad	(<38 d, TBLN had marked lymphoid depletion; >38 d nodes were enlarged with hyperplastic repopulation of lymphocytes)			Hobbs et al. 1972 Beta Particles [90]Y
74	Mouse (CFW)	10-20 min			7 uCi M	(incr. number vacuolated macrophages)			Lundgren et al. 1976 Beta Particles [90]Y
75	Mouse (CFW)	10-20 min			8 uCi M	(equivocal suppression of pulmonary bacterial clearance at 2 and 3 wk post-exposure)			Lundgren et al. 1976 Beta Particles [90]Y
76	Dog (Beagle)	<1 hr					51 uCi/kg	(severe atrophy and fibrosis in both cortex and paracortex)	Hahn et al. 1976 Beta Particles [144]Ce

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
					Less serious	Serious		
	Cancer							
77	Dog (Beagle)	once				180 rad	(CEL: osteoblastic osteosarcomas in 4/15 dogs)	Gillett et al. 1985 Beta Particles [241]AmO2
78	Dog (Beagle)	once				180 rad	(CEL: osteoblastic osteosarcomas in 4/15 dogs)	Gillett et al. 1985 Beta Particles [241]AmO2
79	Dog (Beagle)	once				190 radM	(CEL: oral melanoma)	Muggenburg et al. 1988 Alpha Particles [239]PuO2
80	Dog (Beagle)	once				200 rad	(CEL: 30 lung tumors observed, 1.2 expected)	Hahn et al. 1988 Beta Particles [144]Ce
81	Dog (Beagle)	once				210 rad	(CEL: osteosarcomas in 35/144 exposed dogs)	Hahn et al. 1981 Alpha Particles [238]PuO2
82	Dog (Beagle)	<70 min				310 rad	(CEL: 28/36 lung cancer)	Boecker et al. 1988 Alpha Particles [239]PuO2
83	Dog (Beagle)	once				800 rad	(CEL: nasal squamous cell carcinomas in 5/55)	Benjamin et al. 1979 Beta Particles [144]CeCl3

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
					Less serious	Serious		
84	Dog (Beagle)	once				860 rad	(CEL: 3/46 nasal squamous cell carcinomas)	Benjamin et al. 1979 Beta Particles [91]YCl3
85	Dog (Beagle)	once				1000 rad	(CEL: lung carcinoma)	Muggenburg et al. 1988 Alpha Particles [239]PuO2
86	Dog (Beagle)	once				1400 rad	(CEL: lung tumors in 3/4 dogs)	Galvin et al. 1989 Alpha Particles [239]PuO2
87	Monkey (Rhesus)	once				1400 radM	(CEL: pulmonary sarcoma in 1/12)	Hahn et al. 1987 Alpha Particles [239]PuO2
88	Dog (Beagle)	once				1900 rad	(CEL: 8 lung tumors observed, 1.2 expected)	Hahn et al. 1988 Beta Particles [90]Y
89	Dog (Beagle)	once				2,800 rads	(CEL: 31 bone related sarcomas)	Benjamin et al. 1979 Beta Particles [90]SrCl2
90	Dog (Beagle)	once				3100 rad	(CEL: 36 lung tumors observed, 1.2 expected)	Hahn et al. 1988 Beta Particles [91]Y

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
					Less serious	Serious		
91	Dog (Beagle)	once				3200 rad	(CEL: 2 heart tumors)	Hahn et al. 1988 Beta Particles [144]Ce
92	Dog (Beagle)	once				3200 rad	(CEL: 9 TBLN tumors)	Hahn et al. 1988 Beta Particles [144]Ce
93	Dog (Beagle)	<70 min				3500 rad	(CEL: lung cancer in 32/56)	Boecker et al. 1988 Beta Particles [91]Y
94	Dog (Beagle)	10-15 min				7,000 rad	(CEL: pulmonary carcinomas and sarcomas)	Hahn et al. 1983 Beta Particles [90]Y, [91]Y, [144]Ce, [90]Sr
95	Dog (Beagle)	once				7100 rads	(CEL: 2/72 other carcinomas of the head)	Benjamin et al. 1979 Beta Particles [90]SrCl2
96	Dog (Beagle)	once				7700 rad	(CEL: 14 heart tumors)	Hahn et al. 1988 Beta Particles [90]Sr
97	Dog (Beagle)	once				7700 rad	(CEL: 8 TBLN tumors)	Hahn et al. 1988 Beta Particles [90]Sr

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
					Less serious	Serious		
98	Dog (Beagle)	once				8100 rad	(CEL: 1/55 bone related sarcomas)	Benjamin et al. 1979 Beta Particles [144]CeCl3
99	Dog (Beagle)	once				9600 rad	(CEL: 1 heart tumor)	Hahn et al. 1988 Beta Particles [91]Y
100	Dog (Beagle)	once				9600 rad	(CEL: 2 TBLN tumors)	Hahn et al. 1988 Beta Particles [91]Y
101	Dog (Beagle)	once				13000 rad	(CEL: 1/72 nasal squamous cell carcinomas)	Benjamin et al. 1979 Beta Particles [90]SrCl2
102	Dog (Beagle)	2-48 min				16,000 rad	(CEL: bronchiolo-alveolar carcinomas and pulmonary hemangiosarcomas)	Hahn et al. 1977 Beta Particles [90]Y, [91]Y, [144]Ce, [90]Sr
103	Dog (Beagle)	once				18,000 rad	(CEL: 28 lung tumors observed, 1.2 expected)	Hahn et al. 1988 Beta Particles [90]Sr
104	Dog (Beagle)	once				27,000 rad	(CEL: pulmonary neoplasms in 5/16 dogs)	Benjamin et al. 1978 Beta-Gamma Particles [144]Ce

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
					Less serious	Serious		
105	Rat (Fischer- 344)	once				0.06 uCi	(CEL: pulmonary adenocarcinoma in 1/35)	Hahn and Lundgren 1992 Beta Particles [144]CeO2
106	Rat (Fischer- 344)	7x 1x/2 mo 1 yr				0.35 uCi	(CEL: pulmonary adenocarcinoma and adenoma in 2/36)	Hahn and Lundgren 1992 Beta Particles [144]CeO2
107	Mouse (CFW)	10-20 min				1 uCiM	(CEL: pulmonary adenomas)	Lundgren et al. 1981 Beta Particles [90]Y
108	Monkey (Cynomol- gus)	once				1.08 uCiM	(CEL: lung cancer in 1/8)	Brooks et al. 1992 Alpha Particles [239]Pu
109	Dog (Beagle)	2-22 min				7.02 uCi/kg	(CEL: primary bone neoplasa in 30/66 dogs: osteosarcoma, hemangiosarcomas, fibrosarcomas, myxosarcoma)	Gillett et al. 1987b Beta Particles [90]SrCl2
110	Dog (Beagle)	once				NS	(CEL: 100/144 osteosarcomas)	Gillett et al. 1988 Alpha Particles [238]PuO2
111	Dog (Beagle)	once				NS	(CEL: 28/144 lung tumors)	Gillett et al. 1988 Alpha Particles [238]PuO2

Table 8-1. Levels of Significant Exposure to Radiation and Radioactive Material: Inhalation (continued)

Entry Number	Species (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
					Less serious	Serious		
112	Dog (Beagle)	once				NS	(CEL: lung tumors in 47/144 dogs; bronchioalveolar carcinomas & papillary adenocarcinomas)	Muggenburg et al. 1994 Alpha Particles [238]PuO2
113	Dog (Beagle)	once				NS	(CEL: skeletal tumors in 92/144; osteosarcomas)	Muggenburg et al. 1994 Alpha Particles [238]PuO2
114	Dog (Beagle)	once				NS	(CEL: malignant liver tumors in 13/144)	Muggenburg et al. 1994 Alpha Particles [238]PuO2

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; Con A = concanavalin A; d = day(s); decr = decrease; ECG = electrocardiograph; F = female; Gastro = gastrointestinal; Hemato = hematological; ILB = initial lung burden; incr = increase; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolism; min = minute(s); mo = month(s); NOAEL = no-observable-adverse-effect level; NS = not specified; PHA = phytohaemagglutinin; Resp = respiratory; skel = skeletal; TBLN = tracheobronchial lymph nodes; wk = week(s); yr = year(s); x = times

Table 8-2. Levels of Significant Exposure to Radiation and Radioactive Material: Oral

Entry Number	Species/ (Strain)	Duration/ Frequency of Administration (Specific Route)	System	NOAEL	LOAEL			Reference Chemical Form
					Less Serious	Serious		
	Systemic							
1	Human	4.7 yr	Musc/skel	1,851 F rad (17-19 yr of age)				Polednak and Farnham 1980 Alpha Particles [226]Ra
2	Human	4.7 yr	Musc/skel	10,110 F rad (13-16 yr of age)				Polednak and Farnham 1980 Alpha Particles [226]Ra
	Reproductive							
3	Mouse (Hybrid)	2 wk 1x/d				140 rad	(incr. embryo mortality)	Ramaiya et al. 1994 Beta Particles [137]Cs
4	Mouse (Hybrid)	once				180 rad	(incr. post-implantation embryo mortality)	Ramaiya et al. 1994 Beta Particles [137]Cs
5	Mouse (Hybrid)	once			190 rad M		(decreased fertility)	Ramaiya et al. 1994 Beta Particles [137]Cs
6	Mouse (Hybrid)	2 wk 1x/d			350 rad M		(reduced effective mating)	Ramaiya et al. 1994 Beta Particles [137]Cs

Table 8-2. Levels of Significant Exposure to Radiation and Radioactive Material: Oral (continued)

Entry Number	Species/ (Strain)	Duration/ Frequency of Administration (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
					Less Serious	Serious	
7	Mouse (Hybrid)	once		100 rad M			Ramaiya et al. 1994 Beta Particles [137]Cs

d = day(s); expos. = exposure; F = female; incr. = increase; LOAEL = lowest-observable-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; wk = week(s); yr = year(s)

Table 8-3. Levels of Significant Exposure to Radiation and Radioactive Material: Dermal

Species/ (Strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference Chemical Form
				Less Serious		Serious	
Systemic							
Hamster (Syrian golden & white)	once	Dermal		2000 rad	(epilation)		Garcia and Shubik 1971 Beta Particles [85]Kr
Gn Pig (Albino)	once	Dermal		3000 rep M	(incr. vascular permeability)		Song et al. 1968 Beta Particles [90]Sr-[90]Y
Neurological							
Human	once			38.2 rad M	(tingling, pain, sensitive to touch and temperature changes)		Berger et al. 1996 X-ray ionizing radiation

Cardio = cardiovascular; F = female; Gn pig = guinea pig; incr. = increase; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level.

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL		Reference
					Less serious	Serious	
	Death						
1	Rat (Sprague-Dawley)	once				10 rad M (1/9 died)	Canfi et al. 1990 Gamma Ray [192]Ir
2	Mouse (ICR)	3x/wk <86 wk				150 rad F (13/21 died)	Ootsuyama and Tanooka 1989 Beta Particles [90]Sr-[90]Y
3	Rat (Wistar)	once				800 rad M (45% died through d 15)	Salovsky and Shopova 1992 Gamma Ray NS
4	Human	once (occup)				2250 rad M (death 13 d after exposure)	Stavem et al. 1985 Gamma Ray NS
	Systemic						
5	Pig (Large white)	once	Resp			1280 rad F (severe thickening of interlobular septa)	Rezvani et al. 1989 Gamma Ray [60]Co
6	Rat (Wistar)	once	Resp		400 rad M (30% decr. in BALF LDH, 31% decr. in alkaline phosphatase, and 40% decr. in acid phosphatase)		Salovsky and Shopova 1992 Gamma Ray NS

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL		Reference
					Less serious	Serious	
7	Human	once (occup)	Resp		2250 rad M (few mononuclear cells and no granulocytes in resp. tract)		Stavem et al. 1985 Gamma Ray NS
8	Monkey (Rhesus)	1.38 min	Cardio			10,000 M rad (66% decr. blood pressure 20 min post-exposure)	Cockerham et al. 1986 Gamma Ray [60]Co
9	Human	once (occup)	Cardio		2250 rad M (hypertrophic ventricle)		Stavem et al. 1985 Gamma Ray
10	Dog (Beagle)	once	Cardio		3000 rad M (focal area of pervasculitis, reduction in LVEF)		Durakovic 1986a Gamma Ray [60]Co
11	Mouse (Hybrid)	3-24 hr	Gastro		2.5 rad/hr M (cell death in the crypts of the small intestine and descending colon)		Ijiri 1989 Gamma Ray [137]Cs
12	Mouse (BALB/c)	once	Gastro		1500 rad M (changes in villous shape and reduction in height, tissue cell disintegration)		Indran et al. 1991 Gamma Ray [60]Co
13	Human	once (occup)	Gastro		2250 rad M (atrophy of glands in stomach, small intestine, and large intestine; diarrhea)		Stavem et al. 1985 Gamma Ray

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL				Reference
					Less serious		Serious		
14	Monkey (Rhesus)	1.38 min	Hemato				10,000 M rad	(arterial plasma histamine level incr. 96.8- fold 2 min post-exposure)	Cockerham et al. 1986 Gamma Ray [60]Co
15	Dog (NS)	20-1700 d 22 hr/d	Hemato		1.88 rad/d	(decreased lymphocytes, thrombocytes and neutrophilic granulocytes)			Nothdurft et al. 1995 Gamma Ray [60]Co
16	Dog (NS)	20-1700 d 22 hr/d	Hemato		1.88 rad/d	(decreased lymphocytes, thrombocytes and neutrophilic granulocytes)			Nothdurft et al. 1995 Gamma Ray [60]Co
17	Mouse (ICR)	once	Hemato		5 rad M	(significantly decreased leukocyte counts on day 1 post irradiation)			Lin et al. 1996 Gamma Ray NS
			Bd Wt		5 rad M	(body weight significantly decreased 11.6% on day19 post irradiation)			
18	Dog (Beagle)	150 - 300 d 22 hr/d	Hemato		7.5 rad/d M	(suppression/recovery for granulocytes, monocytes, leukocytes, platelets, & erythrocytes)			Seed et al. 1989 Gamma Ray [60]Co
19	Dog (Beagle)	150-300 d 22 hr/d	Hemato		7.5 rad/d F	(suppression/recovery for granulocytes, monocytes, leukocytes, platelets, & erythrocytes)			Seed et al. 1993 Gamma Ray [60]Co

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL		Reference
					Less serious	Serious	
20	Human	once	Hemato		38.2 rad M (decreased total white blood count)		Berger et al. 1996 X-ray NS
			Dermal		38.2 rad M (itching, swelling, blisters, discoloration and desquamation of the hand)		
21	Mouse (hybrid)	once	Hemato		50 rad M (increase in proliferation of femoral CFU-S, oscillation in granulocytes and CFU-S)		Gidali et al. 1985 Gamma Ray [60]Co
22	Human	once	Hemato		* 159 rad M (decr. leukocyte, neutrophil, and lymphocyte counts)		Klener et al. 1986 Gamma Ray [60]Co
		(occup)					
23	Rat (Sprague-Dawley)	once	Hemato		840 rad M (decrease in arachidonic acid incorporation into membrane phospholipids of platelets)		Lognonne et al. 1985 Gamma Ray [60]Co
24	Human	once	Hemato		2250 rad M (decr. leukocyte count, elevated serum creatinine, and hypocellular bone marrow)		Stavem et al. 1985 Gamma Ray NS
		(occup)					
25	Mouse (CBA/H)	0-177 min	Hemato	12,000 F rad			Hulse 1966 Beta Particles [204]Tl

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL		Reference
					Less serious	Serious	
26	Dog (Beagle)	once	Hepatic		400 rad M (signif. decrease in SGOT)		Durakovic 1986b Gamma Ray [60]Co
27	Mouse (Swiss)	once	Hepatic		1000 rad M (incr. acid phosphatase activity, decr. protein content)		Mazur et al. 1991 Gamma Ray [60]Co
28	Human	once (occup)	Renal		2250 rad M (anuria, enlarged kidneys, and interstitial edema)		Stavem et al. 1985 Gamma Ray NS
29	Rat (Sprague-Dawley)	once	Endocr		1.0 rad M (decr. in hypophyseal and serum FSH)		Canfi et al. 1990 gamma ray [192]Ir
30	Human	2 mo-3 yr	Endocr		200 rad M (decreased LH)		Birioukov et al. 1993 Beta and Gamma NS
31	Rat (Sprague-Dawley)	once	Endocr	0.1 rad M			Canfi et al. 1990 gamma ray [192]Ir
32	Human	once (occup)	Dermal			* 159 rad M (painful hard swelling of deep skin layers of hand resulting in amputation of fingers)	Klener et al. 1986 Gamma Ray [60]Co
33	Human	2 mo-3 yr	Dermal			200 rad M (radiation dermatitis)	Birioukov et al. 1993 Beta and Gamma NS

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference
					Less serious		Serious	
34	Gn Pig (Albino)	once	Dermal				2200 rad M (hyperplastic epidermis)	Etoh et al. 1977 Beta Particles [90]Sr-[90]Y
35	Mouse (CBA/H)	0-177 min	Dermal				3000 rad F (radiation burns)	Hulse 1966 Beta Particles [204]Tl
36	Pig (Large white)	1x or 6x	Dermal				12,000 rad (skin and skeletal muscle ulcerations)	Lefaix et al. 1993 Gamma Ray [192]Ir
37	Human	once (occup)	Dermal		* 159 rad M	(reddening and inflammation of hand and epilation)		Klener et al. 1986 Gamma Ray [60]Co
38	Mouse (CBA/H)	0-177 min	Dermal		750 rad F	(hair depigmentation and hyperkeratotic areas)		Hulse 1966 Beta Particles [204]Tl
39	Mouse (Albino)	0-177 min	Dermal		1500 rad	(slight erythema)		Hulse 1966 Beta Particles [204]Tl
40	Pig (Large white)	1x or 6x	Dermal		3200 rad	(erythma)		Lefaix et al. 1993 Gamma Ray [192]Ir
41	Mouse (Albino)	0-177 min	Dermal	750 rad				Hulse 1966 Beta Particles [204]Tl

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL				Reference
					Less serious		Serious		
42	Gn Pig (Albino)	once	Dermal	1000 rad M					Etoh et al. 1977 Beta Particles [90]Sr-[90]Y
43	Pig (Large white)	1x or 6x	Dermal	1600 rad					Lefaix et al. 1993 Gamma Ray [192]Ir
44	Human	once	Ocular				200 rad	(cataracts)	Lipman et al. 1988 x-ray and beta NS
45	Dog (Beagle)	pcd 2	Ocular				300 rad	(severe bilateral degenerative retinal lesions in 99% of offspring)	Schweitzer et al. 1987 Gamma Ray [60]Co
46	Rat (Wistar)	once	Ocular				1500 rad	(progressive inner retinal ischemia, cytoid bodies, capillary non-perfusion, general atrophy of inner retina in diabetic rats)	Stitt et al. 1994 X-ray NS
47	Human	once (occup)	Ocular		* 159 rad M	(deterioration of visual acuity)			Klener et al. 1986 Gamma Ray [60]Co
48	Human	2 mo-3 yr	Ocular		200 rad M	(vision impairment)			Birioukov et al. 1993 Beta and Gamma NS

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL		Reference
					Less serious	Serious	
49	Rat (Sprague-Dawley)	Gd 13, 15 or 17	Bd Wt	100 rad F			Norton and Kilmer 1988 Gamma Ray [137]Cs
50	Rat (Sprague-Dawley)	Gd 15	Bd Wt	100 rad F			Norton and Kimler 1990 Gamma Ray [137]Cs
51	Rat (Fischer- 344)	Gd 20	Bd Wt	150 rad F			Zaman et al. 1992 Gamma Ray NS
52	Rat (Fischer- 344)	Gd 20	Bd Wt	150 rad F			Zaman et al. 1993 Gamma Ray NS
53	Human	once (occup)	Metab		* 159 rad M (irregular subfebrile temperatures)		Klener et al. 1986 Gamma Ray [60]Co
54	Human	once (occup)	Metab		2250 rad M (fever)		Stavem et al. 1985 Gamma Ray NS
55	Human	2 mo-3 yr	Other			200 rad M (acute radiation sickness)	Birioukov et al. 1993 Beta and Gamma NS

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL				Reference
					Less serious		Serious		
	Immunological/Lymphoreticular								
56	Mouse (NS)	1-30 d			0.6 rad M	(moderate change in stem cell radiosensitivity)			Rozhdestvensky & Fomicheva 1995 Gamma Ray
57	Human	once					2250 rad M	(congestion and hemorrhage of spleen)	Stavem et al. 1985 Gamma Ray NS
		(occup)							
58	Dog (NS)	20-1700 d 22 hr/d			1.88 rad/d	(decreased GM-CFC levels in bone marrow; increased CSA levels)			Nothdurft et al. 1995 Gamma Ray [60]Co
59	Dog (NS)	20-1700 d 22 hr/d			1.88 rad/d	(decreased GM-CFC levels in bone marrow; increased CSA levels)			Nothdurft et al. 1995 Gamma Ray [60]Co
60	Mouse (Swiss)	once			1000 rad M	(decr. spleen wt & levels of protein in spleen, incr. acid phosphatase activity & activity of beta- glucuronidase)			Mazur et al. 1991 Gamma Ray [60]Co
61	Human	once			2250 rad M	(decr. number of lymphocytes and hypocellular lymph nodes)			Stavem et al. 1985 Gamma Ray NS
		(occup)							
62	Mouse (ICR)	once		5 M	50 rad M	(significantly decreased spleen weight on day 12 post irradiation)			Lin et al. 1996 Gamma Ray NS

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL				Reference
					Less serious		Serious		
63	Monkey (Rhesus)	>1 yr		12.5-10 0 rad/min					Stone et al. 1994 High energy protons NS
64	Monkey (Rhesus)	once		10-100 rad/min					Stone et al. 1994 X-ray
	Neurological								
65	Monkey (Rhesus)	1.38 min					10,000 M rad	(51 and 63% decr. blood flow to reticular formation of pons & motor cortex, resp.)	Cockerham et al. 1986 Gamma Ray [60]Co
66	Rat (Sprague-Dawley)	once			200 rad	(increased brain expression of apoptosis-associated protein c-jun)			Ferrer et al. 1996 Gamma Ray [60]Co
67	Rabbit (Burgundy fawn)	once			450 rad M	(increased firing interval in pyramidal cells)			Bassant and Court 1978 Gamma Ray [60]Co
68	Rat (Wistar)	once			1435 rad M	(decreased catecholamine levels)			Pastorova et al. 1997 [60]Co ionizing radiation
	Reproductive								
69	Mouse (B6C3F1)	10-50 wk 1x/wk 20 min/x					5 rad M	(sperm abnormalities)	Grahn and Carnes 1988 Gamma Ray [60]Co

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference
					Less serious	Serious		
70	Mouse (B6C3F1)	60 wk 1x/wk 20 min/x				5 rad M	(sperm abnormalities)	Grahn and Carnes 1988 Gamma Ray [60]Co
71	Mouse (NS)	22-25 d				80 rad	(incr. post-implantation mortality in progeny)	Shevchenko et al. 1992 Gamma and beta NS
72	Human	2 mo-3 yr				200 rad M	(impotency, abnormal sperm, and decr. viability of spermatozoa)	Birioukov et al. 1993 Beta and Gamma NS
73	Mouse (Hybrid)	once				300 rad M	(sterility and decr. fertility)	Ramaiya et al. 1994 Gamma Ray [137]Cs
74	Mouse (Hybrid)	once				300 rad	(incr. total and post-implantation embryo mortality)	Ramaiya et al. 1994 Gamma Ray [137]Cs
75	Mouse (NS)	22-25 d (environ)				300 rad M	(reversible sterility, reduced testes mass)	Shevchenko et al. 1992 Gamma and beta NS
76	Rat (Sprague-Dawley)	once				900 rad M	(decr. testis wt, epididymal wt & epididymal content ABP & damaged spermatocytes)	Pinon-Lataillade et al. 1991 Gamma Ray [60]Co

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference
					Less serious	Serious		
77	Mouse (Hybrid)	28 wk				1,128 rad M	(65% reduced testis mass)	Searle et al. 1976 Gamma Ray [60]Co
78	Mouse (Hybrid)	28 wk				1,128 rad	(incr. pre- and post-implantation loss)	Searle et al. 1976 Gamma Ray [60]Co
79	Mouse (Hybrid)	28 wk				1,128 rad M	(85% reduced epididymal sperm-count)	Searle et al. 1976 Gamma Ray [60]Co
80	Rat (Sprague-Dawley)	once			1 rad M	(25% decrease in fertility)		Canfi et al. 1990 gamma ray [192]Ir
	Developmental							
81	Rat (Sprague-Dawley)	once				1 rad M	(17% decr. pup weight at weaning)	Canfi et al. 1990 gamma ray [192]Ir
82	Mouse (Swiss)	Gd 11.5				25 rad	(13.67% w/ microphthalmia; 2% decr. fetal head length and width; 5% decr. brain weight)	Devi et al. 1994 Gamma Ray [60]Co
83	Rat (Wistar)	Gd 10 3 sec				40 rad	(32.2% fetal mortality, 53 resorption sites)	Roux et al. 1986 Gamma Ray [60]Co
84	Rat (Sprague-Dawley)	16.5 sec				50 rad	(loss of granule cells, atrophied/reduced number of Purkinje cells in cerebellum)	Ralcewicz et al. 1995 Gamma Ray [60]Co

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference
					Less serious	Serious		
85	Rat (Sprague-Dawley)	Gd 13, 15 or 17				75 rad	(decr. performance on functional tests; decr. motor activity PND 21; 11-23 % decr. thickness in 3 areas of cerebral cortex PND 21)	Norton and Kilmer 1988 Gamma Ray [137]Cs
86	Dog (Beagle)	once				83 rad	(premolar hypodontia)	Lee et al. 1989 Gamma Ray [60]Co
87	Rat (Sprague-Dawley)	Gd 11 or 17 2 min				100 rad	(24% decr. body weight; decr. performance on reflex suspension test; decr. thickness of sensorimotor cortex)	Norton and Kilmaer 1987 Gamma Ray [137]Cs
88	Mouse (ICR)	7.5 min				150 rad	(exencephalia, cleft palate, open eyelid & paw malformations)	Kusama and Hasegawa 1993 Gamma Ray [137]Cs
89	Rat (Wistar)	Gd 20				210 rad	(20% decr. body wt; 79% decr. testes, 72% ventral prostate, & 60% seminal vesicle wts; disrupted spermatogenesis & androgen production)	Suzuki et al. 1990 Gamma Ray [60]Co
90	Rat (Wistar)	Gd 13, 14, or 15				400 rad	(31-79% decr. fetal survival)	Koshimoto et al. 1994 Gamma Ray [137]Cs
91	Mouse (Swiss)	Gd 12				400 rad F	(clefts of the secondary palate)	Saad et al. 1991 Gamma Ray [137]Cs

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL				Reference
					Less serious		Serious		
92	Mouse (Swiss)	Gd 12					400 rad F	(reduced litter size, head measurements, & incr. in cleft palate)	Saad et al. 1994 Gamma Ray [137]Cs
93	Rat (Fischer- 344)	Gd 20			15 rad F	(9-11 % decr. in pup relative cerebral cortex weight)			Zaman et al. 1992 Gamma Ray NS
94	Mouse (Swiss)	Gd 11.5			50 rad	(1% incr. incidence of microphthalmia)			Devi et al. 1994 Gamma Ray [60]Co
95	Rat (Sprague-Dawley)	Gd 15			50 rad	(incr. total no. pyknotic cells and no. of macrophages in cortical mantle; decr. no. mitotic figures in ventricular zone)			Norton and Kimler 1990 Gamma Ray [137]Cs
96	Rat (Wistar)	4 or 6 d			56 rad F	(13% decr. in brain weight)			Reyners et al. 1991 Gamma Ray [60]Co
97	Rat (Wistar)	once GD 13, 15, 17, or 19			100 rad	(increase in reactive astrocyte proliferation)			Janeczko et al. 1997 Gamma Ray [60]Co
98	Rat (Wistar)	Gd 13, 14, or 15			100 rad	(incr. ratio of large hematocytes to small hematocytes)			Koshimoto et al. 1994 Gamma Ray [137]Cs

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference
					Less serious		Serious	
99	Mouse (C57BL/6)	Gd 14			100 rad	(9% decr. brain weight, decr. area and length of cerebral hemispheres; incr. area of superior colliculi and its proportion to cerebral hemisphere length)		Minamisawa et al. 1990 Gamma Ray [137]Cs
100	Mouse (C57BL/6)	Gd 14 4-8 min			100 rad	(incr. no. of instances of aggressive behavior in offspring; 16% decr. offspring body weight at 3 mo of age)		Minamisawa et al. 1992 Gamma Ray [137]Cs
101	Dog (Beagle)	Gd 28			100 rad	(mild to moderate degenerative retinal lesions in offspring)		Schweitzer et al. 1987 Gamma Ray [60]Co
102	Mouse (CD-1)	NS			100 rad M	(inherited cell proliferation disadvantage by F1 & F2 embryos conceived at 6 & 7 wks; decr. body weight for rats conceived at week 6)		Wiley et al. 1997 Gamma Ray [137]Cs
103	Rat (Fischer- 344)	Gd 20			150 rad	(altered pivoting, cliff avoidance and upper jaw tooth eruption in offspring)		Zaman et al. 1993 Gamma Ray NS
104	Dog (Beagle)	Gd 55			160 rad	(moderate to severe bilateral degenerative retinal lesions in 75% of offspring)		Schweitzer et al. 1987 Gamma Ray [60]Co

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference
					Less serious	Serious		
105	Rat (Fischer- 344)	Gd 20		6.8 rad F				Zaman et al. 1992 Gamma Ray NS
106	Rat (Fischer- 344)	Gd 20		6.8 rad				Zaman et al. 1993 Gamma Ray NS
107	Rat (Sprague-Dawley)	Gd 9.5 14-17 sec		50 rad				Bruni et al. 1994 Gamma Ray [60]Co
108	Rat (Wistar)	Gd 20			(decr. steroid hormone production)			Inano et al. 1989 Gamma Ray [60]Co
109	Rat (Wistar)	Gd 20					(51-52% decr. body weight, 82% decr. testicular weight, 66% decr. ovarian weight)	Inano et al. 1989 Gamma Ray [60]Co
110	Human	NS				>185 GBq	(incr. absolute 'null' lymphocytes, decr. absolute T lymphocytes, decr. T4 cells)	Petrova et al. 1997 [137]Cs
	Cancer							
111	Human	NS				2.10 rad	(CEL: lung cancer)	Mancuso et al. 1977
112	Human	NS				2.10 rad	(CEL: pancreatic cancers)	Mancuso et al. 1977
113	Human	NS				2.10 rad	(CEL: myelomas)	Mancuso et al. 1977

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL			Reference
					Less serious	Serious		
114	Human	NS (occup)				15 rad	(CEL: estimated doubling dose of cancers of radiosensitive tissues)	Kneale et al. 1981 Gamma Ray
115	Dog (Beagle)	10 min				16 rad	(CEL: cancers in 7 and neoplasms in 16 dogs out of 1,309; primarily squamous papilloma of eyelid)	Benjamin et al. 1986 Gamma Ray [60]Co
116	Mouse (ICR)	3x/wk <86 wk				150 rad F	(CEL: 23/96 osteosaracomas, optimum dose for induction was 250 to 350 cGy)	Ootsuyama and Tanooka 1989 Beta Particles [90]Sr-[90]Y
117	Mouse (CBA/H)	0-177 min				1500 rad F	(CEL: signif. incr. in benign and malignant dermal tumors)	Hulse 1966 Beta Particles [204]Tl
118	Mouse (SAS/4 Albino)	1 hr				2000 rad M	(CEL: 20% skin tumor incidence from 32 2-mm diameter source; 3% skin tumor incid. from 8 2-mm diam. source; 33% skin tumor incid. following uniform expos.)	Charles et al. 1988 Beta Particles [170]Th
119	Mouse (SAS/4 Albino)	1 hr				2000 rad	(CEL: (20% increase in skin tumor incidence)	Charles et al. 1988 Beta Particles [170]Th
120	Human	NS				0-10 mSv	(CEL: childhood cancers associated with paternal exposure to radionuclides)	Sorahan and Roberts 1993 NS

Table 8-4. Levels of Significant Exposure to Radiation and Radioactive Material: External (continued)

Entry Number	Species/ (strain)	Duration/ Frequency of Administration	System	NOAEL	LOAEL		Reference
					Less serious	Serious	
121	Human	NS				0-10+ M rem (CEL: incr. lung cancer)	Checkoway et al. 1988 gamma and alpha [12]Y

* The reported dose at a distant location on the body, so the actual dose to the effected tissue was probably much higher.

BALF = bronchioalveiolar lavage fluid; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; Con A = concanavalin A; d = day(s); decr = decrease; ECG = electrocardiograph; Endocr = endocrine; F = female; Gastro = gastrointestinal; GBq = GigaBecquerel; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); incr = increase; ILB = initial lung burden; incr = increase; LOAEL = lowest-observable-adverse-effect level; LVEF = left ventricular ejection fraction; M = male; Metab = metabolism; min = minute(s); mo = month(s); no. = number; NOAEL = no-observable-adverse-effect level; NS = not specified; occup = occupational; pcd = days post coitus; PDN = post-natal day; Resp = respiratory; sec = second(s); SGOT = serum glutamic oxaloacetic transaminase; signif. = significant; wk = week(s); wt = weight; yr = year(s); x = times

9. GLOSSARY

Absorbed Dose—The energy imparted by ionizing radiation per unit mass of irradiated material. The units of absorbed dose are the rad and the gray (Gy). (See also Rad, Gray, and Units, Radiological.) Absorbed dose is defined per unit mass of absorbing material.

Absorbed Fraction—A term used in internal dosimetry. It is that fraction of energy radiated by the source organ that is absorbed by the target organ. For example, for ^{131}I in the thyroid (source organ), the absorbed fraction could be the fraction of gamma radiation absorbed in the liver (one of the target organs).

Absorber—Any material that absorbs or lessens the intensity of ionizing radiation. Neutron absorbers (boron, hafnium, and cadmium) are used as material in control rods for reactors. Concrete, steel, and lead are typical absorbers for x rays and gamma rays. A thin sheet of paper or metal will absorb alpha particles and all except the most energetic beta particles.

Absorption—The process by which radiation imparts some or all of its energy to any material through which it passes.

Absorption Ratio, Differential—The 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 inducing radioactivity by neutron irradiation of a target material.

Activity—The number of nuclear transformations occurring in a given quantity of material per unit time. (See Curie, Becquerel, and Units, Radiological, for more information on 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 aerosol.

Acute Exposure—An exposure to ionizing radiation for a duration of less than 15 days. Regarding acute radiation syndrome, high radiation levels involve an exposure period up to 2 days.

Acute Radiation Syndrome—The signs and symptoms which, taken together, characterize a person suffering from the effects of intense radiation. The effects occur within hours of exposure.

ALARA—The acronym for "As Low As is Reasonably Achievable." This term refers to the practice of making every reasonable effort to keep exposure to radiation as far below the dose limit as possible while still achieving the purpose for which radiation is licensed to be used. The benefits of reducing dose must be weighed against economic, engineering, and social costs of doing so.

Alpha Particle (symbolized by Greek letter α)—A charged particle emitted from the nucleus of certain radioactive atoms. An alpha particle has a mass of 4 atomic mass units (amu) and is equal to a helium nucleus (i.e., two protons and two neutrons, and a charge of +2).

Annihilation Radiation—The 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 in energy (see pair production).

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. For a given radionuclide, ALI is defined as the smaller of the intakes that would result in a committed effective dose equivalent of 5 rem or a committed dose equivalent of 50 rem to any individual organ or tissue (see also Committed Effective Dose).

Antineutrino— A neutral particle of rest mass near zero that is emitted during beta transformation (nucleus with a neutron excess) which occurs via the pathway by converting a neutron into a proton: n---> p + e^- + anti-nu(e), where n means neutron, p means proton, e^- means electron, and anti-nu(e) means an antineutrino of the electron type.

Artificial Radioactivity—The radioactivity produced by particle bombardment or electromagnetic irradiation in an accelerator or reactor and not existing in nature.

Atomic Mass—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} gm. (Symbol: u)

Atomic Mass Number—The total number of nucleons (neutron plus protons) in the nucleus of an atom.

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 atoms of an element expressed in atomic mass units.

Background Radiation—Radiation resulting from cosmic rays and naturally occurring radioactive material. Background radiation is always present and its level can change with altitude and the amount of radioactive material present in soil and building materials.

Becquerel (Bq)—A unit of measure for the quantity of radioactive material; one becquerel is that quantity of radioactive material in which one atom decays in one second. (See also Units, Radiological.)

Beta Particle (symbolized by Greek letter β) —A charged particle emitted from the nucleus of some radioactive atoms. A beta particle has a mass and charge equal in magnitude to that of the electron. The charge may be either +1 or -1, and may be shown with the respective symbol, β^+ or β^-.

Bioassay—A determination of the kind, quantity, concentration, or location of radioactive material in the body by either direct measurement or the analysis and evaluation of materials excreted or removed from the body.

Bone Seeker—Any compound or ion in the body that preferentially migrates into actively forming bone to become part of the hydroxyapatite mixture.

Branching—The occurrence of two modes by which a radionuclide can undergo radioactive transformation. For example, ^{214}Bi can undergo α or β^- transformation, ^{64}Cu can undergo β^-, β^+, or electron capture transformation. 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 transformation or disintegration).

Bremsstrahlung—Electromagnetic radiation (photons) produced by the acceleration that a fast charged particle (usually an electron) undergoes from the effect of an electric or magnetic field, for instance, from the field of another charged particle (usually a nucleus). Bremsstrahlung is emitted when beta particles or electrons are stopped by a shield.

Cancer Effect Level (CEL)—The lowest dose of chemical 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.

Carcinogen—A chemical capable of inducing cancer.

Carcinoma—A malignant neoplasm composed of epithelial cells, regardless of their derivation.

Cataract—A clouding of the crystalline lens of the eye that obstructs the passage of light.

Chronic Exposure—An exposure to ionizing radiation for 365 days or more, as specified in the ATSDR toxicological profiles.

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, in units such as person @ rem or person @ Sv.

Committed Dose Equivalent (H_{T50})—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-year period following the intake.

Committed Effective Dose—The International Commission on Radiological Protection (ICRP) term for committed effective dose equivalent. (See Committed Effective Dose Equivalent.)

Committed Effective Dose Equivalent (H_{E50})—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 the organs or tissues ($H_{E50} = 3W_T H_{T50}$). The committed effective dose equivalent is used in radiation safety because it implicitly includes the relative carcinogenic sensitivity of the various tissues.

Compton Scattering—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 of energy less than the incident photon.

Contamination, Radioactive—The deposition of radioactive material in any place where it is not desired.

Cosmic Rays—High-energy particulate and electromagnetic radiations that originate outside the earth's atmosphere.

Count (Radiation Measurements)—The external indication of a radiation-measuring device designed to enumerate ionizing events. It may refer to a single detected event or to the total number registered in a given period of time. This term can be used with equipment and geometry efficiencies to quantify the rate of transformation of ionizing events.

Counter—A general description applied to radiation detection instruments or survey meters that detect and measure radiation. The signal that announces the detection of an ionization event is called a count. (See also Counter, Geiger-Mueller and Counter, Scintillation.)

> **Counter, Geiger-Mueller—**A sensitive, gas-filled radiation-measuring device that responds to individual ionizing particles.
>
> **Counter, Scintillation—**The combination of phosphor, a photomultiplier tube, and associated circuits for counting light emissions produced in the phosphors by ionizing radiation.

Cumulative Dose—The total dose resulting from continuous or intermittent exposures of radiation to the same region of the body, or to the whole body, from internally deposited radioisotopes over a period of time. (See Also Weighting Factor.)

Curie (Ci)— The quantity of radioactive material in which 37 billion radioactive atoms transform per second, which is approximately the activity of 1 gram of radium.

Decay Constant—See transformation constant.

Decay Product (Daughter Product, Progeny)—Isotopes that are formed by the radioactive transformation of some other nuclide. In the case of ^{226}Ra, for example, there are 10 successive daughter products or progeny, ending in the stable isotope ^{206}Pb.

Decay, Radioactive—Transformation of the nucleus of an unstable nuclide by spontaneous emission of charged particles and/or photons.

Deep Dose Equivalent (H_d)—The dose equivalent at a tissue depth of 1 cm inside the body surface from external whole-body radiation.

Delayed Health Effects—The health effects that manifest themselves after an extended period.

Derived Air Concentration (DAC)—The concentration of a given radionuclide in the air which, if breathed by the reference man for one working year (2,000 hours) under conditions of light work, results in an intake of one ALI.

Detector—A material or device that is sensitive to radiation and can produce a response signal suitable for measurement or analysis.

Deterministic Effects—Health effects for which there exists a definite threshold and which become more severe as the dose is increased. The dose response curve is sigmoid-shaped. Examples of deterministic effects are acute radiation syndrome and cataracts (previously referred to as non-stochastic effects)

Developmental Toxicity—The occurrence of adverse effects on a developing organism that may result from exposure to a chemical or to ionizing 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, Nuclear—A spontaneous nuclear transformation (radioactivity) characterized by the emission of energy and/or mass from the nucleus. When large numbers of nuclei are involved, the process is characterized by a physical half-life. (See also Transformation, Nuclear.)

Dose (or Radiation Dose)—A general term denoting the amount of energy from radiation that is absorbed per unit mass of absorber. A generic term meaning absorbed dose, dose equivalent, deep dose equivalent, effective dose, effective dose equivalent, committed dose equivalent, committed effective dose equivalent, equivalent dose, or total effective dose equivalent. For special purposes it must be appropriately qualified. If unqualified, it refers to the absorbed dose.

Dose Assessment—An estimate of the radiation dose to an individual or a population group usually by means of predictive modeling techniques, often supplemented by the results of measurement.

Dose Conversion Coefficient (or dose conversion factor)—A factor (Sv/Bq or rem/Ci) that is multiplied by the intake quantity of a radionuclide (Bq or Ci) to estimate the committed dose equivalent from radiation (Sv or rem). The dose conversion factor depends on the route of entry (inhalation or ingestion), the lung clearance class (D, W, or Y) for inhalation, the fractional uptake from the small intestine to blood (f1) for ingestion, and the organ of interest. EPA provides separate dose conversion factor tables for inhalation and ingestion, and each provides factors for the gonads, breast, lung, red marrow, bone surface, thyroid, remainder, and effective whole body.

Dose Equivalent (DE)—A quantity used in radiation protection. It expresses all radiations on a common scale for calculating the dose for purposes of radiation safety. It is the product of the absorbed dose in rad or gray and a quality factor, whose value depends on the radiation. (The unit of dose equivalent is the rem. In SI units, the dose equivalent is the sievert, which equals 100 rem.)

Dose, Fractionation—The division of a therapeutic radiation dose into fractions that are administered over a period of time. Dose is delivered during discrete time periods. Between fractions, there is no dose.

Dose, Radiation—The amount of energy imparted to matter by ionizing radiation per the unit mass of matter, usually expressed as the rad, or in SI units, the gray (Gy), 100 rad = 1 Gy (See also Absorbed Dose.)

Dose Rate—The radiation dose delivered per unit time. The rate can be measured, for example, in gray per hour, sievert per hour, rem per hour, or rad per hour.

Dosimetry—Quantification of radiation doses to individuals or populations resulting from specified exposures.

Early Effects (of radiation exposure)—Effects which appear within 60 days of an acute exposure; usually associated with acute radiation syndrome when whole body is exposed.

Effective Dose—The sum of the weighted equivalent doses in all the tissues and organs of the body.

Effective Dose Equivalent (H_E)—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 ($HE = 3 W_T H_T$). The effective dose equivalent recognizes the carcinogenic radiosensitivity of the several different tissues of the body.

Effective Half-Life (also effective half-time)—The time required for a radioactive element in an animal body to be diminished 50% as a result of the combined action of radioactive transformation and biological elimination. It is described by the following equation:

> Effective Half-Life = (Biological half-life x radioactive half-life) / (biological half-life + radioactive half-life).

Electron—A stable elementary particle having an electric charge equal to $\pm 1.60210 \times 10^{-19}$ Coulombs (C), and a rest mass equal to 9.1091×10^{-31} kg. A positron is a positively charged "electron" (see Positron).

Electron Capture—A mode of radioactive transformation involving the capture of an orbital electron by its nucleus. Capture from a particular electron shell is designated as "K-electron capture," "L-electron capture," and so on. The atom then emits x rays.

Electron Volt—A unit of energy equivalent to the energy gained by an electron in passing through a potential difference of one volt. It is the energy unit for an ionizing particle or photon often expressed as keV for thousand or kilo electron volts or MeV for million or mega electron volts. (symbol: eV, as in $1eV \text{ ' } 1.6x10^{-12}$ erg.)

Embryo/Fetus—The developing human (or animal) from the time of conception up to the time of birth.

Embryotoxicity and Fetal toxicity—Any toxic effect on the conceptus as a result of prenatal exposure to ionizing radiation or 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.

Enriched Material—(1) Any material in which the relative amount of one or more isotopes of a constituent has been increased over its natural abundance. (2) Uranium in which the percentage of ^{235}U to total uranium of all isotopes is increased from its natural value of 0.72% to a higher value.

Equilibrium, Radioactive—In a radioactive series, the state that prevails when the ratios between the activities of two or more successive members of the series remain constant, or when the activities are equal.

Eventration—Disembowelment or protrusion of the bowels from the abdomen.

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.

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 or scattering of photons or from inelastic collisions with particles. The excited state of an atom is an unstable state and will return to the ground state by radiation of the excess energy.

Exposure—A measure of the intensity of an x ray or gamma ray field in air, whose value depends on the ionization produced in air by x or gamma radiation. The traditional unit of exposure is the roentgen (R), and the SI unit is the coulomb per kilogram.

External Dose—The amount of energy, expressed per unit mass of matter, imparted to an organism by ionizing radiation from a source outside the body.

External Radiation—Radiation exposure from a source outside the body.

Eye Dose Equivalent—The dose equivalent of radiation received by the lens of the eye which is at a depth of 0.3 cm below the outside surface (cornea) of the eye, delivered by an external radiation source.

Fission, Nuclear—A nuclear transformation characterized by the splitting of a nucleus into two or three other nuclei and two or three neutrons, and the release of a relatively large amount of energy.

Fundus—the bottom or base of anything. Pertaining to hollow organs, it is the portion farthest from its mouth or opening. Pertaining to the eye, the fundus is the back portion of the interior of the eyeball.

Tapetal fundus—a highly reflective structure in the dorsal portion of the fundus of the eye.

Nontapetal fundus—the nonreflective ventral portion of the fundus of the eye.

Gamma Ray (synbolized by Greek letter γ)—A short wavelength electromagnetic radiation of nuclear origin (range of energy from about 10 keV to about 9 MeV, which is sufficient to cause ionization).

Genetic Effect of Radiation—An inheritable change, chiefly mutations, produced by the absorption of ionizing radiation by germ cells.

Gray (Gy)—The SI unit of the absorbed dose. One Gy equals the absorption of 1 joule of energy (about 1/4 of a calorie) per kilogram of absorber. One gray equals 100 rad. (See also Units.)

Half-Life, Biological (or biological half-time)—The time required for the body to eliminate one-half of any absorbed substance by regular physiological processes of elimination. It is the same for both stable and radioactive isotopes of a particular element.

Half-Life, Effective—The time required for a radioactive element in an animal body to be diminished 50% as a result of the combined action of radioactive transformation and biological elimination.

Half-Life, Physical (see Half-Life Radioactive)

Half-Life, Radioactive—The time required for a radioactive substance to lose 50% of its activity by transformation. Each radionuclide has a unique half-life.

Half-Time (see Half-Life, Biological)

High-LET—The characteristic ionization patterns by alpha particles, protons, or fast neutrons having a high relative specific ionization per unit path length.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to agents such as radiation or chemicals.

***In Vitro*—**The condition of being isolated from a living organism and artificially maintained, as in a test tube.

***In Vivo*—**Any condition occurring within a living organism.

Induced Radioactivity—The 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 humans.

Intensity—The amount of energy per unit time passing through a unit area perpendicular to the line of propagation at the point in question.

Intermediate Exposure—An exposure to radiation for a duration of 15–364 days.

Internal Conversion—One of the possible mechanisms of transformation from the metastable state (isomeric transition) in which the transition energy is transferred to an orbital electron, causing its ejection from the atom. 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."

Internal Radiation— Radiation from radionuclides inside the body.

Ion—An 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 ionizing radiation (photons or particles) remove electrons from an atom. The process in chemical reactions by which a neutral atom or molecule acquires a positive or negative charge.

Ionizing Energy—The average energy lost by ionizing radiation in producing an ion pair. For air, the ionizing energy is about 34eV per ion pair by beta particles.

Ionizing Density—The number of ion pairs per unit volume.

Ionization Path (Track)—The trail of ion pairs produced by ionizing radiation in its passage through matter.

Ionization Potential —The energy, in electron-volts (eV), necessary to separate one electron from an atom, resulting in the formation of an ion pair.

Ionizing Radiation—Any electromagnetic or particulate radiation capable of producing ions, directly or indirectly, in its passage through matter.

Isotopes—Any nuclide of the same element 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. Almost identical chemical properties exist between isotopes of a particular element, but physical properties such as diffusion through a membrane may differ. This term should not be used as a synonym for nuclide.

Joule—The unit for work and energy, equal to one newton expended along a distance of one meter (1 J =1 N x l m). There are 4.2 joules per calorie. In terms of radiological units, 1 J = 1 Gy-kg.

Kerma (k)—The initial kinetic energy of the primary ionizing particles produced by the interaction of the incident radiation per unit mass of interacting medium, expressed as J/kg or grays (rads).

Labeled Compound—A compound consisting, in part, of labeled molecules. These are molecules including radionuclides in their 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)—Any effects that appear 60 days or more following an acute exposure.

Lethal Dose$_{50}$ (LD$_{50}$)—The dose of radiation or a chemical that has been found to cause death in 50% of a defined population.

Lethal Dose$_{50/30}$ (LD$_{50/30}$)—The dose of radiation or a chemical which kills 50% of the population within 30 days.

Linear Energy Transfer (LET)—The average amount of energy transferred locally to the medium per unit of particle or electromagnetic radiation track length.

Linear Hypothesis or Linear No Threshold (LNT) Hypothesis—The assumption that a dose-response curve derived from data in the high dose and high dose-rate ranges may be extrapolated linearly through the low dose and low dose-rate ranges to zero, implying that, theoretically, any amount of radiation will cause some damage.

Low-LET—The characteristic ionization patterns of electrons, x rays, and gamma rays having a low relative specific ionization per unit path length compared to high LET radiation.

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 the frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations—Any permanent structural changes that may adversely affect survival, development, or function as a result of *in utero* exposure.

Mass Absorption Coefficient—The linear absorption coefficient per centimeter divided by the density of the absorber in grams per cubic centimeter. This is the fraction of incident radiation that is absorbed per unit mass of the absorber.

Mass Number—The number of nucleons (protons and neutrons) in the nucleus of an atom. (Symbol: A)

Median Lethal Dose (MLD)—The dose of radiation required to kill 50% of the individuals in a large group of animals or organisms within a specific period, usually 30 days. Also called LD$_{30}$.

Megacurie—One million curies. (Symbol: MCi)

Microcurie—One-millionth of a curie. Amount of material in which 3.7×10^4 radioactive atoms transform per second. (Symbol: μCi)

Millicurie—One-thousandth of a curie. Amount of material in which 3.7×10^7 radioactive atoms transform per second. (Symbol: mCi)

Minimal Risk Level (MRL)—An estimate of daily human exposure to a dose of radiation or a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Monoenergetic Radiation—Radiation of a given type (alpha, neutron, gamma, etc.) in which all particles or photons originate with the same energy.

Mutagen—A substance that causes mutations.

Mutation—A mutation is a change in the genetic material in a body cell. Mutations in germ cells can lead to birth defects and miscarriages; mutations in somatic cells may lead to cancer.

Nanocurie—One-billionth of a curie. Amount of material in which 37 radioactive atoms transform per second. (Symbol: nCi)

Natural Radioactivity—The property of radioactivity exhibited by more than 50 naturally occurring radionuclides.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to radiation or a chemical.

Neutrino—A neutral particle of very nearly zero rest mass emitted during the beta-decay process. It plays no role in radiation bio-effects.

Non-deterministic Effects (stochastic effects) —Health effects which appear to be related to random events. Dose-response is assumed to be linear without threshold in radiation protection.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of radiation or a chemical that produces 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.

Nucleon—Generic 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.

Pair Production—An absorption process for x ray and gamma radiation in which the incident photon is annihilated in the vicinity of the nucleus of the absorbing atom, and its energy is converted into an electron and positron pair. This reaction only occurs for incident photon energies exceeding 1.02 MeV, which is the energy equivalence of the masses of the positron and electron.

Parent Radionuclide—A radionuclide which, upon transformation, yields a specified nuclide, either directly or as a later member of a radioactive series. The radionuclide from which a new nuclide was made as a result of radioactive transformation.

Photoelectric An interaction between an x ray or gamma ray (photon) and an atom in which an orbital electron is knocked out. The photon disappears because it gives up all of its energy in the collision.

Photon—A quantity of electomagnetic radiation whose energy content depends on the frequency or wavelength of the radiation. The equation is: $E=h\nu$. Photon energy for ionizing radiation purposes is usually measured in eV, keV and MeV. 1 eV = 1.6×10^{-19}J.

Picocurie—One-trillionth of a curie (3.7×10^{-2} transformations per second or 2.22 transformations per minute). (Symbol: pCi)

Positron—A particle equal in mass to the electron (9.1091×10^{-31} kg) and having an equal but positive charge ($+1.60210 \times 10^{-19}$ Coulombs). (See also Electron).

Primary Ionization—(1) In collision theory, the ionization produced by the primary particles (photoelectron, Compton electron, or positron-electron pair) as contrasted with 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.

Progeny—The transformation products resulting after a series of radioactive decays. Progeny can also be radioactive, and the chain continues until a stable nuclide is formed.

Proton—An elementary nuclear particle with a positive electric charge equal numerically to the charge of the electron and a rest mass of 1.007277 atomic mass units.

Public Dose—The dose received by a member of the public from exposure to radiation caused by a licensee or to any other source of radiation under the control of a licensee, excluding background and occupational doses.

Quality—A term describing the distribution of the energy deposited by a particle along its tract; radiations that produce different densities of ionization per unit track length 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 the biological effectiveness of the absorbed dose on a common scale for all ionizing radiation.

Rad—The unit of absorbed dose equal to 0.01 J/kg in any medium. (See also Absorbed Dose.)

Radiant Energy—The energy of electromagnetic radiation, such as radio waves, visible light, x and gamma rays.

Radiation—(1) The emission and propagation of energy through space or through a material medium in the form of waves: for instance, the emission and propagation of electromagnetic waves, or of sound and elastic waves. (2) The energy propagated through space or through a material medium such as waves; for example, energy in the form of electromagnetic waves or of elastic waves. The term radiation or radiant energy, when unqualified, usually refers to electromagnetic radiation. Such radiation commonly is classified, according to frequency, as with Hertzian, infrared, visible (light), ultraviolet, x ray and gamma ray (see also Photon). (3) By extension, corpuscular emission, such as alpha and beta radiation, or rays of mixed or unknown type, such as cosmic radiation.

Radioactivity—The property of certain nuclides to spontaneously transform into another element by emitting alpha or beta particles, or undergoing electron capture.

Radioisotope—Radioactive atomic species of an element with the same atomic number and identical chemical properties.

Radionuclide—A radioactive species of an atom characterized by the constitution of its nucleus.

Radiosensitivity—The relative susceptibility of cells, tissues, organs, organisms, or any living substance to the injurious action of radiation. Radiosensitivity and its antonym, radioresistance, are currently used in a comparative sense, rather than in an absolute one. Radiosensitivity depends upon the biological response being measured.

Reaction (Nuclear)—An induced nuclear transformation (i.e., a process occurring when a nucleus comes in contact with a photon, an elementary particle, or another nucleus). In many cases, the reaction can be represented by the symbolic equation: X+a6Y+b or, in abbreviated form, X(a,b) Y, where X is the target nucleus, a is the incident particle or photon, b is an emitted particle or photon, and Y is the product nucleus.

Reference Man —A theoretical human male on which dosimetry calculations related to ionizing radiation exposure are based. Reference man is 70 kg and consists of detailed organ mass data for all major human body organs. Models, which can be other than 70 kg, are also available for different ages and for females (pregnant and non-pregnant).

Relative Biological Effectiveness (RBE)—The RBE is a factor used to compare the biological effectiveness of absorbed radiation doses 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 required to produce an identical biological effect in a particular experimental organism or tissue (see also Quality Factor). RBE depends on several experimental factors including dose, dose rate, and biological end point. RBE is not used in radiation protection practice. Quality factor is used in radiation protection but is derived from LET. RBE is an index of comparison of radiations of different quality.

Rem—A unit of dose equivalent. The dose equivalent in rem is numerically equal to the absorbed dose in rad multiplied by the quality factor. It is used only in the context of radiation safety, administrative, and engineering design purposes.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to radiation or 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 to photon radiation whose energy #3 MeV. One roentgen generates 2.58×10^{-4} Coulomb of charge of either sign per kilogram of air at standard temperature and pressure (0 EC, 1 atm). The roentgen is defined for x and gamma rays only.

Scattered Radiation—Radiation that, during its passage through a substance, has been deviated in direction. It usually will have been modified by a decrease in energy.

Scientific Units

Prefix (Symbol)	Power of 10	Decimal Equivalent
atto (a)	10^{-18}	0.000000000000000001
femto (f)	10^{-15}	0.000000000000001
pico (p)	10^{-12}	0.000000000001
nano (n)	10^{-9}	0.000000001
micro (μ)	10^{-6}	0.000001
milli (m)	10^{-3}	0.001
centi (c)	10^{-2}	0.01
deci (d)	10^{-1}	0.1
kilo (k)	10^{3}	1,000.0
mega (M)	10^{6}	1,000,000.0
giga (G)	10^{9}	1,000,000,000.0
tera (T)	10^{12}	1,000,000,000,000.0
peta (P)	10^{15}	1,000,000,000,000,000.0
exa (E)	10^{18}	1,000,000,000,000,000,000.0

Secondary Radiation—Radiation that results from the interaction of other radiation in matter. It may be either electromagnetic or particulate.

Secular Equilibrium—If a parent element has a much longer half-life than its progeny (so that there is no 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 that are in equilibrium transform in unit time. This means that each has the same activity measured in curies or becquerels. This condition is never exactly attained, but is essentially established after 6 or 7 daughter half-lives. For example, the half-life of radium is about 1,600 years; of radon, approximately 3.82 days; and for each of the subsequent members, a few minutes. After about a month, the equilibrium amount of radon is present; then (and for a long time) all members of the series transform at the same number of atoms per unit time. Thus contained radon gas is in secular equilibrium with its parent ^{226}Ra after about 27 days.

Self-Absorption—The 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).

Shallow Dose Equivalent (H_S)—The dose equivalent at a tissue depth of 0.007 cm averaged over an area of 1 cm^2 from external exposure of the skin or an extremity.

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, Radiation —(1) A syndrome characterized by nausea, vomiting, diarrhea, and psychic depression following exposure to appreciable doses of ionizing radiation within a short period of hours to weeks. Its mechanism is known, and remedies include fluid replacement, antibiotics, electrolyte replacement, and in some cases, marrow stem cell support. It usually appears a few hours after irradiation and may subside within a day. In nuclear medicine applications, it may be sufficiently severe to necessitate

interrupting the treatment series or to incapacitate the patient. (2) The syndrome associated with intense acute exposure to ionizing radiations. The rapidity with which symptoms develop is a rough measure of the dose level. The syndrome also includes certain signs such as changes in peripheral blood cell counts.

Sievert—The SI unit of radiation dose equivalent. It is equal to dose in grays times a quality factor; 1 sievert equals 100 rem.

Somatic Effects—Effects of radiation limited to the exposed individual, as distinguished from genetic effects, which may subsequently affect unexposed future generations.

Specific Activity—The total activity of a given nuclide per volume or mass. It is a concentration defined as the ratio of the amount of radioactivity divided by the mass or volume of radioactive substance, e.g. the specific activity of ^{238}U metal is 0.33 μCi/g.

Stable Isotope—A nonradioactive isotope of an element.

Standard Mortality Ratio (SMR)—The ratio of the disease or accident mortality rate in a certain population compared with that in a standard population. The SMR is usually expressed in percent. Thus, an SMR is the mortality rate for the standard population.

Stopping Power—The average rate of energy loss of a charged particle per unit thickness or per unit mass of a material traversed as a result of Coulomb interactions with electrons and with atomic nuclei.

Stochastic effects—See Non-Deterministic Effects.

Surface-seeking Radionuclide—A bone-seeking radioactive material that is deposited and remains on the surface for a long period of time. This contrasts with a volume seeker, which deposits more uniformly throughout the bone volume.

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 that 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. When the target is “hit,” it is inactivated. A specific biological response (e.g., cell death) may require the inactivation of more than one target. A critical characteristic of target theory in the context of the linear no-threshold theory, is that targets are not repairable once they are hit or inactivated.

Teratogen—Radiation or a chemical that can lead to birth defects.

Tissue Dose—The absorbed dose received by tissue in the region of interest, expressed in Gray or rad. (See also Dose and Rad.)

Total Effective Dose Equivalent (TEDE)—The sum of the effective deep dose equivalent from external exposures and the committed effective dose equivalent from internal exposures.

Total Ionization—The total electric charge of one sign on the ions produced by radiation in a material. It is frequently used as a measure of radiation energy absorbed per unit mass of gas.

Total Organ Dose Equivalent (TODE)—The sum of the dose equivalent to an organ or tissue from external radiation and the committed dose equivalent to that organ or tissue from radioactive materials deposited within the body.

Transformation Constant—The fraction of the number of atoms of a radioactive nuclide that transforms in unit time. λ is the symbol for the transformation constant in the equation $N = N_0 e^{-\lambda t}$, where N_0 is the initial number of atoms present, and N is the number of atoms present after some time, t.

Transformation, Nuclear—The process by which a nuclide is transformed into a different nuclide by absorbing or emitting a particle.

Transient Equilibrium—If the half-life of the parent is short enough, so that 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. An example of this is radon (half-life of approximately 3.82 days), and successive members of the series to ^{210}Pb.

Transition, Isomeric—The process by which an excited nuclide decays to the ground state to produce an isomeric nuclide (i.e., one of the same mass number and atomic number) by emitting a gamma ray.

Tritium—The hydrogen isotope with one proton and two neutrons in the nucleus (Symbol: ^{3}H or T). Tritium is radioactive, with a half-life of 12.3 years; it emits very low energy beta particles.

Unattached Fraction—That fraction of the radon daughters, usually ^{218}Po (Radium A), that has not yet electrostatically attached to an airborne dust particle. As a free atom, it has a high probability of being retained within the lung and depositing alpha energy when it decays.

Units, Radiological

Units	Equivalents
becquerel*	1 Bq = 1 transformation or disintegration per second = 2.7×10^{-11} Ci
curie	1 Ci = 3.7×10^{10} transformations or disintegrations per second = 3.7×10^{10} Bq
gray*	1 Gy = 1 J/kg = 100 rad
rad	1 rad = 100 erg/g = 0.01 Gy
sievert*	1 Sv = 100 rem
rem	1 rem = 0.01 sievert
Roentgen	1 R = 2.58×10^{-4} coulomb of charge of either sign produced in 1 kilogram of air at STP

*International Units are designated as SI.

Weighting Factor (W_T)—A dosimetric factor used in the practice of health physics (radiation safety) to account for the relative carcinogenic susceptibility of the various tissues.

Whole Body—For the purposes of radiation exposure, the part of the body composed of the head, trunk, arms above the elbow, legs above the knee, and gonads.

Working Level (WL)—A unit for measuring the atmospheric concentration of radon progeny. It corresponds to the equilibrium concentration of radon progeny due to 100 pCi radon per liter of air, or any combination of short-lived radon daughters in 1 liter of air that will result in the ultimate emission of $1.3x10^5$ MeV of potential alpha energy.

Working Level Month (WLM)—Inhalation of air with a concentration of 1 WL of radon daughters for 170 working hours results is an exposure of 1 WLM.

X rays—Penetrating electromagnetic radiations whose wave lengths are shorter than those of ultraviolet light. X rays can be classified as characteristic x rays or bremsstrahlung. Characteristic x rays are produced deliberately in x ray machines or directly when ionizing radiation passes through matter. These x rays occur when electrons are ejected from an atom and electrons in higher energy orbitals cascade down to fill in those vacancies, releasing the energy difference between those orbitals as electromagnetic radiation (x rays). Bremsstrahlung is x rays that are radiated from a beta particle as it accelerates (changes direction) in the strong electrostatic field of an atomic nucleus, as occurs when electrons are stopped in a high atomic number element, such as lead.

10. REFERENCES

*AAPM. 1999. American Association of Physicists in Medicine. Home page. http://www.aapm.org

*Aarkrog. 1971. Environmental behavior of plutonium accidentally released at Thule, Greenland. Health Phys 32:271-284.

*Abraham SK, Sarma L, Kesavan PC. 1993. Protective effects of chlorogenic acid, curcumin and beta-carotene against gamma-radiation-induced *in vivo* chromosomal damage. Mutat Res 303(3):109-112.

*ACGIH. 1998. 1998 TLVs and BEIs. Threshold limit values for chemical substances and physical agents. Biological exposure indices. American Conference of Governmental Industrial Hygienists. March 1, 1998.

*ACHRE. 1995. The Marshallese. Final report. Advisory Committee on Human Radiation Experiments. Chapter 12. U.S. Govt. Printing Office Document #064-000-00-848-9. http://nattie.eh.doe.gov/systems/hrad/chap12_3.html

*ACHRE. 1995. The uranium miners. Final report. Advisory Committee on Human Radiation Experiments. Chapter 12, section 2. http://nattie.eh.doe.gov/systems/hrad/chap12_2.html

*Adams GE, Wilson A. 1993. Radiation toxicology. In: Ballantyne B, Marrs T, Turner P, eds. General and applied toxicology, Vol 2, 1397-1415.

*AFRRI. 1998. Armed Forces Radiobiology Research Institute. Home page. http://www.afrri.usuhs.mil/www/index.html

*Aghamohammadi SZ, Goodhead DT, Savage JRK. 1988. Induction of sister chromatid exchanges (SCE) in G0 lyphocytes by plutonium-238 a-particles. Int J Radiat Biol 53(6):909-915.

*Albert RE, Shore RE. 1986. Carcinogenic effects of radiation on the human skin. In: Radiation carcinogenesis. New York, NY: Elsevier, 335-345.

*Albert RE, Shore RE, Harley NH, et al. 1986. Followup studies of patients treated by epilation for tinea capitis. In: Burns F, Upton AC, Silini G, eds. Radiation, carcinogenesis and DNA alterations. New York, NY: Plenum Press, 1-25.

*Amaral EC, Vianna ME, Godoy JM, et al. 1991. Distribution of Cs-137 soils due to the Goiania accident and decisions for remedial action during the recovery phase. Health Phys 60(1):91-98.

*American Airpower Heritage Museum. 1996. The "special" bomb. http://www.avdigest.com/aahm/trspcbmb.html.

*Amundson SA, Chen DJ. 1994. Ionizing radiation-induced mutation of human cells with different DNA repair capacities. Los Alamos National Lab, NM.

*Cited in text

*Andersen ME, MacNaughton MG, Clewell HJ, et al. 1987. Adjusting exposure limits for long and short exposure periods using a physiological pharmacokinetic model. Am Ind Hyg Assoc J 48(4):335-343.

*Andersen ME, Krishnan K. 1994. Relating *in vitro* to *in vivo* exposures with physiologically-based tissue dosimetry and tissue response models. In: H. Salem, ed. Animal test alternatives. U.S. Army Chemical Research Development and Engineering Center, Aberdeen Proving Ground, Maryland.

*Andrews LS, Ahmedna M, Grodner RM, et al. 1998. Food preservation using ionizing radiation. Rev Environ Contam Toxicol 154:1-53.

*Angelo DL, Rittiger CL, Scott RP, et al. 1999. Exposure rates associated with high level fluoroscopic equipment and data recording modes. Health Phys 76(supplement 2):578-582.

*Anonymous. 1995. Advisory committee on human radiation experiments. Supplemental volume 2. Sources and documentation. Final report. Department of Energy, Washington, DC. Advisory Committee on Human Radiation Experiments.

*Anonymous. 1997a. Report on search for human radiation experiment records, 1944-1994 (volume 1). Assistant to the Secretary of Defense for Nuclear and Chemical and Biological Defense Programs, Washington, DC.

*Anonymous. 1997b. Report on search for human radiation experiment records, 1944-1994 (volume 2). Assistant to the Secretary of Defense for Nuclear and Chemical and Biological Defense Programs, Washington, DC.

*ANSI. 1978. American National Standards Institute. Radiation Protection Instrumentation Test and Calibration, ANSI N323, New York, NY. The Institute of Electrical and Electronics Engineer, Inc.

*ANSI. 1993. American National Standards Institute. Personnel Dosimetry Performance Criteria for Testing, ANSI N13.11.

*Artemova AM, Peterkove V. 1994. Thyroid status in children and adolescents living in areas contaminated with radioactive materials after the Chernobyl accidents. In: Nagataki S, ed. International Congress Series, No. 1074, 0(0):233-235.

*Atomic Energy Insights. 1996. Chernobyl Health Effects: Best Available Data. Adams Atomic Engines, Tarpon Springs, vol. 2, No. 1.
http://ans.neep.wisc.edu/~ans/point_source/AE/apr96/effects.html.

*ATSDR. 1990a. Subcommittee report on biological indicators of organ damage. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA.

*ATSDR. 1990b. Toxicological profile for thorium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*ATSDR. 1990c. Toxicological profile for plutonium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*ATSDR. 1990d. Toxicological profile for radium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

10. REFERENCES

*ATSDR. 1990e. Toxicological profile for radon. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*ATSDR. 1999a. Toxicological profile for aluminum. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*ATSDR. 1999b. Toxicological profile for uranium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*Aub JC, Evans RD, Hempelmann LH, et al. 1952. The late effects of internally-deposited radioactive materials in man. Medicine: Analytical Reviews of General Neurology and Pediatrics 31:221-329.

*Ayene SI, Srivastava PN. 1985. Radioprotective effect of 2-mercaptopropionylglycine on radiation-induced microsomal lipid peroxidation. Int J Radiat Biol Relat Stud Phys Chem Med 48(2):197-205.

*Badhwar GD, Cucinotta FA, O'Neill PM. 1994. An analysis of interplanetary space radiation exposure for various solar cycles. Radiat Res 138(2):201-208.

*Balsalobre B. 1991. Complement, circulating immunocomplexes and autoantibodies after ionizing radiation exposure. Rev Esp Fisiol 47(3):147-50.

*Baranov AE, Guskova AK, Nadejina NM, et al. 1995. Chernobyl experience: Biological indicators of exposure to ionizing radiation. Stem Cells 13(Suppl 1):69-77.

*Barnes JE, McClellan RO, Hobbs CH. 1972. Toxicity in the dog of inhaled ^{90}Y in fused clay particles: Distribution, retention kinetics, and dosimetry. Radiat Res 49:416-429.

*Barnthouse LW. 1995. Effects of ionizing radiation on terrestrial plants and animals: A workshop report. Oak Ridge National Lab.

*Bassant MH, Court L. 1978. Effects of whole-body irradiation on the activity of rabbit hippocampal neurons. Radiat Res 75:593-606.

*Bayrakova A, Filev G, Baev I, et al. 1987. Reciprocal translocations in germ cells of male mice receiving external gamma-irradiation. Mutat Res 176(1):53-58.

Baylor College. 1999. Radiation effects. Baylor College of Medicine. http://radefx.bcm.tmc.edu/

*Bazyltchik SV, Astakhova LN. 1995. Mental development of children exposed to ionizing radiation *in utero* and in infancy. In: Nagataki S, Yamashita S, ed. International Congress Series, No. 1103. Nagasaki Symposium: Radiation and Human Health: Proposal from Nagasaki; Nagasaki Symposium '95, 50th Anniversary Meeting of the Atomic Bombing in Nagasaki, Nagasaki, Japan, September 19, 1995. Elsevier Science Publishers B.V.: Amsterdam, Netherlands; New York, New York, USA. 97-102.

*Bebeshko VG. 1995. Health effects of the Chernobyl accident abstract. 1995 Uranium Institute Symposium Abstract. http://www.uilondon.org/uiabs95/bebast/html.

*Bebeshko VG. 1996. Health effects of the Chernobyl accident. Uranium Inst Uranium and Nucl Energy 1995 20th Int Symp, London, UK, 67-73.

*Becker PHB, Matta LESC, Moreira AJC. 1991. Guidance for selecting nuclear instrumentation derived from experience in the Goiania accident. Health Phys 60(1):77-80.

*Beechey CV, Green D, Humphreys ER, et al. 1975. Cytogenic effects of plutonium-239 in male mice. Nature 256(5518):577-578.

*BEIR III. 1980. The effects on populations of exposure to low levels of ionizing radiation. Committee on the Biological Effects of Ionizing Radiations, National Research Council. Washington, DC: National Academy Press.

*BEIR IV. 1988. Health risks of radon and other internally deposited alpha-emitters. Committee on the Biological Effects of Ionizing Radiations, National Research Council. Washington, DC: National Academy Press.

*BEIR V. 1990. Health effects of exposure to low levels of ionizing radiation. Committee on the Biological Effects of Ionizing Radiations, National Research Council. Washington, DC: National Academy Press.

Bellona. 1998. Reprocessing plants in Siberia: Seversk. http://www.bellona.no/e/russia/sibir/sibir2.htm.

*Belot Y, Gauthier D, Camus H, et al. 1979. Prediction of the flux of tritiated water from air to plant leaves. Health Phys 37:575-583.

*Benjamin SA, Boecker BB, Cuddihy RG et al. 1979. Nasal carcinomas in Beagles after inhalation of relatively soluble forms of beta-emitting radionuclides. J Natl Cancer Inst 63:133-139.

*Benjamin SA, Hahn FF, Boecker BB. 1978. Effects of chronic pulmonary irradiation on periheral lymphocytes and their function in the dog. Radiat Res 75:121-137.

*Benjamin SA, Hahn FF, Chiffelle TL, et al. 1975. Occurence of hemangiosarcomas in Beagles with internally deposited radionuclides. Cancer Res 35:1745-1755.

*Benjamin SA, Jones RK, Snipes MB, et al. 1976. Comparative effects of inhaled relatively insoluble forms of ^{90}Y, ^{144}Ce, and ^{90}Sr on canine peripheral lymphocyte function. In: J. E. Ballou, ed. Radiation and the lympathic system. CONF-740930. 90-99.

*Benjamin SA, Lee AC, Angleton GM, et al. 1986. Neoplasms in young dogs after perinatal irradiation. J Natl Cancer Inst 77(2):563-571.

*Bentur Y, Horlatsch N, Koren G. 1991. Exposure to ionizing radiation during pregnancy: Perception of teratogenic risk and outcome. Teratology 43(2):109-112.

*Berger ME, Hurtao R, Dunlap J, et al. 1997. Accidental radiation injury to the hand: Anatomical and physiological considerations. Health Phys 72(3):343-348.

*Bhatia AL, Gupta ML, Singh RP. 1978. Response of mice liver to continuous beta-irradiation from tritiated water. J Radiat Res (Tokyo) 19(3):197-204.

*Biedermann KA, Sun J, Giaccia AJ, et al. 1991. Acid mutation in mice confers hypersensitivity to ionizing radiation and deficiency DNA double-strand break repair. Proc Natl Acad Sci USA 88:1394-1397.

10. REFERENCES

*Bigatti P, Lamberti L, Ardito G, et al. 1988. Cytogenetic monitoring of hospital workers exposed to low-level ionizing radiation. Mutat Res 204(2):343-347.

*Birioukov A, Meurer M, Peter RU, et al. 1993. Male reproductive system in patients exposed to ionizing irradiation in the Chernobyl accident. Arch Androl 30(2):99-104.

*Blocher D. 1988. DNA double-strand break repair determines the RBE of α-particles. Int J Radiat Biol 54(5):761-771.

*Bocian E, Ziemba-zak B, Roseik O, et al. 1977. Chromosome aberrations in human lymphocytes exposed to tritiated water *in vitro*. Current Topics in Radiation Research Quartley 12:168-181.

*Boecker BB. 1972. Toxicity of 137 CsCl in the Beagle: Metabolism and dosimetry. Radiat Res 50:556-573.

*Boecker BB, Hahn FF, Muggenburg BA. 1988. The relative effectiveness of inhaled alpha- and beta-emitting radionuclides in producing cancer. Radiation Protection Practice 2:1059-1062.

*Bogo V, Jacobs AJ, Weiss JF. 1985. Behavioral toxicity and efficacy of WR-2721 as a radioprotectant. Radiat Res 104(2 Pt 1):182-190.

*Booth GF. 1977. The need for radiation controls in phosphate and related Iidustries. Health Phys 32:285-290.

*Borek C, Abraham SK, Sarma L. 1993. Molecular mechanisms in cancer induction and prevention protective effects of chlorogenic acid, curcumin and beta-carotene against gamma-radiation-induced *in vivo* chromosomal damage. Environ Health Perspect 101:237-245.

*BRAMA. 1996. Gateway Ukraine. http://www.brama.com/ukraine/cbyl.html

*Brandao-Mello CE, Oliveira AR, Valverde NJ, et al. 1991. Clinical and hematological aspects of Cs-137: The Goiania radiation accident. Health Phys 60(1):31-39.

*Brandvold LL, Brandvold DK, Popp CJ. 1981. Effects of uranium mining and milling on surface water in New Mexico. In: 7th National Conference: Energy Environ, 467-476.

*Brent et al. 1980. Radiation teratogenesis. Teratology 21:281-298.

*Brodsky A. 1996. Review of radiation risks and uranium toxicity with application to decisions associated with decommissioning clean-up criteria. RSA Publications.

*Brooks AL, Carsten AL, Mead DK, et al. 1976. The effect of continuous intake of tritiated water (HTO) on the liver chromosomes of mice. Radiat Res 68:480-489.

*Brooks AL, Guilmette RA, Hahn FF, et al. 1992. Distribution and biological effects of inhaled $^{239}Pu(NO_3)_4$ in Cynomolgus monkeys. Radiat Res 130:79-87.

*Brooks AL, Mead DK, Peters RF. 1971b. Effect of chronic exposure to ^{60}Co on the frequency of metaphase chromosome aberrations in the liver cells of the Chinese hamster (*in vivo*). Int J Radiat Biol 20:599-604.

*Brooks AL, Peters RF, Rollag MD. 1971a. Metaphase chromosome aberrations in Chinese hamster liver cells *in vivo* after single acute ^{60}Co exposure. Radiat Res 45:191-201.

*Bruni JE, Persaud TVN , Froese G, et al. 1994. Effects of *in-utero* exposure to low-dose ionizing radiation on development in the rat. Histology and Histopathology 9(1):27-33.

*Buc-Calderon P, Roberfroid M. 1990. Increase in the survival time of mice exposed to ionizing radiation by a new class of free radical scavengers. Experientia 46(7):708-710.

*Buell MG, Harding RK. 1989. Proinflammatory effects of local abdominal irradiation on rat gastrointestinal tract. Dig Dis Sci 34(3):390-399.

*Burt C. 1966. The genetic determination of differences in intelligence: A study of monozygotic twins reared together and apart. Brit J Psychol 57(1-2):137-153.

*Caldwell GG, Kelly DB, Heath CW. 1980. Leukemia among participants in military maneuvers at a nuclear bomb test: A preliminary report. JAMA 244:1575-1578.

*Caltech. 1998. Gamma-ray and X-ray spectroscopy with scintillation and semiconductor detectors. http://tweedledee.wonderland.caltech.edu/~derose/labs/exp12.html

*Canfi A, Chayoth R, Weill S, et al. 1990. The reproductive system of male rats exposed to very low doses of ionizing radiation, 1: Hormonal profile of animals exposed after sexual maturity. Andrologia 22(2):129-136.

*Cardis E, Anspaugh L, Ivanov VK, et al. 1996. Estimated long term health effects of the Chernobyl accident. Lawrence Livermore National Lab., CA.

*Cardis SE, Gilbert ES, Carpenter L, et al. 1994. Direct estimates of cancer mortality due to low-doses of ionizing radiation - an international study. Lancet 344(8929):1039-1043.

*Cassoni AM, McMillan TJ, Peacock JH, et al. 1992. Differences in the level of DNA double-strand breaks in human tumour cell lines following low dose-rate irradiation. Eur J Cancer 28A(10):1610-1614.

*CDC. 1995. Centers for Disease Control and Prevention and National Institute for Occupational Safety and Health: Research plan for occupational energy-related analytical epidemiology, 2-12.

*Cember H. 1996. Introduction to health physics, 3rd ed. New York, NY: McGraw Hill.

*Cenajek D, Chodera A, Wojciak Z, et al. 1980. Cystamine effect on the pharmacokinetics of imipramine in radiation sickness. Acta Physiol Pol 31(2):123-129.

*Chang J. 1999. Table of the nuclides. Korea Atomic Energy Research Institute. http://www.dne.bnl.gov/CoN/index.html

*Charles MW, Williams JP, Coggle JE. 1988. Skin carcinogenesis following uniform and nonuniform beta irradiation. Health Phys 55(2):399-406.

Chase. 1985. Medical applications of radioisotopes. In: Remington's pharmaceutical sciences, Chapter.29. Easton, PA: Mack Publishers.

*Checkoway H, Pearce N, Crawford-Brown J, et al. 1988. Radiation doses and cause-specific mortality among workers at a nuclear materials fabrication plant. American Journal of Epidemiology 127(2):255-266.

*Chernousenko VM. 1991. Chernobyl: Insight from the inside. Springer-Verlag. http://www.halcyon.com/blackbox/hw/accounts.html

*Childs JD. 1981. The effect of a change in mutation rate on the incidence of dominant and x-linked recessive disorders in man. Mutat Res 83:145-158.

*Chmelevsky D, Kellerer AM, Spiess H, et al. 1986. A proportional hazard analysis of bone sarcoma rates in German 244 radium patients. In: Gassner and Gerber, eds. The radiobiology of radium and thorotrast, 32-37.

*CIA. 1959. Accident at the Kasli Atomic Plant, Central Intelligence Agency. Report #CS3/389,785 Washington, D.C. March 4, 1959.

*Civil Defense Technology Workshop. 1995. Partnership for peace emergency perparedness program civil defense technology workshop. http://www.dtic.mil/fefenselink/emerg/reports/techwkshp.index.html.

*Clark LS, Albertini RJ, Nicklas JA. 1997. The aminothiol wr-1065 protects t lymphocytes from ionizing radiation-induced deletions of the HPRT gene. Cancer Epidemiol Biomarkers Prev 6(12):1033-7.

*Cleaver JE. 1977. Induction of thioguanine- and ouabain-resistant mutants and single-strand breakes in the DNA of Chinese hamster ovary cells by ^{3}H-thymidine. Genetics 87:129-138.

*Clewell HJ, III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1:111-113.

*Cobb JC, Eversole BC, Archer PG, et al. 1982. Plutonium burdens in people living around the Rocky Flats Plant. EPA-600/4-82-069. Springfield, VA: National Technical Information Service.

*Cockerham LG, Cerveny TJ, Hampton JD. 1986. Postradiation regional cerebral blood flow in primates. Aviat Space Environ Med 57(6):578-582.

*Coggle JE, Lambert BE, Moores SR. 1986. Radiation effects in the lung. Environ Health Prospect 70:261-291.

*Coquerelle TM, Weibezahn KF, Lucke-Huhle C. 1987. Rejoining of double stand breaks in normal human and ataxia-telangeictasia fibroblasts after exposure to ^{60}Co γ-rays, ^{24}1Am α-particles or bleomycin. Int J Radiat Biol 51(2):209-218.

*Court-Brown WM, Doll R. 1957. Leukemia and aplastic anemia in patients treated for ankylosing spondylitis. London: HMSO.

*Court-Brown WM, Doll R. 1959. Adult leukemia. Trends in mortality in relation to aetiology. Br Med J 1:1063.

*Court-Brown WM, Doll R. 1965. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. Br Med J 2:1327.

*Crossen PE, Morgan WF. 1979. The effects of β-radiation on sister-chromatid exchanges in cultured human lymphocytes. Mutat Res 62:125-129.

*Crump KS, Ng T-H, Cuddihy RG. 1987. Cancer incidence patterns in the Denver metropolitan area in relation to the Rocky Flats plant. American Journal of Epidemiology 126(1):127-135.

*Cuddihy RG. 1978. Deposition and retention of inhaled niobium in Beagle dogs. Health Phys 34:167-176.

*Cuddihy RG. 1981. Modeling the metabolism of actnide elements. In: M. E. Wrenn, ed. Actinides in man and animals. Salt Lake City, UT: R. D. Press, 617-628.

*Cuddihy RG. 1984. Mathematical models for predicting clearance of inhaled radioactive materials. Lung modeling for inhalation of radioactive materials, EUR-9382-EN 167-180.

*Cuddihy RG, Boecker BB, 1970. Kinetics of lanthanum retention and tissue distribution in the Beagle dog following administration of $^{140}LaCl_3$ by inhalation, gavage and injection. Health Phys 19:419-426.

*Cuddihy RG, Boecker BB, McClellan RO, 1976. ^{144}Ce in tissues of Beagle dogs after inhalation of $CeCl_3$ with special emphasis on endoctrine glands and reproductive organs. Health Phys 30:53-59.

*Cuddihy RG, Ozog JA. 1973. Nasal absorption of CsCl, $SrCl_2$ $BaCl_2$ and $CeCl_3$ in Syrian hamsters. Health Phys 25:219-224.

*Czeizel A, Sankaranarayanan K. 1984. The load of genetic and partially genetic disorders in man. I. Congential anomalies: Estimates of detriment in terms of years of life lost and years of impaired life. Mutat Res 128:73-103.

*da Silva CJ, Delgado JU, Luiz MTB, et al. 1991. Considerations related to the decontamination of houses in Goiania: Limitations and implications. Health Phys 60(1):87-90.

*Darby SC, Nakashima E, Kato H. 1985. A parallel analysis of cancer mortality among atomic bomb survivors and patients with ankylosing spondylitis given X-ray therapy. J Natl Cancer Inst 72:1.

*Das UN, Ramadevi G, Rao KP, et al. 1989. Prostaglandins can modify gamma-radiation and chemical induced cytotoxicity and genetic damage *in vitro* and *in vivo*. Prostaglandins D 38(6):689-716.

*Dasgupta P. 1970. Beta-ray induced chromosome breakage phenomena in plants. Cytologia 35:1-35.

*Davila DR, Guilmette RA, Bice DE. 1992. Long-term consequences of $^{239}PuO_2$. I. Exposure in dogs: Persistent t lymphocyte dysfunction. Int J Radiat Biol 61:123-133.

*De Luca JC, Dulout FN, Andrieu JM. 1988. The induction of reciprocal translocations in mouse germ cells by chemicals and ionizing radiations. I. Dose-response relationships and combined effects of bleomycin with thio-tepa and gamma-rays. Mutat Res 202(1):65-70.

*De-Chang W, Gong Y-F. 1994. Current status of studies on the biological effects of low-level internal irradiation. Int J Occup Med Toxicol 3(2):219-227.

10. REFERENCES

*Dehos A, Beaufort F, Erzberger A, et al. 1986. Changes in subpopulations of lymphocytes after exposure to ionizing radiation *in vitro* and *in vivo*. First Conference of the European Society for Analytical Cellular Pathology 8940386 Schlo 18N03.

*Demidchik EP, Kazakov VS, Astakhova LN, et al. 1994. Thyroid cancer in children after the Chernobyl accident: Clinical and epidemiological evaluation of 251 cases in the Republic of Belarus. In: Nagataki, S. ed. Nagasaki Symposium on Chernobyl: Update and Future, International Congress Series, No. 1074, 21-30.

*Devi PU, Baskar R, Hande MP. 1994. Effect of exposure to low-dose gamma radiation during late organogenesis in the mouse fetus. Radiat Res 138(1):133-138.

*Diel JH, Mewhinney JA. 1980. Toxicity of inhaled $^{238}PuO_2$. I. Metabolism. In: Book of Papers, 5th International Congress of the International Radiation Protection Association, Israel Health Physics Soc. 107-110.

*DOE. 1970. Staff report on Bikini Atoll environmental levels of plutonium. U.S. Department of Engery Coordination and Information Center, Las Vegas, NV, Accession Number NV0042828, April 11, 1970.

*DOE. 1975. Eneu island ground water and Bikini island cistern water. U.S. Department of Energy Coordination and Information Center, Las Vegas, NV, Accession Number NV0071181.

*DOE. 1978. Preliminary Results: Wholebody counting of Bikini Island residents. U.S. Department of Energy Coordination and Information Center, Las Vegas, NV, Accession Number NV0062367, April, 1978.

*DOE. 1988. Health physics manual of good practices for uranium facilities. U.S. Department of Energy, Idaho National Engineering Laboratory, EGG-2530 UC-41.

*DOE. 1991. Health effects of low-level radiation in shipyard workers. U.S. Department of Energy. DOE Contract No. DE-AC02-79EV10095.

*DOE. 1992. Integrated data base for 1993. U. S. spent fuel and radioactive waste inventories projects, and characteristics. U. S. Department of Energy. Oak Ridge National Laboratory. (ORNL). DOE/RW-0006, Rev 9. Oak Ridge, TN.

*DOE. 1993. Occupational radiation protection. U.S. Department of Energy. Code of Federal Regulations. 10 CFR 835.

*DOE. 1994a. Radiological control manual, U. S. Department of Energy. DOE/EH-0256T, Rev I, Springfield VA. National Technical Information Service.

*DOE. 1994b. External gamma radiation: “gamma dose rates 3 feet above ground on island of Rongelap”. Department of Energy, Nevada Coordination and Information Center, Las Vegas. NV0050785.

*DOE. 1995. Human radiation experiments associated with the U.S. Department of Energy and its predecessors. U.S. Department of Energy, Assistant Secretary for Environment, Safety, and Health, Washington, DC, Document #DOE/EH-0491

10. REFERENCES

*DOE. 1996a. Waste isolation pilot plant (WIPP) fact sheet: About radiation. U.S. Department of Energy. http://www.wipp.carlsbad.nm.us/wippfact/radiatn.html

DOE. 1996b. Yucca Mountain project. U.S. Department of Energy http://yucca_web.ymp.gov/timeline/eis/fact/index.htm

*DOE. 1996c. Environmental Management. U.S. Department of Energy http://www.em.doe.gov/rainplum/fig16.html

*DOE. 1996d. Environmental Management Index. U.S. Department of Energy http://www.em.doe.gov/cgi-bin/tc/tindex.html

*DOE. 1997a. EML procedures manual, HASL-300, 28th edition. Environmental Measurements Laboratory, U. S. Department of Energy, New York.

*DOE. 1997b. Occupational radiation protection. U.S. Department of Energy, Washington, D.C. 10 CFR 835.

*DOE. 1997c. Nuclear power generation and fuel cycle report 1997. Energy Information Administration, U. S. Department of Energy. Washington, DC DOE/EIA-0436(97).

*DOE. 1998. Occupational radiation protection; final rule. U.S. Department of Energy. Federal Register. 63 FR 59662. November 4, 1998.

*DOE. 1999a. DOE openness: Human radiation Experiments. http://www.ohre.doe.gov/

*DOE. 1999b. Comprehensive Epidemiological Data Resource. http://cedr.lbl.gov

*Doggett NA, McKenizie WH. 1983. An analysis of the distribution and dose response of chromosome aberrations in human lymphocytes after *in vitro* exposure to ^{137}cesium gamma radiation. Radiat Environ Biophys 23:33-51.

*DOT. 1995. Carriage by public highway. Class 7 (radioactive) material. U.S. Department of Transportation. Code of Federal Regulations. 49 CFR 177.842.

*DOT. 1996. Radiation protection program. U.S. Department of Transportation, Washington, D.C. 49 CFR 172.803.Subpart I.

*DOT. 1997. General requirements for shipments and packaging. Class 7 (radioactive) materials. U.S. Department of Transportation. Code of Federal Regulations. 49 CFR 173, Subpart I.

*DOT. 1998. Hazardous materials; withdrawal of radiation protection program requirement; final rule. U.S. Department of Transportation. Federal Register. 63 FR 48566. September 10, 1998.

*Dreicer M, Hakonson TE, White GC, et al. 1984. Rainsplash as a mechanism for soil contamination of plant surfaces. Health Phys 46(1):177-187.

*Dreyer NA, Loughlin JE, Fahey FH, et al. 1982. The feasiblity of epdemiologic studies of cancer in residents near the Rocky Flats plant. Health Phys 42(1):65-68.

10. REFERENCES

*Dubrova YE, Jeffreys AJ, Malashenko AM. 1993. Mouse minisatellite mutations induced by ionizing radiation. Nat Genet 5(1):92-94.

*Dufrain RJ, Littlefield LG, Joiner EE, et al. 1979. Human cytogenetic dosimetry: A dose-response relationship from alpha particle radiation from 241Am. Health Phys 37:279-289.

*Durakovic A. 1986a. Heart function studies in dogs after acute gamma irradiation of the precordium. Mil Med 151(5):275-277.

*Durakovic A. 1986b. Hepatobiliary kinetics after whole body irradiation. Mil Med 15(19):487-489.

*Eadie GG, Kaufmann RF. 1977. Radiological evaluation of the effects of uranium mining and milling operations on selected ground water supplies in the Grants Mineral Belt, New Mexico. Health Phys 32:231-241.

Earth and Environmental Sciences Directorate. 1996.
http://www-ep.es.llnl.gov/www-ep/atm/ras/chernob.html

*Eastern Turkestan Information Bulletin. 1996. The consequences of nuclear tests in eastern Turkestan.
http://www.geocities.com/CapitolHill/1730/cnt.html

*Eichholz G. 1982. Environmental aspects of nuclear power. Ann Arbor, MI: Ann Arbor Science.

*Eisenbud M. 1987. Environmental radioactivity from natural, industrial and military sources. Third edition. Academic Press, 84-104.

*EPA. 1976a. Maximum contaminant levels for radium-226, radium-228, and gross alpha particle radioactivity in community water systems. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.15.

*EPA. 1976b. Maximum contaminant levels for beta particle and photon-radioactivity from man-made radionuclides in community water systems. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.16.

*EPA. 1976c. Monitoring frequency for radioactivity in community water systems. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.26.

*EPA. 1977. Environmental radiation protection standards for nuclear power operations. Environmental standards for the uranium fuel cycle. Standards for normal operations. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 190, Subpart B.

*EPA. 1979. Radiological impact caused by emissions of radionuclides into air in the United States. U.S. Environmental Protection Agency. Report No. 520/7-79-006, Washington, D.C. Quoted by Eisenbud 1987.

*EPA. 1980. Prescribed procedures for measurement of radioactivity in drinking water. U. S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory, Cincinnati, OH. EPA-600-4-0-032. 96-111.

10. REFERENCES

*EPA. 1984. Radionuclides: Background information document for final rules. Vol 1. U.S. Environmental Protection Agency, Office of Radiation Program, Washington, DC. EPA 520/1- 84-022-1. NTIS PB85-165751.

*EPA. 1988. Limiting values of radionuclide intake and air concentration and dose conversion factors for inhalation, submersion, and ingestion; Federal Guidance Report No. 11. Oak Ridge National Laboratory and Office of Radiation Programs, Environmental Protection Agency. EPA-520/01-88-020.

*EPA. 1989a. National emission standards for radon emissions from underground mines. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart B.

*EPA. 1989b. Compliance procedures methods for determining compliance with subpart I [40 CFR 61]. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Appendix E.

*EPA. 1989c. Methods for estimating radionuclide emissions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Appendix D.

*EPA. 1989d. National emission standards for emissions of radionuclides other than radon from Department of Energy facilities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart H.

*EPA. 1990. Interim methods for development of inhalation reference doses. U. S. Environmental Protection Agency. EPA-600/8-90/066A.

*EPA. 1991. National emission standards for radionuclide emissions from elemental phosphorus plants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart K.

*EPA. 1992. National emission standards for radon emissions from phosphogypsum stacks. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart R.

*EPA. 1993a. Environmental radiation protection standards for management and disposal of spent nuclear fuel, high-level and transuranic radioactive wastes. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 191.

*EPA. 1993b. Standards for management of uranium byproduct material pursuant to section 84 of the Atomic Energy act of 1954, as amended. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 192, Subpart D.

*EPA. 1993c. Standards for management of thorium byproduct materials pursuant to section 84 of the atomic energy act of 1954, as amended. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 192, Subpart E.

*EPA. 1994a. National emission standards for radon emissions from disposal of uranium mill tailings. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart T.

*EPA. 1994b. Environmental radiation data report 74, April-June 1993. U. S. Environmental Protection Agency. Office of Indoor Air and Radiation. EPA 402-R-93-093.

*EPA 1995a. Standards for the control of residual radioactive materials from inactive uranium processing sites. Standards. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 192, Subpart A.

*EPA. 1995b. Standards for cleanup of land and buildings contaminated with residual radioactive materials from inactive uranium processing sites. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 192, Subpart B.

*EPA. 1995c. Implementation. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 192, Subpart C.

EPA. 1995d. Environmental radiation data report 82. U. S. Environmental Protection Agency. Office of Indoor Air and Radiation. EPA-402-R-97-005 February 1997.

*EPA. 1996a. National emission standards for radionuclide emissions from federal facilities other than nuclear regulatory commission licensees and not covered by subpart H. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart I.

*EPA. 1996b. Test methods. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Appendix B.

*EPA. 1996c. Health and environmental protection standards for uranium and thorium mills. U.S. Environmental Protection Agency, Washington, D.C. 40 CFR 192.

*EPA. 1996d. Radiation exposure and risk assessment manual. U.S. Environmental Protection Agency. EPA-402-R-96-016.

*EPA. 1996e. Sources of information on indoor air quality. http://www.epa.gov/iedweb00/radon/graphics/zonemap.jpg

*EPA 1997a. National primary drinking water regulations: Analytical methods for radionuclides; final rule and proposed rule. U.S. Environmental Protection Agency. Federal Register. 62 FR 10168. March 5, 1997.

*EPA. 1997b. Radiation standards/guidance/criteria. U.S. Environmental Protection Agency, Office of Radiation and Indoor Air, Internet version. http://www.epa.gov/radiation/

*EPA. 1998a. Land disposal restrictions phase IV: final rule promulgating treatment standards for metal wastes and mineral processing wastes; mineral processing secondary materials and bevill exclusion issues; treatment standards for hazardous soils, and exclusion of recycled wood preserving wastewaters. U.S. Environmental Protection Agency. Federal Register. 63 FR 28566. May 26, 1998.

*EPA. 1998b. Class V injection wells underground injection control regulations, revisions; proposed rule. U.S. Environmental Protection Agency. Federal Register. 63 FR 40586. July 29, 1998.

*EPA. 1998c. Current drinking water standards. National primary and secondary drinking water regulations. U.S. Environmental Protection Agency. Office of Water. Office of Ground Water and Drinking Water. http://www.epa.gov/OGWDW/wot/appa.html.

*EPA. 1999a. National Air and Environmental Radiation Laboratory (NAREL). Home page. U.S. Environmental Protection Agency. http://www.epa.gov/narel/index.html

*EPA. 1999b. EPA's Indoor Air Quality (IAQ) Home Page. Office of Radiation and Indoor Air. http://www.epa.gov/iedweb00/radon/graphics/zonemap.jpg

*Etoh H, Taguchi YH, Tabachnick J. 1977. Cytokinetics of regeneration in beta-irradiated guinea-pig epidermis. Radiat Res 71(1):109-118.

*Evans RD. 1966. The effect of skeletally deposited alpha-ray emitters in man. Br J Radiol 39:881-895.

*Evans RD, Keane AT, Kolenkow RJ. 1969. Radiogenic tumor in the radium cases studied at MIT. In: Mays CW, et al. eds. Delayed effects of bone seeking radionuclides. Salt Lake City, UT: University of Utah Press, 157-194.

*Fahim FA, Roshdy HM, Yousri RM, et al. 1993. Some biochemical aspects of the protective effect of strontium chloride on gamma-irradiated rats. Biometals 6(3):163-170.

*Fajgelj A, Lakoski A, Horvat D, et al. 1991. Chromosome aberrations induced in human lymphocytes by U-234 fission neutrons: I. Irradiation of human blood samples in the "dry cell" of the TRIGA Mark II nuclear reactor. Strahlenther Onkol 167:661-666.

*Farooqi Z, Kesavan PC. 1992. Radioprotection by caffeine pre- and post-treatment in the bone marrow chromosomes of mice given whole-body gamma-irradiation. Mutat Res 269(2):225-230.

*Farooqi Z, Kesavan PC. 1993. Low-dose radiation-induced adaptive response in bone marrow cells of mice. Mutat Res 302 (2):83-89.

*Faustman EM, Omenn GS. 1996. Risk assessment. In: Klaassen CD ed. Casarett & Doull's toxicology: The basic science of poisons, 5th edition. New York, NY: McGraw Hill, 75-88.

*Faw RD, Shultis JK. 1993. Radiological assessment: Sources and exposures. Englewood Cliffs, NJ: Prentice-Hall.

*FDA. 1973a. Performance standards for ionizing radiation emitting products. Television receivers. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 1020.10.

*FDA. 1973b. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 1020.20.

*FDA. 1974. Performance standards for ionizing radiation emitting products. Cabinet X-ray systems. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 1020.40.

*FDA. 1977a. Radio frequency radiation for the heating of food including microwave frequencies. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 179.30.

*FDA. 1977b. Ultraviolet radiation for the processing and treatment of food. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 179.39.

*FDA. 1986. General provisions for food irradiation. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 179.25.

10. REFERENCES

*FDA. 1991. Performance standards for ionizing radiation emitting products. Computed tomography (CT) equipment. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 1020.33.

*FDA. 1993a. Irradiation in the production, processing, and handling of animal feed and pet food. Ionizing radiation for treatment of laboratory animal diets. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 579.22.

*FDA. 1993b. Performance standards for ionizing radiation emitting products. Radiographic equipment. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 1020.31.

*FDA. 1994a. Performance standards for ionizing radiation emitting products. Diagnostic X-ray systems and their major components. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 1020.30

*FDA. 1994b. Performance standards for ionizing radiation emitting products. Fluroscopic equipment. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 1020.32.

*FDA. 1995. Irradiation in the production, processing and handling of animal feed and pet food. Ionizing radiation for the treatment of poultry feed and poultry feed ingredients. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 579.40.

*FDA. 1996a. Sources of radiation used for inspection of food, for inspection of packaged food, and for controlling food processing. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 179.21.

*FDA. 1996b. Pulsed light for the treatment of food. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 179.41.

*FDA. 1996c. Packaging materials for use during the irradiation of prepackaged foods. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 179.45.

*FDA. 1996d. Performance standards for ionizing radation emitting products. U.S. Department of Health and Human Services. Food and Drug Administration. U.S. Department of Agriculture. 21 CFR 1020.

*FDA. 1997. Ionizing radiation for the treatment of food. U.S. Department of Health and Human Services. Food and Drug Administration. Code of Federal Regulations. 21 CFR 179.26.

*FDA. 1998. Accidental radioactive contamination of human food and animal feeds: Recommendations for state and local agencies. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Devices and Radiological Health. Rockville, MD 20850. August 13, 1998.

*FEMA. 1996. Radiological Emergency Planning and Preparedness. U.S. Federal Emergency Management Agency, Washington, D.C. 44 CFR 351.

*FEMA. 1997. U.S. Federal Emergency Management Agency. http://fema.gov/home/fema/radiolo.htm

*Ferrer I, Olive M, Ribera J, et al. 1996. Naturally occurring (programmed) and radiation-induced apoptosis are associated with selective c-jun expression in the developing rat brain. European Journal of Neuroscience 8(6):1286-1298.

*Fischbein A, Zabludovsky N, Eltes F, et al. 1997. Ultramorphological sperm characteristics in the risk assessment of health effects after radiation exposure among salvage workers in Chernobyl. Environ Health Perspect 105(suppl. 6):1445-1449.

*Floersheim GL. 1992. Calcium antagonists protect mice against lethal doses of ionizing radiation. Br J Radiol 65(77):1025-1029.

*Floersheim GL, Chiodetti N, Bieri A. 1988. Differential radioprotection of bone marrow and tumour cells by zinc aspartate. Br J Radiol 61(726):501-508.

*Fomenko LA, Kozhanowskaja Ja K, Gaziev AI. 1995. The adaptive repair response in tissues of chronically irradiated mice. Radiation Protection Dosimetry 62(1-2):31-34.

*Forsberg J, Harms-Ringdahl M, Ehrenberg L, 1978. Interaction of ascorbate with the radioprotective effect of mercaptoethylamin. An exploratory study in mice, whole animals and cell cultures. Int J Radiat Biol Relat Stud Phys Chem Med 34(3):245-252.

*Fossett NG, Byrne BJ, Kelley SJ, et al. 1994. The influence of large deletions on the mutation frequency induced by tritiated water and X-radiation in male *Drosophila melanogaster* post-meiotic germ cells. Mutation Research 307:213-222.

*Fujiki H, Mori M, Tanooka H. 1982. Delayed induction of ornithine decarboxylase in mouse skin after irradiation with beta-rays. Cancer Lett 15(1):15-17.

*Fujiwara SRL, Carter M, Akiyama M, et al. 1994. Autoantibodies and immunoglobulins among atomic bomb survivors. Radiat Res137(1):89-95.

*Fukui M. 1978. Evaluation of a combined sorption model for describing cesium transport in a soil. Health Phys 35(4):555-562.

*Galvin JB, Bice DE, Gilmette RA. 1989. Pulmonary immune response of dogs after exposure to 239PuO2. Int J Radiat Biol 55:285-296.

*GAO. 1995. Letter Report. Nuclear safety: Concerns with nuclear facilities and other sources of radiation in the former Soviet Union. U.S. General Accounting Office. Report No. GAO/RCED-96-4, November 07, 1995. http://www.emanifesto.org/OTAEnergyEast/OTAEEEch4.htm

*Garcia H, Shubik P. 1971. Epilation and hair greying in hamsters following one single application of beta rays. J Invest Dermatol 572:94-99.

*Gearhart JM, Diel JH, McClellan RO. 1980. Intrahepatic distribution of plutonium in Beagles. Radiat Res 84:343-352.

*Generoso WM, Cain KT, Cacheiro NL, et al. 1985. ^{239}Plutonium-induced heritable translocations in male mice. Mutat Res152(1):49-52.

*Geraci JP, Mariano MS, Jackson KL. 1991. Hepatic radiation injury in the rat. Radiat Res 125(1):65-72.

*Geraci JP, Mariano MS, Jackson KL, et al. 1992. Effects of dexamethasone on late radiation injury following partial-body and local organ exposures. Radiat Res 129(1):61-70.

*Giambarresi LI, Walker RI. 1989. Prospects for radioprotection. In: Textbook of military medicine: Part 1: Warfare, weaponry and the casualty. Medical Consequences of Nuclear Warfare 2:246-273.

*Gidali J, Istvan E, Feher I. 1985. Long-term perturbation of hemopoiesis after moderate damage to stem cells. Exp Hematol 13(7):647-651.

*Gilbert ES. 1983. An evaluation of several methods for assessing the effects of occupational exposure to radiation. Biometrics 39:161-171.

*Gilbert ES, Omohundro E, Buchanan JA, et al. 1993. Mortality of workers at the Hanford site: 1945-1986. Health Phys 64(6):577-590.

*Gilbert ES, Petersen GR, Buchanan JA. 1989. Mortality of workers at the Hanford site: 1945-1981. Health Phys 56(10):11-25.

*Gillett NA, Hahn FF, Mewhinney JA, et al. 1985. Osteosarcoma development following single inhalation exposure to americium-241 in Beagle dogs. Radiat Res 104:83-93.

*Gillett NA, Muggenburg BB, Boecker FF et al. 1987a. Single inhalation exposure to $^{90}SrCl_2$ in the Beagle dog: Hematological effects. Radiat Res 110:267-288.

*Gillett NA, Muggenburg BB, Boecker WC, et al. 1987. Single inhalation exposure to $^{90}SrCl_2$ in the Beagle dog: Late biological effects. J Natl Cancer Inst 79(2):359-376.

*Gillett NA, Muggenburg BB, Mewhinney et al. 1988. Primary liver tumors in Beagle dogs exposed by inhalation to aerosols of plutonium-238 dioxide. Am J Pathol 133:265-276.

*Gillett NA, Stegelmeier BL, Kelly G. 1992. Expression of epidermal growth factor receptor in plutonium-239 induced lung neoplasms in dogs. Vet Pathol 29:425-449.

*Gilot-Delhalle J, Moutschen J, Garsou J. 1988. Induction of translocations in mouse spermatogonia after fractionated exposure to ^{60}Co gamma-rays. Mutat Res 207(1):29-31.

*Glasstone S, Dolan PJ. 1977. The effects of nuclear weapons. U.S. Govt. Printing Office, Washington, DC.

*Goans RE. 1995. Project sapphire. Health Phys 68:296-298.

*Godoy JM, Guimaraes RJ. Pereira JC, et al. 1991. Cesium-137 in the Goiania waterways during and after the radiological accident. Health Phys 60(1):99-103.

*Gonzalez AJ. 1994. Biological effects of low doses of ionizing radiation: A fuller picture. IAEA Bull 36(4):37-45.

*Gore DJ, Patrick G. 1978. The distribution and clearance of inhaled uranium dioxide particles on the first bifurcation and trachea of rats. Phys Med Biol 23:730-737.

*Gracheva LM, Korolev VG. 1972. The role of β radiation, accompanying the decay of phosphorus-32 incorporated into the cells of diploid yeasts in the induction of recombination. Genetika 8(9):84-91.

*Grahn D, Carnes BA. 1988. Genetic injury in hybrid male mice exposed to low doses of ^{60}Co gamma-rays or fission neutrons. III. Frequencies of abnormal sperm and reciprocal translocations measured during and following long-term weekly exposures. Mutat Res 2:285-294.

*Grahn D, Lee CH, Farrington BF. 1983. Interpretation of cytogenetic damage induced in the germ line of male mice exposed for over 1 year to ^{239}Pu alpha particles, fission neutrons, or ^{60}Co gamma rays. Radiat Res 95(3):566-583.

*Griffith WC, Guilmette RA. 1991. Multiparameter analysis of fall-out plutonium burdens in human hair. Radiation Protection Dosimetry 38(1/3):113-119.

*Griffith WC, Mewhinney JA, Muggenburg BA, et al. 1983. Bioassay model for estimating body burdens of ^{241}Am from excretion analyses. Health Phys. 44:545-554.

*Guilmette RA, Eidson AF. 1992. Using animal dosimetry models to interpret human bioassay data for actinide exposures. Int J Radioanalytical Nucl Chem Articles 1561:449-525.

*Guilmette RA, Mewhinney JA. 1989. A biokinetic model of inhaled curium compounds in dogs: Application to human exposure data. Health Phys 187-198.

*Hahn FF, Barnes JE, Hobbs CH, 1975. Effect of ^{90}Y Inhaled in fused clay particles on the gastrointestinal tract of Beagles. Radiation Research 61:444-456.

*Hahn FF, Benjamin SA, Boecker BB. 1977. Comparative pulmonary carcinogenicity of inhaled beta-emitting radionuclides in Beagle dogs. In: Walton WH, ed. Inhaled particles, IV. New York, NY: Pergamon Press, (Part 1):221-234.

*Hahn FF, Boecher CH, Hobbs CH et al. 1976. Effect of ^{144}Ce inhaled in fused clayed particles on the tracheobronchial lymph nodes. In: Ballou JE, ed. Radiation and the lympatic system, Doc. CONF-740930 218-224.

*Hahn FF, Boecker BB, McClellan RG. 1988. Organs and cells at risk after inhalation of insoluble beta-emitting radionuclides: Lessons from experimental studies. Ann Occup Hyg 32:1123-1128.

*Hahn FF, Lundgren DL. 1992. Pulmonary neoplasms in rats that inhaled cerium-144 dioxide Toxicol Pathol 20:169-178.

*Hahn FF, Mewhinney JA, Merickel BS, et al. 1981. Primary bone neoplasms in Beagle dogs exposed by inhalation to aerosols of plutonium-238 dioxide. J Natl Cancer Inst 67:917-927.

*Hall EJ. 1988. Radiobiology for the radionuclides by workers, Part 1. New York, NY: Pergamon Press, 23-55.

*Hall EJ (ed). 1994. Cell-survival curves. In: Radiobiology for the radiologist (third edition), Philadelphia, PA: Lippincott, 18-38.

*Hall EJ. 1998. Radiation and life. Uranium Information Center. http://www.uic.com.au/ral.htm

*Ham WT. 1953. Radiation cataracts. Arch Opthalmol 50:618.

*Hamlet R, Heryet JC, Hopewell JW, et al. 1986. Late changes in pig skin after irradiation from beta-emitting sources of different energy. Br J Radiol Suppl 19:51-54.

*Handler J. 1992. U.S. Military activity in the Arctic in the 1990s: Is it needed? Greenpeace Nuclear Campaign Report. http://www.greenpeace.org/~usa/reports/nuclear/arctconf.html.

*Harapanhalli RS, Narra VR, Yaghmai V, et al. 1994. Vitamins as radioprotectors *in vivo*. II. Protection by vitamin A and soybean oil against radiation damage caused by internal radionuclides. Radiat Res 139(1):115-122.

*Harley NH. 1991. Toxic effects of radiation and radioactive material. In: Amdur MO, Doull, JD, Klaassen CD, ed. Casarett and Doull's toxicology: The basic science of poisons, 4th ed. New York, NY: Pergamon Press, 723-752.

*Harley NH, Kolber AB, Shore RE, et al. 1983. The skin dose and response for the head and neck in patients irradiated with X-rays for tinea capitis: Implications for environmental radioactivity. In: Proceedings in Health Physics Society Mid-Year Symposium, Albuquerque, NM; Health Physics Society, 125-142.

*Hart DR, McKee PM, Burt AJ, et al. 1986. Benthic community and sediment quality assessment of Port Hope Harbour, Lake Ontario. J Great Lakes Res 12:206-220.

*Hart PM, Archer DB, Chakravarthy U. 1995. Asymmetry of disciform scarring in bilateral disease when one eye is treated with radiotherapy. British Journal of Ophthalmology 79(6):562-568.

*Harvard Medical School, Beth Israel Hospital. 1996. Safety concerns. http://www.bih.harvard.edu/radiology/headings/risks.html

*Harvey RS. 1970. Temperature effects on the sorption of radionuclides by freshwater algae. Health Phys 19(2):293-297.

*Hatch M, Susser M. 1990. Background gamma radiation and childhood cancers within ten miles of a USA nuclear plant. Int J Epidemiol 19(3):546-552.

*Hatch MC, Beyea J, Nieves JW, et al. 1990. Cancer near the Three Mile Island nuclear plant (Pennsylvania, USA): Radiation emissions. Am J Epidemiol 132(3):397-412.

*Havenaar JM, Rumyantzeva GM, van den Brink W, et al. 1997. Long-term mental health effects of the Chernobyl disaster: An epidemiologic survey in two former Soviet regions. Am J Psychiatry 154(11):1605-7.

*Hendee W. 1973. Radioactive isotopes in biological research. New York, NY: John Wiley and Sons.

*Hobb CH, Barnes JE, McCleelan RO, et al. 1972. Toxicity in the dog of inhaled ^{90}Y in fused clay particles: Early biological effects. Radiat Res 49:430-460.

*Hobbs C, McClellan R. 1986. Radiation and radioactive materials. In: Doull J, et al., eds. Cassarett and Doull's toxicology: The basic science of poison, 3rd ed. New York, NY: Macmillan Publishing Co., Inc., 497-530.

*Hoffmann W, Kranefeld A, Schmitz-Feuerhake I. 1993. Radium-226-contaminated drinking water: Hypothesis on an exposure pathway in a population with elevated childhood leukemia. Environ Health Perspect 101(Suppl 3):113-115.

*Holm LE, Eklund G, Lundell G. 1980. Incidence of malignant thyroid tumors in humans after exposure to diagnostic doses of iodine-131. II. Estimation of thyroid gland size, thyroid radiation dose, and predicted versus observed number of malignant thyroid tumors. J Natl Cancer Inst 65:1221-1224.

*Hopewell JW, Coggle JE, Wells J, et al. 1986. The acute effects of different energy beta-emitters on pig and mouse skin. Br J Radiol Suppl 19:47-51.

*HPS. 1996. Health Physics Society (HPS) Standard no. N13.30-1996. Performance Criteria for Radiobioassay published by the Health Physics Society in 1996.

*HPS. 1999. Health Physics Society. Home page. http://www.hps.org

*HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Program (via TOXNET), Bethesda, MD. January 1995.

*Hulse EV. 1966. Incidence and pathogenesis of skin tumours in mice irradiated with single external doses of low energy beta particles. Br J Cancer 21(3):531-547.

*Humphreys ER, Humm JL, Monte-Carlo A. 1988. Approach to the microdosimetry of ^{224}Ra in murine compact and cancellous bone. Health Phys 54(6):607-615.

*Husen T. 1959. Psychological twin research: A methological study. Uppsala, Sweden: Almqvist & Wiksells.

*ICRP. 1977. Recommendations of the ICRP. Publication #26. International Commission on Radiological Protection, Stockholm, Sweden.

*ICRP. 1984. International Commission for Radiation Protection. A compilation of the major concepts and quantities in use by ICRP. ICRP Publication 42. Oxford: Pergamon Press.

*ICRP. 1986. International Commission for Radiation Protection. Developmental effects of irradiation on the brain of the embryo and the fetus. ICRP Publication 49.

*ICRP. 1991. 1990 Recommendations of the International Commission on Radiological Protection, ICRP Publication 60. Oxford: Pergamon Press.

*ICRP. 1995. Limits for intakes of radionuclides by workers. 5. Dosimetric model for the respiratory system. In: Sowby FD (ed). Radiation Protection, ICRP Publication 30 (Part I) - limits for intakes of radionuclides by workers. A report of committee 2 of the International Commission on Radiological Protection. International Commission on Radiological Protection. Oxford, New York, Frankfurt: Pergamon Press, 23-55.

*ICRP. 1997. Work of the International Commission on Radiological Protection, Internet version, http://www.irpa.at/irpa/icrp.htm.

10. REFERENCES

*Iijima K, Morimoto K. 1991. Quantitative analyses of the induction of chromosome aberrations and sister-chromatid exchanges in human lymphocytes exposed to γ rays and mitomycin-C in combination. Mutat Res 263:263-268.

*Ijiri K. 1989. Cell death (apoptosis) in mouse intestine after continuous irradiation with gamma rays and with beta rays from tritiated water. Radiat Res 118(1):180-191.

*Inano H, Suzuki K, Ishii-Ohba H, 1989. Steroid hormone production in testis, ovary, and adrenal gland of immature rats irradiated *in utero* with ^{60}Co. Radiat Res 117(2):293-303.

*Indran M, Carr KE, Gilmore RS, et al. 1991. Mucosal changes in mouse duodenum after gamma-irradiation or reserpine treatment. J Submicrosc Cytol Pathol 23(2):267-278.

*Iranzo E, Rivas P, Mingarro E. 1991. Distribution and migration of plutonium in soils of an accidentally contaminated environment. Radiochim Acta 52/53:249-256.

*Iranzo E, Salvador S, Iranzo CE. 1987. Air concentrations of plutonium-239 and plutonium-240 and potential radiation doses to persons living near plutonium contaminated areas in Palomares, Spain. Health Phys 52(4):453-462.

IRIS. 1999. Integrated risk information system (IRIS). Online. U.S. Environmental Protection Agency. National Center for Environmental Assessment, Cincinnati, OH. http://www.epa.gov/iris/subst/index.html

*ITRI. 1991-1993. Biennial report on long-term dose-resposes studies of inhaled or injected radionuclides (Report 139). Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM, 1-99.

*Jablon S, Hrubec Z, Boice Z, et al. 1990. Cancer in populations near nuclear facilities. NIH Publication No. 90-874. Washington , DC: U.S. Government Printing Office.

*Jacoby R, Glauberman N (eds). 1995. The bell curve debate. History, documents, opinions. New York, NY: Times Books.

*Jagetia GC, Ganapathi NG. 1991. Treatment of mice with a herbal preparation (Liv. 52) reduces the frequency of radiation-induced chromosome damage in bone marrow. Mutat Res 253(2):123-126.

*James A, Roy M. 1987. Dosimetric lung models. In: Gerber G, et al., eds. Age-related factors in radionuclide metabolism and dosimetry. Boston, MA: Martinus Nijhoff Publishers, 95-108.

*James AC, Birchall A, Cross FT. 1989. The current approach of the ICRP Task Group for modeling doses to respiratory tract tissues. Health Phys 57:281-282.

*Janeczko K, Pawlinski R, Setkowicz Z, et al. 1997. Long-term postnatal effect of prenatal irradiation on the astrocyte proliferative response to brain injury. Brain Research 770(1-2):237-241.

*Jenner TJ, deLara CM, O'Neill P, et al. 1993. Induction and rejoining of DNA double-strand breaks in V79-4 mammalian cells following γ- and α-irradiation. Int J Radiat Biol 64(3):265-273.

*Jeter EK, Gadsden RH, Cate JC IV. 1991. Irradiation effect on aging red blood cells. Ann Clin Lab Sci 21(6):420-425.

*Jiang TN, Lord BI, Hendry JH. 1994. Alpha particles are extremely damaging to developing hemopoiesis compared to gamma irradiation. Radiat Res 137(3):380-384.

*Johnson CJ. 1981. Cancer incidence in an area contaminated with radionuclides near a nuclear installation. Ambio 10(4):176-182.

*Johnson NF. 1995. Radiobiology of lung target cells. Radiation Protection Dosimetry 60(4):327-330.

*Josephson ES, Brynjolfsson A, Wierbicki E. 1974. The use of ionizing radiation for preservation of food and feed products. Radiat Res 96-117.

*Kadhim MA, Macdonald DA, Goodhead DT, et al. 1992. Transmission of chromosomal instability after plutonium α-particle irradiation. Nature 355(6362):738-740.

*Kamiguchi Y, Tateno H, Mikamo K. 1990. Dose-response relationship for the induction of structural chromosome aberrations in human spermatozoa after *in vitro* exposure ito tritium β-rays. Mutat Res 228:125-131.

*Kamiguchi Y, Tateno H, Mikamo K. 1991. Micronucleus test in 2-cell embryos as a simple assay system for human sperm chromosome aberrations. Mutat Res 252:297-303.

*Kanwar KC, Verma a. 1992. Alterations in the hematological profile in rat following whole body gamma radiation with and without venoruton and pretreatment. J Environ Pathol Toxicol Oncol 11(4):235-239.

*Kathren RL. 1984. Radioactivity in the environment. Distribution and surveillance. New York, NY: Harwood Academic Publishers, 93-115.

*Kaufman AS. 1996. IQ, lead level, and inferences from research studies - comments addressing the underlying science forming the basis of HUD's regulatory impact analysis. Psychological Assessment Resources, Inc. (PAR): i-ii; 1-56.

*Kazakov VS, Demidchik EP, Astakhova LN. 1992. Thyroid cancer after Chernobyl. Scientific correspondence. Nature 359(3).

*Kelsey KT, Wiencke JK, Liber HL. 1995. Biomarkers to detect radiation exposures. In: Biomarkers and occupational health: Progress and perspectives, 215-225.

*Kempf SR, Port RE, Ivankovic S. 1994. Anticarcinogenic effect of tetrachlorodecaoxide after total-body gamma irradiation in rats. Radiat Res 139(2):226-231.

*Kim TH, Kim SH, Lee YS, et al. 1994. Protective effects of potato extracts and 16,16-dimethyl prostaglandin E2 on the induction of hepatic foci by cotreatment of gamma radiation and diethylnitrosamine. Anticancer Res 14(5A):1979-1982.

*Klener V, Tuscany R, Vejlupkova J, et al. 1986. Long-term follow-up after accidental gamma irradiation from a ^{60}Co source. Health Phys 51(5):601-607.

*Kneale GW, Mancuso TF, Stewart AM. 1981. Hanford radiation study III: A cohort study of the cancer risks from radiation to workers at Hanford (1944-77) by the method of regression models in life-tables. British Journal of Industrial Medicine 38:156-166.

*Kneale GW, Stewart AM. 1986. Prenatal x rays and cancers: Futher tests of data from the Oxford survey of childhood cancers. Health Phys 51(3):369-376.

*Knoll GF. 1989. Radiation detection and measurement. Second edition. New York, NY: John Wiley & Sons.

*Kohn WG, Grossman E, Fox PC, et al. 1992. Effect of ionizing radiation on sympathetic nerve function in rat parotid glands. J Oral Pathol Med 21(3):134-137.

*Kondo S. 1993. Health effects of low-level radiation. Osaka, Japan: Kinki University Press and Madison, WI: Medical Physics Publishing.

*Koshimoto C, Takahashi S, Kubota Y, et al. 1994. Evaluation of the effect of gamma-irradiation on fetal erythropoiesis in rats using blood cell volume as the index. J Radiat Res (Tokyo) 35(2):74-82.

*Kossenko MM, Izhevsky PV, Degteva MO. 1994. Pregnancy outcome and early health status of children born to the Techa River population. Sci Total Environ 142(1,2):91-100.

*Kovacs CJ, Gooya JM, Harrell JP. 1991. Altered radioprotective properties of interleukin I alpha (IL-1) in non-hematologic tumor-bearing animals. Int J Radiat Oncol Biol Phys 20(2):307-310.

*Kovacs CJ, Harrell JP, Evans MJ. 1992. Absence of interleukin I alpha radioprotection in tumor-bearing animals: Elevated plasma levels of prostaglandin E versus a preexisting primed marrow. J Leukoc Biol 51(1):53-58.

*Krieger HL, Whittaker EL. 1980. Prescribed procedure for measurment of radioactivity in drinking water. U. S. Environmental Protection Agency, Office of Research and Development. EPA 600/4-80-032.

*Krisch RE, Krasin F, Sauri CJ. 1976. DNA breakage, repair and lethality after ^{125}I decay in rec+ and recA strains of *Escherichia coli*. Int J Radiat Biol 29(1):37-50.

*Krishnan K, Andersen ME. 1994. Physiologically-based pharmacokinetic modeling in toxicology. In: Wallace Hayes, ed. Principles and methods of toxicology, 3rd edition. New York, NY: Raven Press, Ltd.

*Krishnan K, Andersen ME, Clewell HJ,III, et al. 1994. Physiologically-based pharmacokinetic modeling of chemical mixtures. In: Yang, RSA, ed., Toxicology of chemical mixtures. New York, NY: Academic Press.

*Kuglik P, Slotova J. 1991. Different effects of pretreatment with triated thymidine (^{3}H-dTh) on radiation-induced sister chromatid exchanges (SCEs) and micronuclei in *Vicia faba* root tip cells. Biologia Plantarum 33(4):291-297.

*Kumar S, Kumar A, Goyal PK, et al. 1983. Population kinetic studies in mouse jejunum under continuous beta-exposure from tritiated water. Radiobiol Radiother (Berl) 24(2):239-242.

*Kusama T, Hasegawa Y. 1993. Stage differences in developmental disorders in ICR mouse embryos irradiated with gamma-rays. Senten Ijo 33:115-23.

*LaBauve RJ, Brooks AL, Mauderly JL, et al. 1980. Cytogenetic and other biological effects of $^{239}PuO_2$ inhaled by the Rhesus monkey. Radiat Res 82:310-335.

*Laissue JA, Altermatt HJ, Bally E, et al. 1987. Protection of mice from whole body gamma irradiation by deuteration of drinking water: Hematologic findings. Exp Hematol 15(2):177-180.

*Lazanyi A. 1965. The effect of sulphoguanidine and p-nitrobenzoic acid on the chromosome breakage-reunion process by γ-, X-and β-irradiation in *Vicia faba*. Int J Rad Biol 10(4):329-342.

*Le XC, Xing JZ, Lee J, et al. 1998. Inducible repair of thymine glycol detected by an ultrasensitive assay for DNA damage. Science 280(5366):1066-1069.

*Leadon SA. 1996. Repair of DNA damage produced by ionizing radiation: A minireview. Seminars in Radiation Oncology 6(4):295-305.

*Lee AC, Angleton GM, Benjamin SA. 1989. Hypodontia in the Beagle after perinatal whole-body ^{60}Co gamma irradiation. Radiat Res 118(3):467-475.

*Leemhorst JG. 1993. Potentials of ionizing-radiation in reducing hazards to man and environment. Radiat Phys Chem 42(3:)19-21.

*Lefaix JL, Martin M, Tricaud Y, et al. 1993. Muscular fibrosis induced after pig skin irradiation with single doses of ^{192}Ir gamma-rays. Br J Radiol 66(786):537-544.

*Leung H. 1993. Physiologically-based pharmacokinetic modeling. In: Ballantine B, Marro T, Turner T, eds., General and applied toxicology, Vol. I. New York, NY: Stockton Press, 153-164.

*Lide DR. 1994. In: CRC handbook of chemistry and physics, 74th ed. 50-51, 54, 73, 83-84, 90102, 106, 122.

*Lieberman R. 1984. Facility radiochemistry procedures manual. Eastern Environmental Radiation Facility. U. S. Environmental Protection Agency. EPA 520/5-84-006.

*Lin I-H, Hau D-M, Chen W-C, et al. 1996. Effects of low-dose gamma-ray irradiation on peripheral leukocyte counts and spleen of mice. Chinese Medical Journal (English edition) 109(3):210-214.

*Lipman RM, Tripathi BJ ,Tripathi RC. 1988. Cataracts induced by microwave and ionizing radiation. Surv Ophthalmol 33(3):200-210.

*Lippmann M, Schlesinger RB. 1984. Interspecies comparisons of particle deposition and mucociliary clearance in tracheobronchial airways. J Tox Environ Health 13:441[261]-469[289].

*Liu VF, Boubnov NV, Weaver DT. 1995. Cell cycle checkpoints and repair of ionizing radiation damage. Stem Cells 13(Suppl 1):117-28.

*Lloyd DC, Edwards AS, Fitzsimons EJ. 1994. Death of a classified worker probably caused by overexposure to gamma radiation. Occupational and Environmental Medicine 51(10):713-718.

*Lognonne JL, Ducousso R, Rocquet G, et al. 1985. Influence of whole-body gamma irradiation upon arachidonic acid metabolism in rat platelets. Biochimie 67(9):1015-1021.

*Loucas BD, Geard CR. 1994. Initial damage in human interphase chromosomes from alpha particles with linear energy transfers relevant to radon exposure. Radiat Res 13:9-14.

*Lowry JD, Lowry SB. 1988. Radiaonuclides in drinking water. American Water Works Association Journal 80:51-64.

*Lubin JH, Boice JD, Edling C, et al. 1995. Lung cancer in randon-exposed miners and estimation of risk from indoor exposure. J Natl Canc Instit. 87:817-826. http://cancer.med.upenn.edu/cancer_news/lung_radon. html

*Lucas JN. 1998. Cytogenetic signature for ionizing radiation. Int J Radiat Biol 73(1):15-20.

*Luckey TD. 1994. Radiation hormesis in cancer mortality. Int J Occup Med Toxicol 3(2):175-193.

*Luckey TD. 1997. Radiation hormesis: Biopositive effect of radiations. In: Bastide M, ed. Signals and images (7th and 8th Groupe), 31-39.

*Lumniczky K, Antal S, Unger E, et al. 1997. Oncogenic changes in murine lymphoid tumors induced by *in utero* exposure to ionizing radiation. Radiat Oncol Investig 5(3):158-62.

*Lundell M, Hakulinen T, Holm L-E. 1994. Thyroid cancer after radiotherapy for skin hemangioma in infancy. Radiat Res 140(3):334-339.

*Lundgren DL, Hahn FF, McClellan RO. 1980a. Influence of age at the time of inhalation exposure to aerosols of $^{144}CeO_2$ on ^{144}Ce retention, dosimetry and toxicity in mice. Health Phys 38:643-655.

*Lundgren DL, Hahn FF, McClellan RO. 1981. Toxicity of ^{90}Y inhaled in relatively insoluble fused aluminosilicate particles when inhaled by mice. Radiat Res 88:510-523.

*Lundgren DL, Hahn FF, Rebar AH. 1983. Effects of the single or repeated inhalation exposure of Syrian hamsters to aerosols of $^{239}PuO_2$. Int J Radiat Biol Relat Stud Phys Chem Med 43(1):1-18.

*Lundgren DL, Hahn FF, Sanchez A et al. 1976. Effect of inhaled yttrium-90 in fused clay particles on the pulmonary clearance of inhaled staphyloccoccus aureus in mice. Radiat Res 66:231-246.

*Lundgren DL, Mauderly JL, Carlton WW. 1990. Biological effects of inhaled $^{239}PuO_2$ in rats with pre-existing pulmonary emphysema. Hum ExpToxicol 9(5):295-308.

*Lundgren DL, Mauderly JL, Rebar AH. 1991. Modifying effects of preexisting pulmonary fibrosis on biological responses of rats to inhaled $^{239}PuO_2$. Health Phys 60(3):353-363.

*Lundgren DL, McClellan RO, Hahn FF. 1980b. Repeated inhalation exposure of mice to $^{144}CeO_2$ I. Retention and dosimetry. Radiat Res 82:106-122.

*Lundgren DL, McClellan RO, Thomas RL, et al. 1974. Toxicity of inhaled $^{144}CeO_2$ in mice. Radiat Res 58:448-461.

*Lushbaugh C, Eisele G, Burr W Jr, et al. 1991. Current status of biological indicators to detect and quantify previous exposures to radiation. Biological Indicators Working Group. Health Phys 60:103-109.

*Lynch L, Bowen M, Malone L. 1994. Patient exposure to ionizing radiation in the intensive care unit due to protable chest radiography. Irish Journal of Medical Science 163:136-137.

*Macintyre WJ, Saha GB. 1995. Sources of ionizing radiation and their effects on humans. In: Cordasco EM, Sr., Demeter SL, Zenz C, eds. Environmental respiratory diseases. Van Nostrand Reinhold Co. Inc.: New York, New York, USA; Van Nostrand Reinhold Co. Ltd.: Wokingham, England, UK, 337-348.

*Maes AA, Hilali ED, Leonard A, et al. 1993. Stable chromosome aberrations 25 years after severe accidental radiation exposure. Radiation and Environmental Biophysics 32(4):319-324.

*Maisin JR. 1988. Protection against ionizing radiation by combinations of radioprotectors. Pharmacol Ther 39(1-3):189-193.

*Malhotra N, Rani N, Rana K, et al. 1990. Radiation induced blood pathology in chick-erythrocytes and related parameters. Exp Pathol 38(4):241-248.

*Mancuso TF, Stewart A, Kneale G. 1977. Radiation exposures of Hanford workers dying from cancer and other causes. Health Phys 33:369-385.

*Martland HS. 1931. The occurrence of malignancy in radioactive persons: A general review of data gathered in the study of the radium dial painters, with special reference to the occurrence of osteogenic sarcoma and the inter-relationship of certain blood diseases. The American Journal of Cancer 15(4):2435-2516.

*Maruyama H, Yamamoto I. 1992. Suppression of ^{125}I-uptake in mouse thyroid by seaweed feeding: Possible preventative effect of dietary seaweed on internal radiation injury of the thyroid by radioactive iodine. Kitasato Arch Exp Med 65(4):209-216.

*Masse F. 1996. Personal communication (via http://www.fi.uib.no/~ladi/ADNAN/radiationprimer.txt).

*Masse R, Cross FT. 1989. Risk considerations related to lung modeling. Health Phys 57:283-289.

*Matanoski GM. 1991. Health effects of low-level radiation in shipyard workers, Report by Johns Hopkins University.

*Mathur S, Nandchahal K, Bhartiya HC. 1991. Radioprotection by MPG of mice ovaries exposed to sublethal gamma radiation doses at different postnatal ages. Acta Oncol 30(8):981-983.

*Matsushita S, Ando K, Koike S, et al. 1994. Radioprotection by WR-151327 against the late normal tissue damage in mouse hind legs from gamma ray radiation. Int J Radiat Oncol Biol Phys 30(4):867-872.

*Mays CW. 1988. Alpha-particle-induced cancer in humans. Health Phys 55(4):637-652.

*Mays CW, Aamodt RL, Inn KGW, et al. 1992. External gamma ray counting of selected tissue from a throatrast patient. Health Phys 63:33-40.

*Mazur L, Manowska J, Bobik R. 1991. Effects of ^{60}Co gamma-irradiation of mice on the temporal changes of acid phosphatase activity in spleen and liver. Acta Physiol Hung 78(2):135-141.

*McClellan RO, Barnes JE, Boecker BB, et al. 1970. Toxicity of beta-emitting radionuclides inhaled in fused clay particles—An experimental approach. In: Nettesheim P, Hanna MB, Deatherage JW, eds. Morphology of experimental respiratory carcinogenesis. CONF-700501. 395-415.

*McClellan RO, Benjamin SA, Boecker TL, et al. 1973. Neoplasms in dogs that inhaled $^{90}SrCl_2$. In: Sanders CL, et al. eds. Radionuclide carcinogenesis. CONF-720505. 215-232.

*McClellan RO, Boecker BB, Cuddihy RG, et al. 1982. Health effects from internally deposited radionuclides released in nuclear disasters. In: The control of exposure of the public to ionizing radiation in the event of accident or attack. National Council on Radiation Protection and Measurements, Bethesda, MD, 28-39.

*McCurdy D, Tai LQ, Frias S, et al. 1997. Delayed repair of DNA damage by ionizing radiation in cells from patients with juvenile systemic lupus erythematosus and rheumatoid arthritis. Radiat Res 147(1):48-54.

McGuire SA, Peabody CA. 1982. Working safely in gamma radiology. National Research Council.

*Merck. 1989. Merck index: An encyclopedia of chemicals, drugs, and biologicals. 11th ed. Budavari S, ed. Rahway NJ: Merck & Co., Inc.

*Mettler F, Moseley R. 1985. Medical effects of ionizing radiation. New York, NY: Grune and Stratton.

*Mewhinney JA, Griffith WC. 1982. Model of am metabolism in Beagles and humans. Health Phys 42:629-644.

*Mewhinney JA, Griffith WC. 1983. Tissue distribution model for assessment of human inhalation exposures to $^{241}AmO_2$. Health Phys 44:537-544.

*Mikamo K, Kamiguchi Y, Tateno H. 1990. Spontaneous and *in vitro* radiation-induced chromosome aberrations in human spermatozoa: Applications of a new method. Mutation and the Environment: Part B: Metabolism, testing methods, and chromosomes 340B:447-456.

*Mikamo K, Kamiguchi Y, Tateno H. 1991. The interspecific *in vitro* fertilization system to measure human sperm chromosomal damage. New Horizons in Biological Dosimetry 372:531-542.

*Milkovic-Kraus S, Kubelka D, Vekic B. 1992. Biological monitoring of three cobalt-60 radiation incident victims. Am J Ind Med 22(2):243-247.

*Miller RC, Randers-Pehrson G, Geard CR, et al. 1999. The oncogenic transformation potential of the passage of single α particles through mammalian cell nuclei. Proc Natl Acad Sci, USA. 96:19-22.

*Milner SM, Nguyen TT, Herndon DN, et al. 1996. Radiation injuries and mass casualties. In: Herndon DN, ed. Total burn care. W. B. Saunders, 425-431.

*Minamisawa T, Hirokaga K, Sasaki S. 1990. Gross morphological changes of the mouse brain exposed prenatally to ionizing radiation. J Radiat Res (Tokyo) 31(2):214-218.

*Minamisawa T, Hirokaga K, Sasaki S, et al. 1992. Effects of fetal exposure to gamma rays on aggressive behavior in adult male mice. J Radiat Res (Tokyo) 33(3):243-249.

*Misurova E, Kropacova K. 1992. Synthesis of nucleic acids in blood cells in mice after irradiation with gamma rays. Neoplasma 39(1):29-33.

*Mitchel REJ, Trivedi A. 1992. Chronic exposure to ionizing radiation as a tumor promoter in mouse skin. Radiat Res 129(2):192-201.

*Mlekodaj RL. 1995. Basic units and concepts in radiation exposures. In: Young JP, Yalow RS, ed. Advances in chemistry series, 23-37.

*Moisoi N, Petcu I. 1995. A bone marrow peroxidation study on low-dose irradiated rats. Nutrition 11(5Suppl):585-587.

*Moreira MCF. 1991. Radiological survey of Goiania by a mobile monitoring unit. Health Phys 60(1):81-85.

*Morgan KZ, Turner JE. 1973. Principles of radiation protection. New York, NY: John Wiley and Sons.

*Morrissey P, Charrier K, Bressler L, et al. 1988. The influence of IL-1 treatment on the reconstitution of the hemopoietic and immune systems after sublethal radiation. J Immunol 140(12):4204-4210.

*Mossman KL. 1992. Ionizing radiation at low doses: The question of cancer. J NIH Research 4:51-53.

*MSHA. 1997. MSHA's Mission Statement. Mine Safety and Health Administration, Department of Labor. Internet version. http://www.msha.gov/MISSION.HTM

*Muggenburg BA, Boecker BB, Hahn FF, et al. 1990. Lung lavage therapy to lessen the biological effects of inhaled cerium-144 in dogs. Radiat Res 124(2):147-155.

*Muggenburg BA, Guilmette RA, Griffith WC, et al. 1994. The toxicity of inhaled particles of $^{238}PuO_2$ in dogs. Ann Occup Hyg 38:269-274.

*Muggenburg BA, Wolff RK, Mauderly JL, et al. 1988. Cardiopulmonary function of dogs with plutonium-induced chronic lung injury. Radiat Res 115(2):314-324.

*Munson LH. 1988. Health physics manual of good practices for reducing radiation exposure to levels that are as low as reasonably achievable. U.S. Department of Energy, Pacific Northwest Laboratory. DE89 000406, PNL-7\6577, UC-610.

*Murphy CE, Jr. 1993. Tritium transport and cycling in the environment. Health Phys 65(6):683-697.

*Murray RL. 1994. Understanding radioactive waste, 4th edition. Columbus, OH and Richland WA: Batelle Press.

*Myrden JA, Hiltz JE. 1969. Breast cancer following multiple fluoroscopies during artificial pneumothorax treatment of pulmonary tuberculosis. Can Med Assoc J (22):1032-1034 .

*Nagasawa H, Little JB, Inkret WC, et al. 1990b. Cytogenic effects of extremely low doses of plutonium-238 alpha-particle irridation in CHO K-1 cells. Mutation Research 244:233-238.

*Nagasawa H, Robertson J, Little JB. 1990a. Induction of chromosal aberrations and sister chromatid exchanges by alpha particles in density-inhibited cultures of mouse 10T1/2 and 3T3 cells. Int J Radiat Biol 57(1):35-44.

*Najarian T, Colton T. 1978. Mortality from leukemia and cancer in shipyard nuclear workers. Lancet 1:1018-1020.

*Nakashima E. 1994. Relationship of five anthropometric measurements at age 18 to radiation dose among atomic bomb survivors exposed *in utero*. Radiat Res 138(1):121-126.

*Narra VR, Harapanhalli RS, Goddu SM. 1995. Radioprotection against biological effects of internal radionuclides *in vivo* by S-(2-aminoethyl)isothiouronium bromide hydrobromide (AET). J Nucl Med 36(2):259-266.

*NAS. 1994. Specific measures needed to reduce radiation exposure to resettlers of Marshall Islands atoll. In: National Research Council News, National Academy of Sciences. July 21, 1994.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Reserach Council. Washington, DC: National Academy Press, 15-35.

*NASA. 1995. Radiation safety aspects of commercial high-speed flight transportation. National Aeronautics and Space Administration, Hampton, VA. http://heasarc.gsfc.nasa.gov/docs/asca/new_results.html#sn1006.

*Natarajan AT, Vyas RC, Wiegant J. 1991. A cytogenetic follow-up study of the victims of a radiation accident in Goiania (Brazil). Mutat Res 247(1):103-112.

National Academies. 1994. http://www2.nas.edu/whatsnew/22f2.html

*NCI. 1990. Cancer in populations living near nuclear facilities. National Cancer Institute. NIH publication NO. 90-874.

NCI. 1996. NCI fact sheet: Questions and answers about radon and cancer - updated 06/96. National Cancer Institute. http://oncolink.upenn.edu/pdq_html/6/engl/600352.html.

*NCRP. 1976. Environmental radiation measurements. National Council on Radiation Protection and Measurements. Report No. 50. Washington, DC.

*NCRP. 1978. Instrumentation and monitoring methods for radiation protection. National Council on Radiation Protection and Measurements. Report No. 57. Washington, DC.

*NCRP. 1979. Tritium in the environment. National Council on Radiation Protection and Measurements. Report No.62. Bethesda, MD.

*NCRP. 1983. Environmental radioactivity. Proceedings of the Nineteenth Annual Meeting. National Council on Radiation Protection and Measurements. Proceedings No.5. Bethesda, MD.

*NCRP. 1984a. Neutron contamination from medical electron accelerators. National Council on Radiation Protection and Measurements. Report No.79. Bethesda, MD.

*NCRP. 1984b. Exposures from the uranium series with emphasis on radon and its daughters. National Council on Radiation Protection and Measurements. Report No. 77. Bethesda, MD.

*NCRP. 1984c. Radiological assessment predicting the transport, bioaccumulation, and uptake by man of radionuclides released to the environment. National Council on Radiation Protection and Measurements. Report No. 76. Bethesda, MD.

NCRP. 1984d. Evaluation of occupational and environmental exposures to radon and radon daughters in the United States. National Council for Radiation Protection and Measurements. Report No. 78. Bethesda, MD.

*NCRP. 1985. A handbook of radioactivity measurements procedures. 2nd ed. National Council on Radiation Protection and Measurements. NCRP Report No. 58. Bethesda, MD.

*NCRP. 1987a. Ionizing radiation exposure of the population of the United States. National Council on Radiation Protection and Measurements. NCRP Report No. 93. 1-69.

*NCRP. 1987b. Exposure of the population in the United States and Canada from natural background radiation. National Council on Radiation Protection and Measurements. Report No. 94. Bethesda, MD.

*NCRP. 1987c. Public radiation exposure from nuclear power generation in the United States. National Council on Radiation Protection and Measurements. Report No. 92. Bethesda, MD.

*NCRP. 1987d. Use of bioassay proceedures for assessent of internal radionuclide deposition. National Council on Radiation Protection and Measurements. Report No. 87. Washington, DC.

*NCRP. 1989a. Exposure of the U.S. population from diagnostic medical radiation. National Council on Radiation Protection and Measurements. Report No. 100. Bethesda, MD.

*NCRP. 1989b. Radiation protection for medical and allied health personnel. National Council on Radiation Protection and Measurements. Report No. 105. Bethesda, MD.

*NCRP. 1989c. Exposure of the U. S. population from occupational radiation. National Council on Radiation Protection and Measurements. Report No. 101. Bethesda, MD.

*NCRP. 1991. Calibration of survey instruments used in radiation protection for the asessment of ionizing radiation fields and radioactive surface contamination. National Council on Radiation Protection and Measurements. Report No. 112. Washington, DC.

*NCRP. 1993. Limitation of exposure to ionizing radiation. National Council on Radiation Protection and Measurements. Report No. 116. National Council on Remediation Protection and Measurement.

*NCRP. 1996. Sources and magnitude of occupational and public exposures from nuclear medicine procedures. Report No. 124. Bethesda, MD.

*NCRP. 1997. Mission and goals and background information. National Council on Radiation Protection and Measurements. Internet version, http://www.ncrp.com.

*Needleman HL, Gatsonis CA. 1990. Low-level lead exposure and the IQ of children: A meta-analysis of modern studies. JAMA 263(5):673-678.

*Needleman HL, Rabinowitz M, Leviton A, et al. 1984. The relationship between prenatal exposure to lead and congenital anomalies. JAMA 251(22):2956-2959.

*Needleman HL, Schell A, Bellinger D, et al. 1990. The long-term effects of exposure to low doses of lead in childhood - an 11-year follow-up report. New Engl J Med 322(2):83-88.

*Neel JV. 1992. The genetic effects of human exposures to ionizing radiation. In: Young JP, Yalow RS, ed. Advances in Chemistry Series, 243. Radiation and Public Perception: Benefits and Risks; 203rd National Meeting of the American Chemical Society, San Francisco, California, USA, April 5-10, 1992. American Chemical Society: Washington, DC, USA, 115-131.

*Neel JV, Schull WJ, Awa AA. 1990. The children of parents exposed to atomic bombs: Estimates of the genetic doubling dose of radiation for humans. Am J Hum Genet 46:1053-1072.

*Nelson JM, Stevens RG. 1996. Body iron stores may modify sensitivity to occupational radiation exposure. Applied Occupational and Environmental Hygiene 11(4):421-424.

*Neta RS, Steve M, Finkelman FH, et al. 1994. IL-12 protects bone marrow from and sensitizes intestinal tract to ionizing radiation. J Immunol 153(9):4230-4237.

*NFPA. 1992. National Fire Protection Association. Fire protection handbook. 3-144.

NIE. 1995. Soviet-designed nuclear power plants. NIE Source Book. Nuclear Energy Institute. Washington, D.C. Third Edition.

*NIH. 1994. Radon and lung cancer risk: A joint analysis of 11 underground miner studies. U.S. Department of Health and Human Services, National Institutes of Health, NIH publication 94-3644, Bethesda, MD.

*NIH. 1999. Fact Sheet. What we know about radiation. U.S. Department of Health and Human Services, National Institutes of Health. http://www.nih.gov/health/chip/od/radiation

*NIST. 1991. Calibration services users guide. National Institute of Standards and Technology, Special Publication 250. Washington, DC.

*NIST. 1995. Standard reference materials catalog. National Institute of Standards and Technology, Special Publication 260. Washington, DC.

*Nogam MJT, Huang SJ, James JM, et al. 1993. Mice chronically exposed to low dose ionizing radiation possess splenocytes with elevated levels of HSP70 mRNA, HSC70 and HSP72 and with an increased capacity to proliferate. Int J Radiat Biol 63(6):775-783, 27.

*Nogami M, Huang JT, Nakamura LT, et al. 1994. T cells are the cellular target of the proliferation-augmenting effect of chronic low-dose ionizing radiation in mice. Radiat Res 139(1):47-52.

*Norman A, McBride WH, Bennett LR, et al. 1988. Postirradiation protection of chromosomes by linoleate. Int J Radiat Biol 54(4):521-524.

*Norton S, Kimler BF. 1987. Correlation of behavior with brain damage after *in utero* exposure to toxic agents. Neurotoxicol Teratol 9(2):145-150.

*Norton S, Kimler BF. 1988. Comparison of functional and morphological deficits in the rat after gestational exposure to ionizing radiation. Neurotoxicol Teratol 10(4):363-371.

*Norton S, Kimler BF. 1990. Early effects of low doses of ionizing radiation on the fetal cerebral cortex in rats. Radiat Res 124(2):235-241.

*Nothdurft W, Fliedner TM, Fritz TE, et al. 1995. Response of hemopoiesis in dogs to continuous low dose rate total body irradiation. Stem Cells 13(suppl 1):261-267.

Nussbaum RH, Wolfgang K. 1996. Health consequences of exposures to ionizing radiation from external and internal sources: Challenges to radiation protection standards and biomedical research . http://www.healthnet.org/MGS/Article1.html

*O'Hare NJ, Gilligan P, Murphy D, et al. 1997. Estimation of foetal brain dose from I-131 in the foetal thyroid. Physics in Medicine and Biology 42(9):1717-1726.

*Ohba M, Benson J. 1998. A-bomb www museum. http://www.csi.ad.jp/ABOMB/

*Oliveira AR, Brandao-Mello CE, Valverde NJL, et al. 1991a. Localized lesions induced by Cs-137 during the Goiania accident. Health Phys 60(1):25-29.

*Oliveira AR, Hunt JG, Valverde NJL, et al. 1991b. Medical and related aspects of the Goiania accident: An overview. Health Phys 60(1):17-24.

*Ootsuyama A, Tanooka H. 1986. Unscheduled DNA synthesis after beta-irradiation of mouse skin *in situ*. Mutat Res 166(2):183-185.

*Ootsuyama A, Tanooka H. 1989. Induction of osteosarcomas in mouse lumbar vertebrae by repeated external β-irradiation. Cancer Research 49:1562-1564.

*Orfanos SE, Chen XL, Burch SE, et al. 1994. Radiation-induced early pulmonary endothelial ectoenzyme dysfunction *in vivo*: Effect of indomethacin. Toxicol Appl Pharmacol 124(1):112-122.

*OSHA. 1996a. Toxic and hazardous substances. Ionizing radiation. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1096.

*OSHA. 1996b. Safety and health regulations for construction. Ionizing radiation. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.53.

*OSHA. 1997. OSHA Regulations, Ionizing Radiation. Occupational Safety and Health Administration, Department of Labor. Code of Federal Regulations. Washington, D.C. 29 CFR 1910.1096.

*Ossenkopp KP, Giugno L. 1985. Taste aversions conditioned with multiple exposures to gamma radiation abolition by area postrema lesions in rats. Brain Res 346(1):1-7.

*OTA. 1990. Neurotoxicology: Identifying and controlling poisons of the nervous system. Office of Technology Assessment, Washington, DC. OTA-BA-438.

*OTA. 1994. Fueling reform: Energy technologies for the former East Bloc, Chapter 4: Non-fossil fuel technologies, August 9, 1994. Office of Technology Assessment. http://www.emanifesto.org/OTAEnergyEast/OTAEEEch4.htm

*Otake M, Schull W. 1984. Mental retardation in children exposed *in utero* to the atomic bombs: A reassessment. Technical Report RERF TR 1-83, Radiation Effects Research Foundation, Japan.

*Padovani L, Mauro F, Caporossi D, et al. 1993. Cytogenetic study in lymphocytes from children exposed to ionizing radiation after Chernobyl accident. GRAI9423; ERA9444.

*Panizzon RG, Hanson WR, Schwartz DE, et al. 1988. Ionizing radiation induces early, sustained increases in collagen biosynthesis: A 48-week study in mouse skin and skin fibroblast cultures. Radiat Res 116(1):145-156.

*Paretzke HG. 1997. Late somatic health effects. Ciba Found Symp 203:167-177.

*Pastorova B, Ahlersova E, Ahlers I, et al. 1997. The effect of a single whole-body irradiation with a lethal dose on catecholamine levels in the pineal glands of rats. Journal of Physiology and Pharmacology 48(1):73-79.

*PBS. 1999. Race for the superbomb; nuclear weapons test map. Public Broadcast System. http://www.pbs.org/wgbh/pages/amex/bomb/maps.

*Peter RU, Braun-Falco O, Birioukov A, et al. 1994. Chronic cutaneous damage after accidental exposure to ionizing radiation: The Chernobyl experience. J Am Acad Dermatol 30(5 Pt 1):719-723.

*Peterson VM, Adamovicz JJ, Elliott TB, et al. 1994. Gene expression of hematoregulatory cytokines is elevated endogenously after sublethal gamma irradiation and is differentially enhanced by therapeutic administration of biologic response modifiers. J Immunol 153(5):2321-2330.

*Petridou E, Proukakis C, Tong D, et al. 1994. Trends and geographical distribution of childhood leukemia in Greece in relation to the Chernobyl accident. Scandinavian Journal of Social Medicine 22(2):127-131.

*Petrova A, Gnedko T, Maistrova I, et al. 1997. Morbidity in a large cohort study of children born to mothers exposed to radiation from Chernobyl. Stem Cells 15(suppl. 2):141-150.

*Pierce BA, Yukyko S, Preston BL, et al. 1996. Studies of the mortality of atomic bomb survivors. Rep Rad Res 146:1-27.

*Pinon-Lataillade G, Viguier-Martinez MC, Touzalin AM, et al. 1991. Effect of an acute exposure of rat testes to gamma rays on germ cells and on Sertoli and Leydig cell functions. Reprod Nutr Dev 31(6):617-629.

*Pitot III HC, Dragan YP. 1996. Chemical carcinogenesis. In: Klassen CD, ed. Casarett & Doull's toxicology: The basic science of poisons, 5th edition. New York, NY: McGraw Hill, 201-267.

*Pohl-Ruling J, Fischer P. 1979. The dose-effect relationship of chromosome aberrations to alpha and gamma irradiation in a population subjected to an increased burden of natural radioactivity. Radiat Res 80(1):61-81.

*Polednak AP. 1979. Long-term effects of radium exposure in female dial workers: Liver function and liver disease. Environ Res 18(2):454-465.

*Polednak AP. 1980. Fertility of women after exposure to internal and external radiation. J Environ Pathol Toxicol 4(1):457-470.

*Polednak AP, Farnham JE. 1980. Osteometry and autoradiography of the long bones of skeletons of women exposed to internal radiation at 13-19 years of age. Am J Phys Anthropol 52(3):335-340.

*Pomerantseva MD, Ramaya LK, Shevchenko VA. 1989. Evaluation of the genetic effects of ^{238}Pu incorporated into mice. Mutat Res 226(2):93-98.

*Poretti G. 1989. Radiation exposure of a population through X-ray and nuclear medicine. Radiat Phys Chem 342:317-326.

*Pospisil M, Hofer M, Pipalova I, et al. 1992. Enhancement of hematopoietic recovery in gamma-irradiated mice by the joint use of diclofenac, an inhibitor of prostaglandin production, and glucan, a macrophage activator. Exp Hematol 20(7):891-895.

*Potten CS. 1985. Radiation and skin. London: Taylor & Francis.

*Potter GD, Mcintyre Dr, Pomeroy D. 1969. Transport of fallout radionuclides in the grass-to-milk food chain studied with a germanium lithium-drifted detector. Health Phys 16:197-300.

*PSU. 1999. Earth and Mineral Sciences, Penn State University. http://www.ems.psu.edu/~radovic/TMI.html

*Pukkala E, Auvinen A, Wahlberg G. 1995. Incidence of cancer among Finnish airline cabin attendants, 1967-92. British Medical Journal 311(7006):649-652.

*Purrott RJ, Edwards AA, Lloyd DC, et al. 1980. The induction of chromosome aberrations in human lymphocytes by *in vitro* irradiation with a-particles from plutonium-239. Int J Radiat Biol 38(3):277-284.

*Raabe O. 1993. Cancer and injury risks from internally deposited radionuclides. In: Actualités sur le césium, Journée organisée par le comité de radioprotection d'électricité de France, Paris, March 25, 1993, 39-48.

*Raabe OG. 1994. Three dimensional models of risk from internally deposited radionuclides. In: Internal radiation dosimetery. Madison, WI: Medical Physics Publishing.

*Raabe O. 1996. Oh, wunder. The inverse dose-rate effect is quelled by the effective threshold. 1996 International Congress on Radiation Protection, 9th International Congress, Vienna, Austria. 2:378-380.

*Raabe OG, Book SA, Parks NJ, et al. 1981. Lifetime studies of ^{226}Ra and ^{90}Sr toxicity in Beagles—a status report. Radiat Res 86(3):515-28.

*Raabe OG, Bushberg JT. 1996. Ionizing radiation and the lungs. Occupational and Environmental Respiratory Disease 535-560.

*Radford EP, Renard KGS. 1984. Lung cancer in Swedish iron miners exposed to low doses of radon daughters. New Engl J Med 310:1485-1494.

*RADNET. 1996. Information about source points of anthropogenic radioactivity. A freedom of nuclear information resource 1-15. http://home.acdia.net/cbm/Rad5.html

*RADRES. 1999. Radiation Research Society. Home page. http://www.radres.org/intro.htm

*Raicevic JJ, Merkle M, Ehrhardt J, et al. 1997. Loss of lifetime due to radiation exposure: Averaging problems. Health Phys 72(4):550-557.

*Ralcewicz TA, Persaud TV. 1995. Effects of prenatal exposure to low dose ionizing radiation on the development of the cerebellar cortex in the rat. Histol Histopathol 10(2):371-83.

*Ramaiya LK, Pomerantseva MD, Chekhovich AV, et al. 1994. Genetic effects of testicular incorporation of ^{137}Cs in mice. Mutat Res 324(4):139-145.

*Rao DV, Narra VR, Howell RW, et al. 1990. Biological consequence of nuclear versus cytoplasmic decays of ^{125}I: Cysteamine as a radioprotector against Auger cascades *in vivo*. Radiat Res 124(2):188-193.

*Rasey JS, Magee S, Nelson N, et al. 1990. Response of mouse tissues to neutron and gamma radiation protection by WR-3689 and WR-77913. Radiother Oncol 17(2):167-173.

*Reitz G, Horneck G, Facius R, et al. 1995. Results of space experiments. Radiation and Environmental Biophysics 34(3):139-144.

*Remington JP. 1985. Remington's pharmaceutical sciences. 17th edition. Easton, PA: Mack Publishers.

*Remington JP, Gennaro AR. 1995. Remington, the science and practice of pharmacy. 19th edition. Easton, PA: Mack Publishers.

*RERF. 1998. Radiation Effects Research Foundation. Home page. http://www.rerf.or.jp/

*Revsin BK, Watson JE Jr. 1993. Long-term environmental trends. Selection of sampling locations in a reactor-aquatic cooling system. Health Phys 64:178-182.

*Reyners H, Gianfelici E, De Reyners, et al. 1992. Brain atrophy after foetal exposure to very low doses of ionizing radiation. Int J Radiat Biol 62(5):619-626.

*Rezvani M, Heryet JC, Hopewell JW. 1989. Effects of single doses of gamma-radiation on pig lung. Radiother Oncol 14(2):133-142.

*Ribas G, Carbonell E, Xamena N, et al. 1994. Genotoxicity of tritiated water in human lymphocytes. Toxicology Letters 70:63-69.

*Richardson RB, Eatough JP, Henshaw DL. 1991. Dose to red bone marrow from natural radon and thoron exposure. Br J Radiol 64(763):608-624.

*Ricoul M, Dutrillaux B. 1991. Variations of chromosome radiation sensitivity in fetal and adult mice during gestation. Mutat Res 250(1-2):331-335.

*Rinsky RA, Waxweiler RJ, Murray WE Jr., et al. 1981. Cancer mortality at a naval nuclear shipyard. Lancet 231-235.

*Roberts DHJ, White GRM, Ockey CH. 1987. Sister chromatid induction by β-irradiation from incorporated ^{3}H-thymidine: A paradox explained. Chromosoma 96:72-76.

*Roesch WC, ed. 1987. U.S.-Japan joint reassessment of atomic bomb radiation dosimetery in Hiroshima and Nagasaki. Radiation Effects Research Foundation, Minami-ku, Japan 732:1-36.

*Ron E, Modan B. 1984. Thyroid and other neoplasms following childhood scalp irradiations. In: Boice JD, Fraumeni JF, eds. Radiation carcinogenesis: Epidemiology and biological significance, New York, NY: Raven Press, 139-151.

*Roux C, Elefant E, Gaboriaud G. 1986. Association of microwaves and ionizing radiation: Potentiation of teratogenic effects in the rat. Radiat Res 108(3):317-326.

*Rosenthal JJ, de Almeida CE, Mendonca AH. 1991. The radiological accident in Goiania: The initial remedial action. Health Phys 60(1):7-15.

*Rowland RE, Stehney AF, Lucas HF. 1978. Dose-response relationships for female radium dial workers. Radiat Res 76:368-383.

*Rozhdestvensky LM, Fomicheva EI. 1995. The estimation of haematopoietic stem cell reaction to low level ionising radiation. Radiation Protection Dosimetry 62(1-2):49-51.

*Rozhdestvensky LM, Fomicheva EI. 1995. The estimation of hematopoietic stem cell reaction to low level ionizing radiation. Radiation Protection Dosimetry 62(1-2):49-51.

S. Cohen & Associates, Inc. 1994. Routine environmental sampling procedures manual for radionuclides. May 17, 1994.

*Saad AY, Abdelazim AA, el-Khashab MM, et al. 1991. Effects of gamma radiation on incisor development of the prenatal albino mouse. J Oral Pathol Med 20(8):385-388.

*Saad AY, Abdelazim AA, el-Khashab MM, et al. 1994. Induction of cleft palate by gamma-irradiation of prenatal CD-1 mice. Cleft Palate Craniofac J 31(5):351-355.

*Sabatier L, Martin M, Crechet F, et al. 1992. Chromosomal anomalies in radiation-induced fibrosis in the pig. Mutat Res 284:2257-2263.

*Saccomanno G, Archer VE, Auerbach MD, et al. 1971. Histologic types of lung cancer among uranium miners. Cancer 27:515-523.

*Saccomanno G, Archer VE, Saunders RP, et al. 1976. Early indices of cancer risk among uranium miners with reference to modifying factors. Ann NY Acad Sciences 271:377-383.

*Saccomanno G, Yale C, Dixon W, et al. 1986. An epidemiological analysis of the relationship between exposure to radon progeny, smoking and bronchogenic carcinoma in the uranium-mining population of the Colorado Plateau (USA): 1960-1980. Health Phys 50:605-618.

*Saku T, Hayashi Y, Takahara O, et al. 1997. Salivary gland tumors among atomic bomb survivors, 1950-1987. Cancer 79(8):1465-1475.

*Salovsky PT, Shopova VI. 1992. Early biological effects of whole body irradiation on rat lungs. Radiat Environ Biophys 31(4):333-341.

*Sanders CL, Kathren, RL. 1983. Ionizing radiation. Tumorigenic and tumoricidal effects. Columbus, OH: Battelle Press.

*Sanders CL, Kathren RL. 1997. Ionizing radiation tumorigenic and tumoricidal effects. New York, NY: Battelle Press, Springer-Verlag.

*Sandia Lab News. 1995. Palomares "bomb number four" - it crashed, it fell, it sank, but (whew!) it never blew up. http://www.sandia.gov/LabNews/LN01-19-96/palo.html

*Sasaki MS, Takatsuji T, Ejima Y, et al. 1987. Chromosome aberration frequency and radiation dose to lymphocytes by alpha-particles from internal deposit of Thorotrast. Radiat Environ Biophys 26(3):227-238.

*Scheid W, Weber J, Petrenko S, et al. 1993a. Chromosome aberrations in human lymphocytes apparently induced by Chernobyl fallout. 64(5):531-534.

*Scheid W, Weber J, Traut H. 1993b. Chromosome abberations induced in the lymphycytes of pilots and stewardesses. Naturwissenschaften 80:528-530.

*Schimmerling, W. 1995. Space and radiation protection: Scientific requirements for space research. Radiation and Environmental Biophysics 34(3):133-137.

*Schultz MK. 1996. Irish Sea sediment IAEA-135, the Irish Sea,and the Sellafield reprocessing discharges. http://ocean.fsu.edu/oce/mschultz/Irish.html

*Schultz SC, Schultz V. 1994. Bikini and Enewetak Marshallese: Their atolls and nuclear weapons testing. Critical Reviews in Environmental Science and Technology 24(1):33-118.

*Schweitzer DJ, Benjamin SA, Lee AC. 1987. Retinal dysplasia and progressive atrophy in dogs irradiated during ocular development. Radiat Res 111(2):340-353.

*Scott BR. 1990. A model for early death caused by radiation pneumonitis and pulmonary fibrosis after inhaling insoluble radioactive particles. Bull Math Biol 42(3):447-459.

*Scott BR, Dillehay LE. 1990. A model for hematopoeitic death in man from irradiation of bone marrow during radioimmunotherapy. Br J Radiol 63:862-870.

*Scott BR, Hahn FF. 1980. A model that leads to the Weibull distribution function to characterize early radiation response probabilities. Health Phys. 39:521-530.

*Searle AG, Beechey CV, Green D, et al. 1976. Cytogenetic effects of protracted exposures to alpha-particles from plutonium-239 and to gamma-rays from cobalt-60 compared in male mice. Mutat Res 41(2-3):297-310.

*Searle AG, Beechey CV, Green D, et al. 1980. Comparative effects of protracted exposures to ^{60}Co gamma-radiation and ^{239}Pu alpha-radiation on breeding performance in female mice. Int J Radiat Biol Relat Stud Phys Chem Med 37(2):189-200.

*Seed T, Carnes B, Tolle D, et al. 1993. Blood responses under chronic low daily dose gamma irradiation: II. Differential preclinical responses of irradiated female dogs in progression to either aplastic anemia or myeloproliferative disease. Leuk Res 17(5):411-420.

*Seed TM, Carnes BA, Tolle DV, et al. 1989. Blood responses under chronic low daily dose gamma irradiation: I. Differential preclinical responses of irradiated male dogs in progression to either aplastic anemia or myeloproliferative disease. Leuk Res 13(12):1069-1084.

*Selig C. 1995. The use of biological indicators to assess consequences of radiation exposure at the cell system level. Stem Cells 13(suppl. 1):323-325.

*Sellins KS, Cohen JJ. 1987. Gene induction by gamma-irradiation leads to DNA fragmentation in lymphocytes. J Immunol 139(10):3199-3206.

*Serio CS, Henning CB, Toohey RE, et al. 1983. Measurement of lymphoblastogenic activity from thorium workers. Int J Radiat Biol Relat Stud Phys Chem Med 44(3):251-256.

*Sevan'kaev AV, Tsyb AF, Lloyd DC, et al. 1993. Rogue cells observed in children exposed to radiation from the Chernobyl accident. Int J Radiat Biol Mar 63(3):361-367.

*Sever LE, Gilbert ES, Hessol NA, et al. 1988. A case-control study of congentital malformations and occupational exposure to low-level ionizing radiation. Am J Epidemiol 127(2):226-242.

*Shaheen AA, Hassan SH. 1994. Role of vitamin A in modulating the radiation-induced changes in intestinal disaccharidases of rats exposed to multifractionated gamma-radiations. Strahlenther Onkol 170(8):467-470.

*Shapiro J. 1990a. Practical aspects of the use of radionuclides. In: Shapiro J, ed. Protection: A guide for scientists and physicians, 3rd edition. Cambridge MA: Harvard University Press, 264-333.

*Shapiro J. 1990b. Ionizing radiation and public health. In: Shapiro J, ed. Protection: A guide for scientists and physicians, 3rd edition. Cambridge MA: Harvard University Press, 334-429.

*Shapiro J. 1990c. Radiation protection, 3rd edition. Cambridge MA: Harvard University Press.

*Shcherbak YM. 1996. Ten years of the Chernobyl era. Sci Am 274(4):44-49.

*Shearer SD, Jr., Sill CW. 1969. Evaluation of atmospheric radon in vicinity of uranium mill tailings. Health Phys 17:77-88.

*Shevchenko VA, Pomerantseva MD, Ramaiya LK, et al. 1992. Genetic disorders in mice exposed to radiation in the vicinity of the Chernobyl nuclear power station. Sci Total Environ 112(1):45-56.

*Shevchenko VA, Ramaya LK, Pomerantseva MD, et al. 1989. Genetic effects of ^{131}I in reproductive cells of male mice. Mutat Res 226(2):87-91.

*Shimizu Y, Kato H, Schull WJ. 1988. Life span study report 11 part 2. Cancer mortality in the years 1950-1985 based on the recently revised doses (DS86). Radiation Effects Research Foundation, Minami-ku, Japan 732:1-102.

*Shlein B. 1992. The health physics and radiological health handbook. Silver Spring, MD: Scinta, 264-265.

*Shyr LJ, Griffith WC, Boecker BB. 1991. An optimization strategy for a biokinetic model of inhaled radionuclides. Fundam Appl Toxicol 16:423-434.

*Sigdestad CP, Grdina DJ, Connor AM, et al. 1986. A comparison of radioprotection from three neutron sources and ^{60}Co by WR-2721 and WR-151327. Radiat Res 106(2):224-233.

*Simon SL, Vetter, RJ (eds). 1997. Consequences of nuclear testing in the Marshall Islands. Health Phys 73(1).

*Smith JN, Ellis KM, Aarkrog A, et al. 1994. Sediment mixing and burial of the $^{239, 240}$Pu pulse from the 1968 Thule, Greenland, nuclear weapons accident. J Environ Radioactivity 25:135-1593.

*Smith PG. 1984. Radiation carcinogen: Epidemiology and biological signficance, In: Late effects of X-ray treatment of ankylosing spondylitis. Vol 1, 1AEA, Vienna, 107-118.

*Smith WN, Doll R. 1978. Age and time dependent changes in the rates of radiation-induced cancers in patients with ankylosing spondylitis following a single course of X-ray treatment. In: Late effects of ionizing radiation. Vol 1, 1AEA, Vienna, 205.

*Snipes MB, Spoo JW, Muggenburg BA, et al. 1996. Evaluation of the clearance of particles deposited on the conducting airways of Beagle dogs. J Aerosol Med 9(4):477-499.

*Song CW, Drescher JJ, Tabachnick J. 1968. Effect of anti-inflammatory compounds on beta-irradiation-induced increase in vascular peremeability. Radiat Res 34(3):616-625.

*Sorahan T, Roberts PJ. 1993. Childhood cancer and paternal exposure to ionizing radiation: preliminary findings from the Oxford Survey of Childhood Cancers. Am J Ind Med 23 (2):343-354.

*Spiess H, Mays CW. 1970. Bone cancers induced by ^{224}Ra (Th X) in children and adults. Health Phys 19:713-729.

*Spiess H, Mays CW. 1973. Protraction effect on bone-sarcoma induction of ^{224}Ra in children and adults. In: Sanders CL, Busch RH, Ballow Je, Mahlum DD, eds. Radionuclides carciongensis. Springfield, VA: National Technical Information Service 437-450.

*Stahlhofen W, Gebhart J, Heyder J. 1980. Experimental determination of the regional deposition of aerosol particles in the human respiratory tract. J Amer Ind Hyg Assoc 41(6)385-398a.

*Stahlhofen W, Gebhart J, Heyder K, et al. 1981. Intercomparison of regional deposition of aerosol particles in the human respiratory tract and their long-term elimination. Experimental Lung Research 2:131-139.

*Stavem P, Brogger A, Devik F, et al. 1985. Lethal acute gamma radiation accident at Kjeller, Norway. Report of a case. Acta Radiol Oncol 24(1):61-63.

*Steinstrasser A. 1981. Biophysical investigations of the dose-effect relationship in chromosome aberrations of human lymphocytes caused by thorotrast deposits. I. Physical aspects. Radiat Environ Biophys 19(1):1-15.

*Sternberg RJ, Kaufman JC. 1998. Human abilities. Annu Rev Psychol 49:479-502. http://biomedical.AnnualReviews.org/cgi/content/full/17/49/479.

*Sternglass EJ, Gould JM. 1993. Breast cancer: Evidence for a relation to fission products in the diet. Int J Health Services 23(4):783-804.

*Stewart AM, Kneale GW. 1991. An overview of the Hanford controversy. Occup Med 6(4):641-63.

*Stitt AW, Anderson HR, Gardiner TA, et al. 1994. The combined effects of diabetes and ionising radiation on the rat retina: An ultrastructural study. Curr Eye Res 13(1):79-86.

*Stokinger HE. 1981. Uranium U. In: Clayton GD, Clayton FE, eds. Industrial hygiene and toxicology. Vol 2A, 3rd ed. New York, NY: John Wiley & Sons, 1995-2013.

*Stone WH, Saphire DG, Hackleman SM, et al. 1994. Effect of radiation and age on immunoglobulin levels in Rhesus monkeys (*Macaca mulatta*). Radiat Res 138(3):401-408.

*Stram DO, Sposto R, Preston D, et al. 1993. Stable chromosome aberrations among A-bomb survivors: An update. Radiat Res 136(1):29-36.

*Sublette C. 1995. Section 5.0 Effects of nuclear exposions. Nuclear weapons frequently asked questions, version 2.13. http://www.pal.xgw.fi/hew/NFAQ5.HTML.

*Sublette C. 1996. Section 8.0 The first nuclear weapons. Nuclear weapons frequently asked questions, version 2.15. http://www.pal.xgw.fi/hew/NFAQ8.HTML.

*Suzuki K, Takahashi M, Ishii-Ohba H, et al. 1990. Steroidogenesis in the testes and the adrenals of adult male rats after gamma-irradiation *in utero* at late pregnancy. J Steroid Biochem 35(2):301-305.

*Swanson SM. 1985. Food chain transfer of U-series radionuclides in northern Saskatchewan aquatic system. Health Phys 49:747-770.

*Sweet CW, Murphy CE Jr, Lorenz R. 1983. Environmental tritium transport from an atmospheric release of tritiated water. Health Phys 44(1):13-18.

*Symons MCR. 1994. Direct and indirect damage to DNA by ionising radiation. Radiat Phys Chem 43(4):403-405.

*Takatsuji T, Saski MS. 1984. Dose-effect relationship of chromosome aberrations induced by 23 MeV alpha particles in human lymphocytes. Int J Radiat Biol 45(3):237-243.

*Takatsuji T, Saski MS, Takekoshi H. 1989. Effect of static magnetic field on the induction of chromosome aberrations by 4.9 MeV protons and 23 MeV alpha particles. J Radiat Res 30:238-246.

*Tanaka K, Sawada S, Kamada N. 1994. Relative biological effectiveness and dose rate effect of tritiated water on chromosomes in human lymphocytes and bone marrow cells. Mut Res 323:53-61.

*Thacker J. 1986. The nature of mutants induced by ionising radiation in cultured hamster cells: III. Molecular characterization of HPRT-deficient mutants induced by γ-ray or α-particles showing that the majority have deletions of all or part of the HPRT gene. Mutat Res 160:267-275.

*Thun MJ, Baker DB, Steenland K, et al. 1985. Renal toxicity in uranium mill workers. Scand J Work Environ Health 11:83-90.

*Tobari I, Matsuda Y, Gu XH, et al. 1988. Dose-response relationship for translocation induction in spermatogonia of the crab-eating monkey (*Macaca fascicularis*) by chronic gamma-ray-irradiation. Mutat Res 201(1):81-87.

10. REFERENCES

*Tomonaga M, Matsuo T, Carter RL, et al. 1993. Differential effects of atomic bomb irradiation in inducing major leukemia types: Analyses of open-city cases including the life span study cohort based upon updated diagnositic systems and the dosimetry system 1986. (DS86). Radiation Effects Research Foundation, Minami-ku, Japan. 732:1-102.

*Trakhtenberg I, Ivanitskaya N, Talakin Y, et al. 1996. Follow-up consequences of ionizing irradiation low dose effects on the body immune system. Fresenius Environmental Bulletin 5(3/4):121-125.

*U of Michigan. 1999. Introduction to radiation. http://www.umich.edu/~radinfo/introduction

*U.S. Congress. 1990. Clean Air Act. Title III. Section 112. Hazardous air pollutants. One Hundred and First Congress of the United States. Public Law 101-549. 42 USC 7412. November 15, 1990.

*U.S. Congress. 1998. Mammography quality standards reauthorization act of 1998. House Reports: No. 105-713 Congressional Record Vol. 144.

*U.S. House of Representatives. 1999. Office of the Law Revision. Home page. http://uscode.house.gov/

*Umegaki K, Ichikawa T. 1994. Decrease in vitamin E levels in the bone marrow of mice receiving whole-body X-ray irradiation. Free Radical Biology and Medicine 17(5):439-444.

*Umegaki K, Takeuchi N, Ikegami S, et al. 1994. Effect of beta-carotene on spontaneous and X-ray-induced chromosomal damage in bone marrow cells of mice. Nutr Cancer 22(3):277-284.

*UNSCEAR. 1977. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. New York, NY.

*UNSCEAR. 1982. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. New York, NY.

*UNSCEAR. 1986. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. New York, NY.

*UNSCEAR. 1988a. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. New York, NY.

*UNSCEAR. 1988b. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. New York, NY.

*UNSCEAR. 1993. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. New York, NY.

*UPI. 1999. Japanese nuclear accident. Global Impact Net at http://www.upi.com. October 1, 1999.

*Upton AC. 1991. Risk estimates for carcinogenic effects of radiation. Annals of the ICRP 22(1):1-118.

*Uranium Information Center. 1995. Fifty years of nuclear threat and promise: Hiroshima and Nagasaki 1945, and subsequent weapons testing. Nuclear issues briefing paper No. 29. http://www.uic.com.au/nip29.html

*Urquhart JD, Black RJ, Muirhead MJ, et al. 1991. Case-control study of leukaemia and non-Hodgkin's lymphoma in children in Caithness near the Dounreay nuclear installation. BMJ 302:692-696.

*USDA. 1997. Animal and plant health inspection service, department of agriculture. Hawaiian fruits and vegetables. U.S. Department of Agriculture. Code of Federal Regulations. 7 CFR 318.

*USDOC. 1995. National Trade Data Bank. U.S. Department of Commerce. July 10, 1995.

*USERD. 1975. Preliminary external-dose estimates for future Bikini Atoll inhabitants. U.S. Energy Research and Development. Preliminary report No. UCRL-51879.

*USNRC. 1974. Regulatory guide 1.86. Termination of operating licenses for nuclear reactors. U.S. Nuclear Regulatory Commission. Washington, DC.

*USNRC. 1975. Regulatory guide 4.1. Programs for monitoring radioactivity in the environs of nuclear power plants. U.S. Nuclear Regulatory Commission. Washington, DC.

*USNRC. 1977a. Regulatory guide 1.109. Calculation of annual doses to man from routine releases of reactor effluents for the purpose of evaluating compliance with 10CFR part 50, appendix I Rev I, U.S. Nuclear Regulatory Commission. Washington DC.

*USNRC. 1977b. Regulatory guide 1.111. Methods for estimating atmospheric transport and dispersion of gaseous effluents in routine releases from light-water-colled reactors, Rev I. U.S. Nuclear Regulatory Commission. Washington DC.

*USNRC. 1977c. Regulatory guide 1.113. Estimating aquatic dispersion of effluents from accidental and routine reactor releases for the purposes of Implementing Appendix I Rev I, Washington DC.

*USNRC. 1979. Regulatory guide 4.15. Quality assurance for radiological monitoring programs: Effluent streams and environment. U.S. Nuclear Regulatory Commission. Washington, DC.

*USNRC. 1991. Occupational dose limits. U.S. Nuclear Regulatory Commission. Code of Federal Regulations. 10 CFR 20, Subpart C.

*USNRC. 1992. Nuclear regulatory commission digest. U.S. Nuclear Regulatory Commission. Washington, DC. NUREG-1350-V4.

*USNRC. 1993. Standards for protection against radiation. Annual limits on intake (ALIs) and derived air concentrations (DACs) of radionuclides for occupational exposure; effluent concentrations; concentrations for release to sewerage. U.S. Nuclear Regulatory Commission. Code of Federal Regulations. 10 CFR 20, Appendix B.

*USNRC. 1994. Standards for protection against radiation. Code of Federal Regulations. 10 CFR 20. U.S. Nuclear Regulatory Commission. Washington, DC.

*USNRC. 1995. Standards for protection against radiation. Quantities of licensed material requiring labeling. U.S. Nuclear Regulatory Commission. Code of Federal Regulations. 10 CFR 20, Appendix C.

*USNRC. 1996. Radiation dose limits for individual members of the public. U.S. Nuclear Regulatory Commission. Washington, D.C. Code of Federal Regulations. 10 CFR 20.1301, Subpart D.

10. REFERENCES

*USNRC. 1997a. Standards for protection against radiation. U.S. Nuclear Regulatory Commission, Washington, D.C. Code of Federal Regulations. 10 CFR 20, Subpart A.

*USNRC. 1997b. Radiation dose limits for individual members of the public. U.S. Nuclear Regulatory Commission. Code of Federal Regulations. 10 CFR 20, Subpart D.

*USNRC. 1998. Physical protection for spent nuclear fuel and high-level radioactive waste; final rule. U.S. Nuclear Regulatory Commission. Federal Register. 63 FR 26955. May 15, 1998.

*USNRC. 1999. U.S. Nuclear Regulatory Commission. Home page. http://www.nrc.gov/

*van Wyngaarden KE, Pauwels EK. 1995. Hormesis: are low doses of ionizing radiation harmful or beneficial? Eur J Nucl Med 22(5):481-6.

*Vicker MG, Bultmann H, Glade U, et al. 1991. Ionizing radiation at low doses induces inflammatory reactions in human blood. Radiat Res 128 (3):251-257.

*Vigneulle RM, Herrera J, Gage T, et al. 1990. Nonuniform irradiation of the canine intestine. I. Effects. Radiat Res 121(1):46-53.

*Vijayalaxmi, Reiter RJ, Meltz ML. 1995. Melatonin protects human blood lymphocytes from radiation-induced chromosome damage. Mutat Res 346(1):23-31.

*Vulpis N. 1984. The induction of chromosome aberrations in human lymphocytes by *in vitro* irradiaton and B particles from tritiated water. Radiat Res 97:511-518.

Vulpis N, Scarpa G. 1986. Induction of chromosome aberrations by ^{90}Sr β particles in cultured human lymphocytes. Mutat Res163(3):277-283.

*Vyas DR, Dick RM, Crawford J. 1994. Management of radiation accidents and exposures. Pediatr Emerg Care 10(4):232-237.

*Wang B, Takeda H, Gao W-M, Zhou X-Y et al. 1999. Induction of apoptosis by beta radiation from tritium compounds in mouse embryonic brain cells. Health Phys 77(I):16-23.

*Wasserman H, et al. 1982. Killing our own: The disaster of America's experience with atomic radiation. New York, NY: Delacorte Press.

*Wasserman J. 1986. Immunological indicators. In: Biological indicators for radiation dose assessment. Munchen: MMV Medizin Verlag. 85-105.

*Watanabe M, Suzuki M, Suzuki K, et al. 1990. Radioprotective effects of dimethyl sulfoxide in golden hamster embryo cells exposed to gamma rays at 77 K. II. Protection from lethal, chromosomal, and DNA damage. Radiat Res 124(1):73-78.

*Wei L. 1992. Health effects on populations exposed to low-level radiation in China. In: Young JP, Yalow RS, eds. Advances in Chemistry Series, 243. Radiation and Public Perception: Benefits and Risks; 203rd National Meeting of the American Chemical Society, San Francisco, California, USA, April 5-10, 1992. American Chemical Society: Washington, DC USA, 219-238.

*Welleweerd J, Wilder Me, Carpenter SG, et al. 1984. Flow cytometroc determination of radiation-induced chromosome damage and its correlation with cell survival. Radiat Res 99:44-51.

*Whittemore AS, McMillan A. 1983. Lung cancer mortality among U.S. uranium miners: A reappraisal. JNCI 71(3):489-499.

*WHO 1995. Health consequences of the Chernobyl accident: Results of the IPHECA pilot projects and related national programmes-summary report. http://pllwww.who.ch/programmes/pll/dsa/newpub/env.htm#hea

*Whyte RK. 1992. First day neonatal mortality since 1935: Re-examination of the cross hypothesis. BMJ 304:343-346.

*Wick RR, Chmelevsky D, Gossner W. 1986. 244Ra: Risk to bone and haematopoietic tissue in ankylosing spondylitis patients. In: Gossner and Gerber, eds. The radiobiology of radium and Thorotrast, 38-44.

*Wiley LM. 1994. Male mice receiving very low doses of ionizing radiation transmit an embryonic cell proliferation disadvantage to their progeny embryos. In: Olshan AF, Mattison DR, eds. Male-mediated developmental toxicity. New York, NY: Plenum Press, 81-91.

*Wiley LM, Baulch JE, Raabe OG, et al. 1997. Impaired cell proliferation in mice that persists across at least two generations after paternal irradiation. Radiat Res 148(2):145-151.

*Wilkins RJ. 1971. Alpha-ray induced breakes in the DNA of *Escherichia coli*. Int J Radiat Biol 20(5):497-500.

*Wilkinson GS, Dreyer NA. 1991. Leukemia among nuclear workers with protracted exposure to low-dose ionizing radiation. Epidemiology 2(4):305-309.

*Wing S, West CM, Wood JL, et al. 1994. Recording of external radiation exposures at Oak Ridge National Laboratory: Implications for epidemiological studies. Journal of Exposure Analysis and Environmental Epidemiology 4(1):83-93.

*Wojcik A ,Tuschl H. 1990. Indications of an adaptive response in C57BL mice pre-exposed *in vivo* to low doses of ionizing radiation. Mutat Res 243(1):67-73.

*Wolff S, Jostes R, Cross FT, et al. 1991. Adaptive response of human lymphocytes for the repair of radon-induced chromosomal damage. Mutat Res 250:299-306.

*Woodard HQ. 1980. Radiation carcinogenesis in man: A critical review. Environmental measurments laboratory report EML-380. U.S. Department of Energy, New York.

*Worgul BV, Medvedovsky C, Wu B. 1995. Use of non-subjective analysis of lens transparency in experimental radiation cataract research. Ophthalmic Research 27(suppl. 1):110-115.

*Wu L-J, Randers-Pehrson G, Xu A, et al. 1999. Targeted cytoplasmic irradiation with alpha particles induces mutations in mammalian cells. Proc Natl Acad Sci 96:4959-4964.

*Xiao S, Jacobson-Kram D, Piantadosi S, et al. 1989. Increased chromosomal radiosensitivity in patients undergoing radioimmunoglobulin therapy. Mutat Res 227:39-45.

10. REFERENCES

*Yang IC, Edwards KW. 1984. Releases of radium and uranium into Ralston Creek and Reservoir, Colorado, USA, from uranium mining. In: Barney GS, Navratil JD, Schulz W, eds. 185th meeting: American Chemical Society Symposium Series 246. Geochemical behavior of disposed radioactive waste, Seattle WA. March 20-25, 1983. Washington, DC: American Chemical Society, 271-286.

*Yarilin AA, Sharova NI, Kuzmenok OI, et al. 1995. The role of the thymus in the appearance of immunologic effects of low dose irradiation. Radiat Protect Dosimetry 62(1-2):77-79.

*Yashimoto Y, Schull WJ, Kato H, et al. 1991. Mortality among the offspring (F1) of the atomic bomb survivors, 1946-1985 (REFR TR 1-91). Radiation Effects Research Foundation, Hiroshima, Japan.

*Zaman MS, Hipp EW, Lancaster FE. 1992. Brain myelination in rats treated with ionizing radiation *in utero*. J Environ Sci Health 27(5):621-639.

*Zaman MS, Hupp EW, Lancaster FE. 1993. Locomotion and physical development in rats treated with ionizing radiation *in utero*. J Environ Sci Health B28(1):105-125.

*Zhou XY, Dong JC, Geng XS, et al. 1986. Tritium beta-ray and cobalt-60 gamma-ray caused dominant lethal mutation in mice. Chin Med J 99(5):420-423.

*Zucali JR, Moreb J, Gibbons W, et al. 1994. Radioprotection of hematopoietic stem cells by interleukin-1. Exp Hematol 22(2):130-135.

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 effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral, inhalation, and external 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 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 a hundredfold 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 agencywide 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, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Ionizing Radiation
CAS number: Multiple
Date: October 1, 1999
Profile status: Final
Route: [ ] Inhalation [ ] Oral [X] External
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Species: Human

MRL: 4 [ ] mg/kg/day [ ] ppm [ ] mg/m^3 [X] mSv (400mrem)

References:

Schull WJ, Otake M and Yoshimaru H (1988). Effect on intelligence test score of prenatal exposure to ionizing radiation in Hiroshima and Nagasaki: A comparison of the T65DR and DS86 dosimetry systems.

Burt C. (1966). The genetic determination of differences in intelligence: A study of monozygotic twins reared together and apart. Brit. J. Psychol. 57 (1& 2): pp. 137-153

Experimental design:

Schull et al. (1988) study: Schull et al. (1988) evaluated the quantitative effect of exposure to ionizing radiation on the developing fetal and embryonic human brain. The end point measured was changes in intelligence test scores. The effects on individuals exposed *in utero* to the atomic bombing of Hiroshima and Nagasaki were based on the original PE86 samples (n=1759; data on available intelligence testing) and a clinical sample (n=1598). The original PE86 sample included virtually all prenatally exposed individuals who received tissue-absorbed doses of 0.50 Gy or more. There were many more individuals in the dose range 0-0.49 Gy in the PE86 sample than in the clinical sample. The clinical sample does not include children prenatally exposed at distances between 2,000-2,999 m in Hiroshima and Nagasaki. Children exposed at greater distances or not present in the city were selected as controls. In 1955-1956, Tanaka-B (emphasis on word-sense, arithmetic abilities, and the like which were associated with the more subtle processing of visual clues than their simple recognition and depended more on connectedness) and the Koga (emphasis on perception of spatial relationships) intelligence tests were conducted in Nagasaki and the Koga test in Hiroshima.

Burt (1966) study: This study determined differences in intelligence in monozygotic twins reared together (n=95) and apart (n=53). All tests conducted in school consisted of (1) a group test of intelligence containing both non-verbal and verbal items, (2) an individual test (the London Revision of the Terman-Binet Scale) used primarily for standardization and for doubtful cases, and (3) a set of performance tests, based on the Pitner-Paterson tests and standardization. The methods and standard remained much the same throughout the study. Some of the reasons for separation of the twins were given as follows: death of the mother (n=9), unable to bring them up properly, mother's poor health (n=12), unmarried (n=6), and economic difficulties. The children were brought up by parents or foster parents (occupation ranged from unskilled to professional). IQ scores in the study group ranged from 66 to 137. The standard deviation of the group of separated monozygotic twins was reported at 15.3 as compared to

15.0 of ordinary siblings. Twins brought up in different environments were compared with those brought up in similar circumstances.

Effects noted in study and corresponding doses:

Schull et al. (1986) study: No evidence of radiation-related effect on intelligence was observed among individuals exposed within 0-7 weeks after fertilization or in the 26th or subsequent weeks. The highest risk of radiation damage to the embryonic and fetal brain occurs 8-15 weeks after fertilization under both dosimetric systems. The regression of intelligence score on estimated DS86 uterine absorbed dose is linear with dose, the diminution in intelligence score is 21-29 points per Gy for the 8-15 week group and 10-26 points per Gy for the 16-25 week group. The results for 8-15 weeks applies regardless whether the mentally retarded individuals were included. The cumulative distribution of test scores suggested a progressive shift downwards in individual scores with increasing exposure. The mean IQ scores decrease significantly and systematically with uterine or fetal tissue dose within the 8-15 and 16-25 week groups.

In summary, analysis of intelligence test scores at 10-11 years of age of individuals exposed prenatally showed that:

- There is no evidence of a radiation-related effect on intelligence scores among those individuals exposed within 0-7 weeks of fertilization or in the 26th week of gestation and beyond;
- The cumulative distribution of test scores suggests a progressive shift downwards in intelligence scores with increasing exposure to ionizing radiation (dose-response relationship).
- The most sensitive group was the 8-15 weeks exposure group. The regression in intelligence scores was found to be linear, with 1 Gy dose resulting in a 21-29 point decline in intelligence scores.
- There was no indication of groups of individuals with differing sensitivities to radiation.

Burt (1966) study: The average intelligence of the twins measured on a conventional IQ scale (SD=15) was 97.8 for the separated monozygotes, 98.1 for monozygotes brought up together, 99.3 for the dizygotes as compared with 100.2 for the siblings, and 100.0 for the population as a whole. The difference of 0.3 IQ point between the separated and unseparated identical twins is considered a no-observed-adverse-effect level (NOAEL) for this study.

Dose endpoint used for MRL derivation:

[X] NOAEL [ ] LOAEL 0.3 IQ point reduction in twins, between those raised together and those raised apart.

Uncertainty factors (UF) used in MRL derivation:

[X] 1 [ ] 3 [ ] 10 (for use of a NOAEL)
[X] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [X] 3 [ ] 10 (for human variability/sensitive population)

Was a conversion factor used from nnm in food or water to a me/body weight dose?
If so, explain:

No.

If an inhalation study in animals, list conversion factors used in determining human eauivalent dose:

Not applicable.

Was a conversion used from intermittent to continuous exposure?

No.

Other additional studies or pertinent information that lend sunport to this MRL:

Husen (1959) reported a study involving 269 pairs of Swedish monozygotic (identical) twins where the intrapair IQ difference was 4 IQ points for a combination of twins raised together and apart. This is somewhat lower than the value of 7 IQ points for identical twins raised apart, and just larger than the range of IQ scores for Washington DC children repetitively tested (Jacobi and Glauberman 1995).

Supporting evidence for the acute MRL is provided by Jacobi and Glauberman (1995). Children in the Ist, 3rd, and 5th grades born in Washington DC were tested, and average IQ levels of 94.2,97.6, and 94.6 were reported. The range of 3.4 IQ points is considered to be a LOAEL for this study, which, if used for MRL derivation, would yield an MRL of 0.004 Sv (3.4 IQ points x 1 Sv/25 IQ points ÷ 30 [10 for use of a LOAEL and 3 for a sensitive population]).

Additional supporting evidence for the acute MRL is provided by Berger et al. 1997, in a case study of accidental radiation injury to the hand. A Mexican engineer suffered an accidental injury to the hand while repairing an x ray spectrometer. The day after the accident, his symptoms included a tingling sensation and itching in the index and middle fingers. On days 4 and 7, a “pinching” sensation, swelling, and slight erythema were observed. By day 7, the tip of his index fingers was erythematous and a large blister developed with swelling on other fingers. On day 10, examination by a physician showed that the lesions had worsened and the fingers and palms were discolored. On day 10, he was admitted to the hospital where hyperbaric oxygen therapy was administered without success. One month after the accident, the patient entered the hospital again with pain, discoloration, and desquamation of his hand. Clinical examination showed decreased circulation in the entire hand, most notably in the index and middle finger. Total white blood count decreased to 3,000/μL (normal range 4,300-10,800/μL). Cytogenic studies of peripheral blood lymphocytes revealed four dicentrics, two rings, and eight chromosomal fragments in the 300 metaphases studied. The estimated whole body dose was reported to be 0.382 Gy (38.2 rad). This dose is a potential LOAEL for acute ionizing radiation and would yield an MRL of 0.004 Sv (0.38 Sv ÷100 [10 for use of LOAEL and 10 for sensitive human population]).

The Nuclear Regulatory Commission set a radiation exposure limit of 0.5 rems (50 mSv) for pregnant working women over the full gestational period (USNRC 1991). For the critical gestational period of 8 to 15 weeks ATSDR believes that the conservative acute MRL of 4 mSv is consistent with the NRC limit and could be applied to either acute (0-14 day) or intermediate (15-365 day) exposure periods.

Calculations

Given: 0.3 IQ point is a NOAEL. A 1 Sv dose results in a 25 IQ point reduction (range = 21-29 pts; mean = 25) and provides a conversion factor from IQ prediction to radiation dose. Assume that the radiation dose and the subsequent reduction in IQ is a linear relationship.

MRL=NOAEZL x CF ÷ UF
MRL = 0.3 x 1/25 ÷ 3
MRL = 0.004 Sv = 4 mSv (400 mrem)

Agency Contact (Chemical Manager): Sam Keith.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Ionizing Radiation
CAS number: Multiple
Date: October 1, 1999
Profile status: Final
Route: [ ] Inhalation [ ] Oral [X] External
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Species: Human

MRL: 1 [] mg/kg/day [ ] ppm [ ] mg/m^3 [X] mSv/yr (100 mrem/yr)

Reference: BEIR V. 1990. Health effects of exposure to low levels of ionizing radiation. Committee on the Biological Effects of Ionizing Radiations, National Research Council. National Academy Press. Washington, DC.

Experimental design: Not applicable

Effects noted in study and corresnonding doses:

No individual studies were identified that could be used to base a chronic-duration external exposure MRL that did not result in a cancer-producing end point. However, two sources of information were identified that did provide doses of ionizing radiation that have not been reported to be associated with detrimental effects (NOAELs). These sources provide estimates of background levels of primarily natural sources of ionizing radiation that have not been implicated in producing cancerous or non-cancerous toxicological endpoints. BEIR V states that the average annual effective dose to the U.S. population is 3.6 mSv/yr. A total annual effective dose equivalent of 3.6 mSv (360 mrem)/year to members of the U.S. population is obtained mainly by naturally occuring radiation from external sources, medical uses of radiation, and radiation from consumer products. The largest contribution (82%) is from natural sources, two-thirds of which if from naturally occurring radon and its decay products. Specific sources' of this radiation are demonstrated in Table A- 1.

The annual dose of 3.6 mSv per year has not been associated with adverse health effects or increases in the incidences of any type of cancers in humans or other animals.

Dose endpoint used for MRL derivation: 3.6 rnSv/yr

[X] NOAEL [ ] LOAEL 3.6 mSv/yr

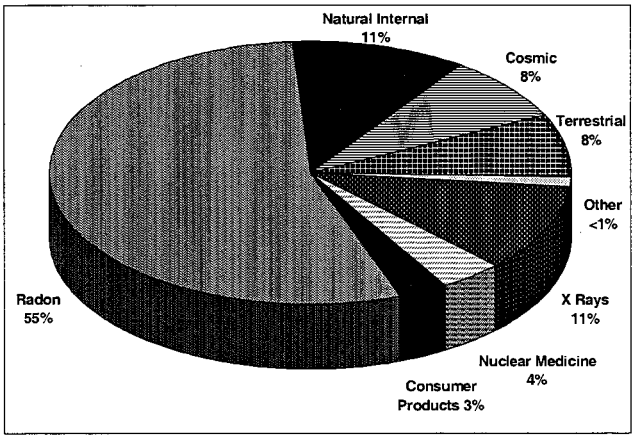
Uncertainty factors (UF) used in MRL derivation:

[X] 1 [ ] 3 [ ] 10 (for use of a NOAEL)
[X] 1 1] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [X] 3 [ ] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/bodv weight dose?
If so, explain: No.

Table A-1. Average Annual Effective Dose Equivalent of Ionizing Radiation to a Member of the U.S. Population[a]

Source	Effective Dose Equivalent	
	mSv	Percent of Total Dose
Natural		
Radon[b]	2.0	55
Cosmic	0.27	8.0
Terrestrial	0.28	8.0
Internal	0.39	11
Total Natural	3.0	82
Artificial		
Medical		
X-ray	0.39	11
Nuclear	0.14	4.0
Consumer Products	0.10	3.0
Other		
Occupational	<0.01	<0.3
Nuclear Fuel Cycle	<0.01	<0.03
Fallout	<0.01	<0.03
Miscellaneous[c]	<0.01	<0.03
Total Artificial	0.63	18
Total Natural and Artificial	3.6	100



[a] adapted from BEIR V, Table 1-3 , page 18.
[b] Dose equivalent to bronci from radon daughter products
[c] DOE facilities, smelter, transportation, etc.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Not applicable.

Was a conversion used from intermittent to continuous exposure?

No.

Other additional studies or pertinent information that lend support to this MRL:

ICRP has developed recommended dose limits for occupational and public exposure to ionizing radiation sources. The ICRP recommends limiting public exposure to 1 mSv/yr (100 mrem/yr), but does note that values at high altititues above sea level and in some geological areas can sometimes be twice that value (≥2 mSv). In Annex C of ICRP 60, the commission provides data that suggests increasing the dose from 1 mSv to 5 mSv results in a very small, but detectable, increase in age-specific human mortality rate. ICRP states that the value of 1 mSv/yr was chosen over the 5 mSv value because 5 mSv/yr (500 mremlyr) causes this increase in age specific mortality rate, and 1 mSv/yr (100 rnrem/yr) is typical of the annual effective dose from background, less radon (ICRP 1991). The 1 mSv estimate may underestimate the annual exposure to external sources of ionizing radiation to the U.S. population, as it does not include radiation from radon. Conversely, the 5 mSv estimate may be high, in that increases in mortality rate been reported. The most useful estimate appears to be the BEIR V estimate of 3.6 mSv, in that it accounts for an annual exposure to radon, is specific to the U.S. population, has not been associated with increases mortality, and it falls short of the 5 mSv value associated with small increases in human mortality.

Calculations

$MRL = NOAEL_{(ADJ)} \div Uf$
MRL = 3.6 mSv/yr ÷ 3
MRL = 1.20 mSv/yr
MRL = 1.0 mSv/yr = 100 mrem/yr above background

Agency Contact (Chemical Manager): Sam Keith.

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 separate 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 for finding specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that direct the reader to chapters in the profile that provide more information on the given topic.

Chapter 2. Principles of Ionizing Radiation

This chapter is an introductory discussion of the principles of ionizing radiation. It addresses what ionizing radiation is and provides a brief overview of the history of ionizing radiation as it pertains to health effects and uses, both peaceful and military. The chapter goes on to discuss the concept of radioactive transformation and the concept of half-life, characteristics of nuclear radiation, how radiation interacts with matter, ionizing radiation and DNA interactions, energy deposition in biological tissues, radiation dosimetry, and internal vs. external exposure. Chapter 2 also introduces the concept of dose-response and the concept of acute and chronic (delayed) health effects, in addition to briefly summarizing the major health effects caused by exposure to ionizing radiation. This chapter concludes with a thorough discussion of how ionizing radiationis measured, internally, externally, and in media using a variety of instruments.

Chapter 3. Summary of Health Effects of Ionizing Radiation

This chapter provides an overview of the health effects related to ionizing radiation exposure in humans and laboratory animals. The top 25 radionuclides present currently or in the past at Department of Energy (DOE) waste sites are identified and some information on their physical half-life and retention characteristics in the body are summarized. The health effects associated with exposure to ionizing radiation are summarized and divided into non-carcinogenic and carcinogenic responses for discussion purposes. A discussion of the non-carcinogenic health effects by major organ system iss presented, followed by a discussion of the carcinogenic responses using data from laboratory animals and the limited amount of human data available. The effects of ionizing radiation on teratogenesis, reproduction, genotoxicity, and ocular toxicities, including the available information on human risk assessments, are also addressed. Readers are encouraged to use Chapter 8 as a supplement to the discussion of the health effects presented in Chapter 3 of this profile.

Chapter 4. Radiation Accidents

This chapter discusses the major radiation accidents of this century, including health effects data, if such data were reported.

Chapter 5. Mechanisms of Biological Effects

This chapter discusses the major mechanisms by which ionizing radiation exerts it toxic effects on cellular activities and organ systems. This discussion addresses the major target molecules of ionizing radiation, with emphasis on how ionizing radiation interacts with DNA. The concept of direct vs. indirect damage to DNA and other macromolecules is also introduced, followed by a discussion of how these mechanisms induce specific types of damage to macromolecules, cells, tissues, and organs to elicit a toxic or adverse event. A brief discussion of the mechanisms by which ionizing radiation induces cancer in laboratory animals and humans is presented, along with a number of models that reflect possible mechanisms of cancer induction and a brief discussion of the three steps of cancer formation.

Chapter 6. Sources of Population Exposure to Ionizing Radiation

There are many ways humans and animals can be exposed to ionizing radiation. This chapter addresses the potential for exposure to sources of ionizing radiation to the human population. Exposure to ionizing radiation is divided into natural external (cosmic rays, terrestrial, coal production, crude oil and natural gas, hot springs and caves, etc.), anthropogenic external (nuclear weapons, fallout, nuclear fuel cycle, medical, dental, and occupational) and internal exposure (inhalation, oral and dermal routes). Discussion of the human health hazards associated with each type of exposure is also presented in this chapter.

Chapter 7. Regulations

This chapter provides summarizes the regulations pertaining to radionuclides.

Chapter 8. Levels of Significant Exposure to Radiation and Radioactive Material

Tables 8-1 (inhalation exposure), 8-2 (oral exposure), 8-3 (dermal exposure), and 8-4 (external exposure) are used to summarize health effects associated with exposure to ionizing radiation. These tables cover the health effects observed at increasing radiation doses and durations, the specific isotope and activity used, and the differences in response by species. These tables provide a quick review of the health effects and a convenient way to locate data for a specific exposure scenario. The tables should be used in conjunction with the text in chapters 2, 3 and 4. All entries in these tables represent studies that provide reliable, quantitative estimates of no-observed-adverse-effect levels (NOAELs), lowest-observed-adverse-effect levels (LOAELs), or cancer effect levels (CELs).

Chapter 9. Glossary

This chapter contains of definitions and terminology pertaining to ionizing radiation and should be consulted when reviewing and interpreting the data present in chapters 2 through 8 of this toxicological profile.

Chapter 10. References

This chapter lists the references used to construct this profile and references that the reader may use to obtain more information on many of the topics discussed in this profile.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AMAD	Activity Median Aerodynamic Diameter
ATSDR	Agency for Toxic Substances and Disease Registry
Bq	becquerel
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
cm	centimeter
CNS	central nervous system
d	day
DHHS	Department of Health and Human Services
DOD	Department of Defense
DOE	Department of Energy
DOT	Department of Transportation
ECG	electrocardiogram
ED_{50}	Effective Dose 50%
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
ERAMS	Environmental Radiation Ambient Monitoring System
ERD	Environmental Radiation Data
F	Fahrenheit
F_1	first filial generation
ft	foot
g	gram
Gy	gray
HPS	Health Physics Society
hr	hour
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
ILB	Initial Lung Burden
IPB	Initial Pulmonary Burden
in	inch
J	joule
kg	kilogram
L	liter
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
$LD_{50/30}$	Lethal Dose 50%/30 days
LOAEL	lowest-observed-adverse-effect level
mg	milligram

min	minute
mL	milliliter
mm	millimeter
MRL	Minimal Risk Level
NAREL	National Air and Radiation Environmental Laboratory
NCRP	National Council on Radiation Protection and Measurements
NRC	Nuclear Regulatory Commission
ng	nanogram
nm	nanometer
NPL	National Priorities List
NRC	Nuclear Regulatory Commission
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PHS	Public Health Service
ppm	parts per million
R	roentgen
sec	second
SCE	sister chromatid exchange
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
STP	standard temperature and pressure
Sv	sievert
TWA	time-weighted average
U.S.	United States
yr	year
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent

Greek letters

α	alpha
β	beta
γ	gamma
μ	micro

APPENDIX C

Prefixes for radiological and physical units

a	atto	10^{-18}
c	centi	10^{-2}
d	deci	10^{-1}
E	exa	10^{18}
f	femto	10^{-15}
G	giga	10^{9}
k	kilo	10^{3}
p	pico	10^{-12}
m	milli	10^{-3}
M	mega	10^{6}
n	nano	10^{-9}
P	peta	10^{15}
T	tera	10^{12}
µ	micro	10^{-6}

Radiation units

Bq	becquerel
Ci	Curie
Gy	Gray
R	roengten
Sv	Seivert

APPENDIX D

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