TOXICOLOGICAL PROFILE FOR PLUTONIUM

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

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Plutonium, Draft for Public Comment was released in October 2007. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
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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 these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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.

Each profile includes the following:

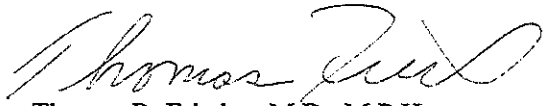
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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. Staffs 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 under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health related authorities" of the statute. This includes the preparation of 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. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

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

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

Other Sections of Interest:

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

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

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

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

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

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

Other Agencies and Organizations

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

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

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

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

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Referrals

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

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

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

1. Lynn Anspaugh, Ph.D., Research Professor, Department of Radiology, Radiobiology Division, University of Utah, Salt Lake City, Utah;

2. Fletcher Hahn, D.V.M., Ph.D., Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, New Mexico;

3. Richard Leggett, Ph.D., Research Scientist, Life Sciences Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee;

4. Nicholas Priest, Ph.D., Head, Radiobiology Section, AECL Chalk River Laboratory, Chalk River, Ontario, Canada; and

5. Ethel Gilbert, Ph.D., M.P.H., Expert (biostatistician), Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland.

These experts collectively have knowledge of plutonium'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.

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 plutonium and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Plutonium has been found in at least 16 of the 1,689 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, strict regulations make it unlikely that the number of sites at which plutonium is found would increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may be harmful.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are normally exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact. However, since plutonium is radioactive, you can also be exposed to its radiation if you are near it.

External exposure to radiation may occur from natural or man-made sources. Naturally occurring sources of radiation are cosmic radiation from space or radioactive materials in soil or building materials. Man-made sources of radioactive materials are found in consumer products, industrial equipment, atom bomb fallout, and to a smaller extent from hospital waste and nuclear reactors.

When you are exposed to plutonium, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS PLUTONIUM?

Radioactive metal	Plutonium is a radioactive element. Pure plutonium is a silvery-white metal. Most plutonium is found combined with other substances, for example, plutonium dioxide (plutonium with oxygen) or plutonium nitrate (plutonium with nitrogen and oxygen). Plutonium is usually measured in terms of its radioactivity (curies or becquerels). Both the curie (Ci) and the becquerel (Bq) tell us how much a radioactive material decays every second.
Exists in various forms called isotopes	The most common plutonium isotope is plutonium-239.
Plutonium is not stable	Each radioactive isotope of an element constantly gives off radiation, which changes it into an isotope of a different element or a different isotope of the same element. This process is called radioactive decay. Plutonium-238 and plutonium-239 give off alpha particles (sometimes referred to as alpha radiation) and transform into uranium-234 and uranium-235, respectively. The half-life is the time it takes for half of the atoms of a radionuclide to undergo radioactive decay and change it into a different isotope. The half-life of plutonium-238 is 87.7 years. The half-life of plutonium-239 is 24,100 years. The half-life of plutonium-240 is 6,560 years.
Produced in nuclear power plants and used in nuclear weapons and batteries	Very small amounts of plutonium occur naturally. Plutonium-239 and plutonium-240 are formed in nuclear power plants when uranium-238 captures neutrons. Plutonium is used to produce nuclear weapons. Plutonium-238 is used as a heat source in nuclear batteries to produce electricity in devices such as unmanned spacecraft and interplanetary probes.

More information about the properties and uses of plutonium can be found in Chapters 4, 5, and 6.

1.2 WHAT HAPPENS TO PLUTONIUM WHEN IT ENTERS THE ENVIRONMENT?

Released during testing of nuclear weapons	Plutonium released during atmospheric testing of nuclear weapons, which ended in 1980, is the source of most of the plutonium in the environment worldwide. The plutonium released during these tests was deposited on land and water. The small amount that remains in the atmosphere continues to be deposited as it slowly settles out. Plutonium is also released to the environment from research facilities, waste disposal, nuclear fuel reprocessing facilities, nuclear weapons production facilities, and accidents at facilities where plutonium is used.

Deposited in water or soil	Plutonium can be transported in the atmosphere usually when it is attached to particles in the air. It can be deposited on land or water by settling or by rain. Plutonium can stick to particles in soil, sediment, and water. Plutonium isotopes will undergo radioactive decay in the environment.

For more information on plutonium in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO PLUTONIUM?

You may be exposed to plutonium by breathing air, drinking water, or eating food containing plutonium; however, the levels of plutonium in air, water, soil, and food are very low.

Soil	Average plutonium levels in surface soil from fallout range from 0.01 to 0.1 picocuries (pCi) per gram of soil (1 picocurie equals one-trillionth [10^{-12}] of a curie).
Air	Plutonium concentrations in air are generally low. Baseline plutonium-239 concentrations in air ranging from 1.6×10^{-6} to 3.8×10^{-6} pCi per cubic meter of air (pCi/m^3) have been reported.
Workplace	Persons who work at nuclear fuel and weapons production facilities have a greater chance of being exposed than individuals in the general population.
Accident	You could be exposed to plutonium if there was an accidental release of plutonium during use. It is very unlikely you would be exposed as the result of a traffic accident or disposal. Plutonium transport containers are virtually indestructible by accident or fire. The disposal site is deep underground and away from the public.

Further information on how you might be exposed to plutonium is given in Chapter 6.

1.4 HOW CAN PLUTONIUM ENTER AND LEAVE MY BODY?

Plutonium can enter your body when it is inhaled or swallowed	When you breathe air that contains plutonium, some of it will get trapped in your lungs. Some of the trapped plutonium will move to other parts of your body, mainly your bones and liver. The amount of plutonium that stays in your lungs depends on the solubility of the plutonium that is in the air you breathe. A small amount of the plutonium you swallow (much less than 1%) will enter other parts of your body (mainly your bones and liver). If plutonium gets onto your healthy skin, very little, if any, plutonium will enter your body. More plutonium will enter your body if gets onto injured skin, such as a cut or burn.
Plutonium in your body will remain there for many years	Plutonium leaves your body very slowly in the urine and feces. If plutonium were to enter your lungs today, much of the plutonium would still be in your body 30–50 years later.

Further information on how plutonium enters and leaves the body is given in Chapter 3.

1.5 HOW CAN PLUTONIUM AFFECT MY HEALTH?

Plutonium may remain in the lungs or move to the bones, liver, or other body organs. It generally stays in the body for decades and continues to expose the surrounding tissues to radiation.

Lung, liver, and bone cancer	You may develop cancer depending on how much plutonium is in your body and for how long it remains in your body. The types of cancers you would most likely develop are cancers of the lung, bones, and liver. These types of cancers have occurred in workers who were exposed to plutonium in air at much higher levels than is in the air that most people breathe.
Affect ability to fight infections	In laboratory animals, plutonium affected the animal's ability to resist disease (immune system).

More information on the health effects of plutonium is presented in Chapters 2 and 3.

1.6 HOW CAN PLUTONIUM AFFECT CHILDREN?

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

There are differences between children and adult	Studies in young animals have shown that a larger amount of the plutonium deposited in the lung will move to growing bones. Therefore, it is possible that the bones of children could be more severely affected by plutonium than the bones of adults; however, this has not been shown in humans or laboratory animals. Studies in animals have also shown that a larger amount of plutonium that enters the gut of newborn animals is absorbed into the body.
Effects in unborn children	We do not know if plutonium causes birth defects or affects the ability to have children, although some plutonium that reaches the blood can be found in ovaries and testes. A large portion of the plutonium in the body of adults is in bone. It is possible that plutonium in the bones of a pregnant woman may move to the fetus, when the calcium from the mother's bone is being used to build the bones of the fetus.

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

Exposure of the general population to plutonium will be small. Plutonium levels in water, air, and food are generally low in areas that have not been contaminated by accidents or other releases of radioactive materials.

Risk for working adults	People working at facilities using plutonium that is not highly contained will be more highly exposed to plutonium than the general population.
Risk near the home	People do not generally live near facilities that use plutonium in their operations. Some people may be slightly more exposed to plutonium due to releases of plutonium through filtered stack-emissions or waste water. Any releases are to be within regulatory limits. Disposal sites are deep underground and away from the public.
Risk in the air you breathe	Breathing plutonium-contaminated air is the most dangerous way to be exposed to plutonium. If you know or suspect that plutonium has been released to the air, you should leave the area immediately.

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

Can be measured in urine and feces	Plutonium can be measured in the urine and feces even at very low levels. These measurements can be used to estimate the total amount of plutonium that has entered the body. The levels of plutonium in body can be used to predict the kind of health effects that might develop from that exposure.
Plutonium inside the body can be detected from outside the body	Some sensitive equipment can measure the weak gamma rays that travel to the outside of the body after they are released from plutonium and other radioactive materials inside the body. In the United States, this equipment is only available in a few locations.

Further information on how plutonium can be measured in exposed humans is presented in Chapters 3 and 7.

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

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

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

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday, a 24-hour day, or a work-year), different animal studies, or other factors.

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

The USNRC has recommended the following radiation exposure limits for the general public and for workers:

General public	0.1 rem/year for the general public and 0.5 rem/year for people who work with medical patients. These regulations are for all forms of radiation combined, so they are not only for plutonium.
Workers	5 rem/year for workers in industries where exposure to radiation may occur and 0.5 rem for the pregnancy period following the declaration of pregnancy by a woman in an industry where exposure to radiation may occur.

These recommended radiation exposure limits are for all forms of radiation combined and are not specific to plutonium. The limits are expressed in units called rem (roentgen equivalent man). A rem is a radiation unit that expresses the radiation equivalent dose to a particular organ or tissue. The limits on equivalent dose are used to calculate the limits on the amount of radioactive substances that can be inhaled or ingested.

Additional information on governmental regulations regarding plutonium can be found in Chapter 8.

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 contact ATSDR at the address and phone number below.

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

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical

assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-62
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

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

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PLUTONIUM IN THE UNITED STATES

Plutonium is primarily a human-made radioactive element of the actinide series and was the first human-made element to be synthesized in weighable amounts. Plutonium was first synthesized by the bombardment of uranium with deuterons (^{2}H) by Seaborg and co-workers in 1940. Although 20 isotopes of plutonium ($^{228-247}Pu$) have been identified, the alpha-emitting ^{238}Pu and ^{239}Pu isotopes are the ones most commonly encountered and widely studied for potential adverse health effects. The isotope ^{239}Pu was first used in fission weapons beginning in 1945 and is produced during the bombardment of uranium (^{235}U) by neutrons in nuclear reactors. Approximately one-third of the total energy produced in a typical commercial nuclear power plant comes from the fission of ^{239}Pu produced from ^{235}U. The isotope ^{238}Pu has been used as a heat source in nuclear batteries to produce electricity in devices such as unmanned spacecraft and interplanetary probes. Plutonium is a carefully regulated material under government and International Atomic Energy Agency (IAEA) control and has no commercial usage, with the exception of small quantities used in research laboratories. Approximately 1,855 metric tons of plutonium was estimated to exist worldwide at the end of 2003; most of which was found in spent fuel from nuclear power plants. A plutonium production rate of 70–75 metric tons/year was estimated for reactors worldwide in 2003.

The main sources of plutonium in the environment are releases from research facilities, nuclear weapons testing, waste disposal, nuclear weapons production facilities, and accidents. Atmospheric testing of nuclear weapons, which ended in 1980, is the source of most of the plutonium in the environment worldwide, which released approximately 10,000 kilograms of plutonium. Trace amounts of plutonium (including ^{238}Pu, ^{239}Pu, ^{240}Pu, and ^{241}Pu) are found worldwide, mostly due to fallout from atmospheric nuclear testing. Trace amounts of ^{239}Pu are found in naturally occurring uranium ores, although in such small amounts that extraction is not practical. Small amounts of ^{244}Pu also exist in nature from remnants of primordial stellar nucleosynthesis and from “natural” reactors such as the Oklo natural reactor in the African nation of Gabon, which existed about 2 billion years ago. Plutonium released to the atmosphere reaches the earth's surface through wet and dry deposition to the soil and surface water. Once in these media, soluble plutonium can sorb to soil and sediment particles or bioaccumulate in terrestrial and aquatic food chains.

Humans may be exposed to plutonium by breathing air, drinking water, or eating food containing plutonium; however, the levels of plutonium in air, water, soil, and food are generally very low, and of little health consequence. Average plutonium levels in surface soil from fallout range from 0.01 to 0.1 picocuries (pCi) per gram of soil (1 picocurie equals one-trillionth [10^{-12}] of a curie). In general, plutonium concentrations in air are low. Baseline ^{239}Pu concentrations in air ranging from $1.6x10^{-6}$ to $3.8x10^{-6}$ pCi per cubic meter of air (pCi/m^3) have been reported.

2.2 SUMMARY OF HEALTH EFFECTS

Risks for adverse outcomes of plutonium exposures are strongly dependent on radiation doses received by specific tissues and organ systems. Most of the body burden of plutonium resides in the skeleton and liver, and following inhalation exposures, in the lung and lung-associated lymph nodes. As a result, these tissues receive relatively high radiation doses following exposures to plutonium. Radiation-induced toxicity to these tissues has been documented in human epidemiological studies and in animal models. The relatively high radiation doses received by bone, liver, and lung lend greater credibility to the epidemiological findings for these tissues than for outcomes in other tissues that receive much smaller radiation doses. All epidemiological studies that have reported adverse outcomes in these tissues have studied populations (i.e., workers in plutonium production and processing facilities) that experienced exposures and radiation doses that greatly exceed those experienced by the general public. Accordingly, risks for these outcomes in the general population are substantially lower than reported for these more highly exposed worker populations.

Death. Possible associations between exposure to plutonium and mortality have been examined in studies of workers at the U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (e.g., Mayak) and the United Kingdom (e.g., Sellafield). The Mayak studies provide relatively strong evidence for an association between cancer mortality (bone, liver, lung) and exposure to plutonium. Plutonium dose-response relationships for lung cancer mortality have been derived from studies of Mayak workers, who received much higher uptakes of plutonium compared to other epidemiological cohorts (i.e., mean body burdens 0.09–9.2 kBq, with much higher individual exposures [up to 470 kBq] in relatively large numbers of these workers). Excess relative risk (ERR) estimated in three studies (adjusted for smoking) were 3.9 per Gy (95% confidence interval [CI]: 2.6–5.8) in males, and 19 per Gy (95% CI: 9.5–39) in females (attained age 60 years), 4.50 per Gy (95% CI: 3.15–6.10) in males, and 0.11 per Sv (95% CI: 0.08–0.17) or 0.21 per Sv (95% CI: 0.15–0.35), depending on the smoking-radiation interaction model that was assumed (these estimates per Sv

correspond to 2.2 or 4.3 per Gy, respectively, assuming a radiation weighting factor of 20 for α-radiation). The ERR per Gy in Mayak workers declined strongly with attained age. In a recent cohort mortality study of the Mayak workers, significant plutonium dose-response relationships ($p<0.001$) were found for deaths due to lung or liver cancer, and for deaths in which bone cancer was considered a contributing cause. At attained age of 60 years, ERRs for lung cancer were 7.1 per Gy (95% CI: 4.9–10) in males and 15 per Gy (95% CI: 7.6–29) in females. Averaged-attained age ERRs for liver cancer were 2.6 per Gy (95% CI: 0.7–6.9) for males and 29 per Gy (95% CI: 9.8–95) for females, and averaged-attained age ERRs for bone cancer were 0.76 per Gy (95% CI: <0–5.2) for males and 3.4 per Gy (95% CI: 0.4–20) for females. Elevated risks for bone cancer were observed only for workers with plutonium doses exceeding 10 Gy. For lung and bone cancer, the ERR declined with attained age, and for lung cancer, the ERR declined with age at first plutonium exposure.

Decreased survival was noted in beagle dogs exposed to plutonium aerosols ($^{238}PuO_2$, $^{239}PuO_2$, or $^{239}Pu(NO_3)_4$) at levels resulting in initial lung burdens in the range of ≥1 kBq/kg body weight. Early deaths were attributed to radiation pneumonitis and decreased survival late in life was typically associated with tumor development.

Cancer. Possible associations between exposure to plutonium and cancer mortality and morbidity have been examined in studies of workers at the U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). Compared to studies of U.K. and U.S. facilities, the Mayak cohorts had relatively high uptakes of plutonium (i.e., mean body burdens as high as 9.2 kBq, with much higher individual uptakes [up to 470 kBq] in relatively large numbers of these workers). Collectively, the Mayak studies provide evidence for an association between cancer mortality (lung, liver, bone) and uptake of plutonium. Studies of U.K. and U.S. facilities have examined cohorts of workers who had substantially lower estimated plutonium uptakes and corresponding internal radiation doses than the Mayak cohorts (e.g., Sellafield: ≤1 kBq in 97% of the assessed workers; Los Alamos: mean body burden 0.970 kBq, range 0.05–3.18 kBq). Although a significantly higher incidence of cancer mortality in certain groups of plutonium workers has been found in some studies, higher cancer incidence and/or risks for tissues that received the highest plutonium radiation doses (i.e., lung, liver, bone) have not been found, making causal connections of these outcomes to plutonium exposure more uncertain. The Sellafield study is by far the strongest of these studies and did not find associations between plutonium exposure and cancers to tissues receiving the highest radiation doses from plutonium.

2. RELEVANCE TO PUBLIC HEALTH

Plutonium dose-response relationships for lung cancer mortality and morbidity have been corroborated in four Mayak studies. Estimated excess relative risk in these four studies (adjusted for smoking) were as follows: (1) 3.9 per Gy (95% CI: 2.6–5.8) in males and 19 per Gy (95% CI: 9.5–39) in females; (2) 7.1 per Gy (95% CI: 4.9–10) in males and 15 per Gy (95% CI: 7.6–29) in females at attained age of 60 years; (3) 4.50 per Gy (95% CI: 3.15–6.10) in males; and (4) 0.11 per Sv (95% CI: 0.08–0.17) or 0.21 per Sv (95% CI: 0.15–0.35), depending on the smoking-radiation interaction model that was assumed (these estimates per Sv correspond to 2.2 or 4.3 per Gy, respectively, assuming a radiation weighting factor of 20 for α-radiation).

The risks of mortality and morbidity from bone and liver cancers have also been studied in Mayak workers. Increasing estimated plutonium body burden was associated with increasing liver cancer mortality, with higher risk in females compared to males. Relative risk for liver cancer for a cohort of males and females was estimated to be 17 (95% CI: 8.0–26) in association with plutonium uptakes >7.4 kBq; however, when stratified by gender, the relative risk estimates for females was 66 (95% CI: 16–45) and higher than for males, 9.2 (95% CI: 3.3–23). Risk of bone cancer mortality in this same cohort (n=11,000) was estimated to be 7.9 (95% CI: 1.6–32) in association with plutonium uptakes >7.4 kBq (males and females combined). Risks of leukemia mortality, in the same cohort, were not associated with internal plutonium exposure. In a case control study of Mayak workers, the odds ratio for liver cancer was 11.3 (95% CI: 3.6–35.2) for subjects who received doses >2.0–5.0 Gy (relative to 0–2.0 Gy) and the odds ratios for hemangiosarcomas were 41.7 (95% CI: 4.6–333) for the dose group >2.0–5.0 Gy, and 62.5 (95% CI: 7.4–500) for the dose group >5.0–16.9 Gy; doses were estimated based on periodic urine sampling. A study reported averaged-attained age ERRs for liver cancer of 2.6 per Gy (95% CI: 0.7–6.9) for males and 29 per Gy (95% CI: 9.8–95) for females, and averaged-attained age ERRs for bone cancer of 0.76 per Gy (95% CI: <0–5.2) for males and 3.4 per Gy (95% CI: 0.4–20) for females. Elevated risks for bone cancer were observed only for workers with plutonium doses exceeding 10 Gy. For lung and bone cancer, the ERR declined with attained age, and for lung cancer, the ERR declined with age at first plutonium exposure.

Consistent with findings from human epidemiological studies, results of animal studies show that tissue location of plutonium-induced cancer is compound-dependent. A significant amount of plutonium from relatively soluble $^{239}Pu(NO_3)_4$ and $^{238}PuO_2$ (more soluble than $^{239}PuO_2$ due to higher specific activity of ^{238}Pu compared to ^{239}Pu) is distributed to bone and liver. In contrast, relatively insoluble $^{239}PuO_2$ is primarily retained in lung and associated lymph nodes, with approximately 10, 1, 0.2, and 0.002% relocating to liver, skeleton, spleen, and kidney, respectively. Bone tumors (predominantly

osteosarcomas) were the primary cause of cancer deaths in dogs exposed once to $^{238}PuO_2$ aerosols; lung tumor incidences were also relatively high in these dogs, and liver tumors appeared to be a contributing cause of death in a few $^{238}PuO_2$-exposed dogs. The pattern of tumor development in dogs exposed to $^{239}Pu(NO_3)_4$ was similar to that of dogs exposed to $^{238}PuO_2$, with tumors observed in lung, bone, and liver (principally of bile- duct epithelium). Bone tumors were the main cause of death in the exposure groups with mean initial lung burdens of 1 and 5.9 kBq/kg. In contrast to the high incidences of bone tumors in the dogs exposed to $^{238}PuO_2$ or $^{239}Pu(NO_3)_4$ aerosols, cancer deaths in dogs exposed to aerosols of the relatively insoluble $^{239}PuO_2$ were predominantly associated with lung tumors consisting mainly of papillary adenocarcinomas based on a lifespan composite study. Tumor incidences at other sites in the $^{239}PuO_2$-exposed dogs were not statistically significantly different from those of controls. Earlier and shorter studies reported bronchiolo-alveolar carcinoma as the most frequently identified cancer type.

Respiratory Effects. Possible associations between exposure to plutonium and respiratory tract disease have been examined in studies of workers at U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). Collectively, these studies have not found significant associations between mortality rates from respiratory tract disease, other than cancer, and exposures to plutonium among workers at these facilities. Possible associations between exposure to plutonium and pulmonary fibrosis were examined in a cohort of workers (n=326) at Rocky Flats. The study assessed lung interstitial abnormalities from the most recent available x-rays in relation to estimated lung equivalent dose from plutonium. Estimated lung equivalent doses ranged from 0 to 28 Sv (approximately 73% <1 Sv). The odds ratio (adjusted for age, smoking status, and evidence from pleural abnormalities from possible asbestos exposure) was significant for the dose group ≥10 Sv (5.3, 95% CI: 1.2–23.4). A report of one study was based on scoring radiographs for the severity of chest abnormalities considered consistent with fibrosis, and did not include information regarding a possible association between these lung abnormalities and clinical symptoms of disease.

Radiation pneumonitis has been observed following inhalation exposure of dogs, nonhuman primates (monkeys and baboons), and rodents to plutonium (primarily insoluble) compounds, and was identified as primary, major contributing, or incidental cause of death in some dogs and nonhuman primates that inhaled $^{238}PuO_2$, $^{239}PuO_2$, or $^{239}Pu(NO_3)$. Results of lifetime studies in dogs indicate that radiation pneumonitis in the $^{239}PuO_2$-exposed dogs occurred at lower ILBs and had a shorter time to onset compared to $^{238}PuO_2$- or $^{239}Pu(NO_3)_4$-exposed dogs. This observation is consistent with the toxicokinetic differences observed for inhaled plutonium compounds, showing that inhaled $^{239}PuO_2$ is cleared from the

lung more slowly than $^{238}PuO_2$ and $^{239}Pu(NO_3)_4$. The radiation pneumonitis/pulmonary fibrosis progressively impaired lung function, including alveolar-capillary gas exchange, resulting in increases in respiratory rate, minute volume, arterial CO_2 pressure, and lung stiffness, along with decreases in tidal volume and arterial O_2 pressure. Increases in radiation dose and dose rate corresponded to reduced times to the onset of symptoms and increased severity of effects. Radiation pneumonitis tended to be observed at lower ILBs in the 0.75 and 1.5 μm AMAD groups than in the 3.0 μm AMAD group.

Hematological Effects. Possible associations between exposure to plutonium and mortality from hematopoietic diseases have been examined in studies of workers at plutonium production and/or processing facilities in the United States (Rocky Flats), United Kingdom (Sellafield). Collectively, these studies have not found significant associations between mortality rates from diseases of blood or blood-forming organs and exposures to plutonium among workers at these facilities.

Compound- and dose-dependent decreased numbers of selected white blood cells were observed in dogs exposed to plutonium aerosols. Primary hematological effects following pulmonary deposition of $^{238}PuO_2$ and $^{239}Pu(NO_3)_4$ were lymphopenia and neutropenia, whereas lymphopenia was both the first biological effect to be observed and the primary hematological effect of inhaled $^{239}PuO_2$. Persistent hematological effects occurred in $^{238}PuO_2$- and $^{239}PuO_2$-exposed dogs with initial lung burdens as low as 0.28 kBq/kg initial lung burdens that elicited hematological effects in $^{239}Pu(NO_3)_4$-exposed dogs appeared to be somewhat higher (mean initial lung burdens ≥5.91 kBq/kg. For $^{239}PuO_2$-exposed dogs, the time of onset for significant lymphopenia was inversely related to dose (112 days, 180 days, 1 year, or up to 5 years for ILBs of 29, 14, 6.4, and 3.7 kBq/kg lung, respectively). Decreased lifespan was observed, although some of these dogs exhibited a return to normal lymphocyte counts after 5 years. No changes in red blood cell counts were observed through year 7 other than a compensatory increase in animals with pneumonitis or pulmonary fibrosis. Plutonium accumulated in the lymph nodes of the $^{239}PuO_2$-exposed dogs, resulting in lymphoid atrophy and fibrosis, especially in the trachiobronchial region. The lymphopenia was considered to be the result of lymphocytes being irradiated as they passed through pulmonary lymph nodes.

Hepatic Effects. Possible associations between exposure to plutonium and mortality from liver disease (e.g., liver cancer) have been examined in studies of workers at U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). Collectively, these studies have not found significant associations

between mortality rates for liver disease, other than cancer, and exposures to plutonium among workers at these facilities.

Elevated serum liver enzymes (indicative of adverse liver effects),were the most consistent indicators of non-neoplastic liver effects in dogs exposed to aerosols of $^{238}PuO_2$ and $^{239}Pu(NO_3)_4$ at levels resulting in mean initial lung burdens ≥0.36 and ≥0.19 kBq/kg, respectively. No consistent changes in serum liver enzymes were seen in $^{239}PuO_2$-exposed dogs. Although elevated liver enzymes may serve as indicators of hepatotoxicity, clinical signs of liver dysfunction (i.e., ascites, icterus clotting disorders) were not observed in the $^{238}PuO_2$-exposed dogs.

Musculoskeletal Effects. Possible associations between exposure to plutonium and mortality from bone disease (e.g., bone cancer) and other musculoskeletal diseases have been examined in studies of workers at U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). Collectively, these studies have not found significant associations between mortality rates for bone or musculoskeletal disease, other than cancer, and exposures to plutonium among workers at these facilities. Radiation osteodystrophy, observed in dogs with high intakes of plutonium, would be expected in humans following intake of large amounts of plutonium.

Radiation osteodystrophy, characterized by peritrabecular fibrosis, osteosclerosis, and osteoporosis, was observed on necropsy in dogs exposed to $^{238}PuO_2$. The incidence and severity was dose-related and was seen at mean initial lung burdens as low as 1.17 kBq/kg; necrotic osteoblasts and empty lacunae near endosteal surfaces were observed at relatively high initial lung burdens. Although osteodystrophy in $^{238}PuO_2$ exposed dogs was often associated with bone tumors, it also occurred in the absence of bone tumors. Radiation osteodystrophy has also been reported in dogs that inhaled $^{239}Pu(NO_3)_4$.

Immunological Effects. Possible associations between exposure to plutonium and mortality from immunological or lymphoreticular diseases have been examined in studies of workers at plutonium production and/or processing facilities in the United States (Rocky Flats) and the United Kingdom (Sellafield). Collectively, these studies have not found statistically significant associations between mortality rates from diseases of the immunological or lymphoreticular systems and exposures to plutonium among workers at these facilities.

Histopathologic lesions of lymph nodes, particularly tracheobronchial lymph nodes, have been observed following exposure of dogs to aerosols of $^{238}PuO_2$, $^{239}PuO_2$, or $^{239}Pu(NO_3)_4$. Fibrosis and loss of lung-associated and mediastinal lymph nodes were observed in dogs exposed to $^{238}PuO_2$ at levels resulting in mean initial lung burdens ≥10 kBq/kg. Severity of non-neoplastic lesions was dose-related, progressing from lymphoid atrophy of medullary cords to significant lymph node atrophy with hypocellular scar tissue replacing lymphoid tissue. Similar dose-related atrophy and fibrosis of lung-associated, mediastinal, sternal, and hepatic lymph nodes were observed in dogs exposed to $^{239}PuO_2$. Sclerotic lymph nodes were observed in the groups of $^{239}Pu(NO_3)_4$-exposed dogs with mean initial lung burdens ≥5.91 kBq/kg, but lymph node lesions in these dogs were considered less severe than those observed in $^{238}PuO_s$- or $^{239}PuO_2$-exposed dogs.

Results of studies on immunological function indicate that inhalation exposure to $^{239}PuO_2$ impairs T-cell response to antigens, as indicated by decreased response to antigen. A study detected accelerated aging of the T-cell response to mitogenic stimulation in dogs that had been exposed to $^{239}PuO_2$ 10 years earlier. Other reports of $^{239}PuO_2$-induced effects from plutonium exposure include decreases in pulmonary alveolar macrophages in mice and depressed antibody-forming cells in hamsters.

Cardiovascular Effects. Possible associations between exposure to plutonium and cardiovascular disease have been examined in studies of workers at production and/or processing facilities in the United Kingdom (Sellafield). One study compared mortality rates between plutonium workers and other radiation workers within a cohort of Sellafield workers and found the mortality rate ratios were significantly elevated for cerebrovascular disease (1.27, $p<0.05$) in a cohort of Sellafield workers. The cumulative internal uptakes of plutonium in the cohort were estimated to range from 0 to 12 kBq, with approximately 75% of the cohort having cumulative uptakes ≤250 Bq. Another study compared mortality rates between plutonium workers and other radiation workers within a cohort of Sellafield workers and found that morality rate ratios for plutonium workers were significantly elevated for deaths from circulatory disease (2.18, $p<0.05$) and ischemic heart disease (4.46, $p<0.01$).

No significant changes in cardiovascular function were seen in dogs exposed to $^{239}PuO_2$ at initial lung burdens up to and including those resulting in radiation pneumonitis; observed right ventricular hypertrophy was most likely a compensatory response to decreased respiratory function.

Gastrointestinal Effects. Gastrointestinal effects were observed in rats following oral administration of ^{238}Pu/kg (as plutonium citrate) by gavage. Effects included mild hypertrophy of the crypts of the small

intestine in neonatal rats that received an oral dose of 5,300 kBq ^{238}Pu/kg; total obliteration of epithelial cells and crypts, combined with intestinal hemorrhaging, were noted in rats that received 17,400 kBq ^{238}Pu/kg. Increased neutrophils were noted on the surface epithelium and superficial cellular layers of the large intestine in adult rats given 155 μCi $^{238}PuO_2$/kg (5,740 kBq/kg). This effect was noted at 3 (but not 6) days posttreatment.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for plutonium due to the lack of suitable human or animal data regarding health effects following inhalation exposure to plutonium. The strongest evidence for plutonium exposure-response and radiation dose-response relationships in humans is for cancers of the lung, liver, and bone. Although non-neoplastic lesions have been observed in animals exposed to $^{238}PuO_2$, $^{239}PuO_2$, and $^{239}Pu(NO_3)_4$, these lesions occurred in association with acute exposures that also resulted in fatal cancers.

Oral MRLs

No acute-, intermediate-, or chronic-duration oral MRLs were derived for plutonium due to the lack of suitable human or animal data regarding health effects following oral exposure to plutonium. No data are available on exposure- and radiation dose-response relationships in humans for oral exposures to plutonium. Animal studies of health effects of oral exposures to plutonium have not examined major health outcomes that would be expected to occur from absorbed plutonium (e.g., effects on skeleton, liver, and lymphopoietic systems).

2. RELEVANCE TO PUBLIC HEALTH

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of plutonium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

Plutonium (Pu) is a radioactive element and a member of the actinides in the periodic table. Although trace amounts of plutonium exist naturally in the environment, the plutonium in the environment today has been (and continues to be) formed primarily from anthropogenic activity related to nuclear fission. Environmental plutonium levels are generally low and not of significant health concern. Anthropogenic isotopes with masses ranging from 228–247 have been produced and recorded on the chart of the nuclides; however, ^{238}Pu and ^{239}Pu, in their oxide and nitrate forms, are the plutonium isotopes most widely used in health effects studies. They are also the dominant isotopes that contribute to environmental and occupational exposure. Plutonium nitrates are associated with dissolving uranium-plutonium metal matrices after plutonium is produced in a nuclear reactor or by an accelerator. Plutonium oxides form on the surface of plutonium metal and are released through the machining of plutonium metal parts or the incomplete fissioning of plutonium during weapons detonation.

Most plutonium isotopes emit a high energy (generally >5 MeV) alpha particle and low energy (<20 keV) gamma and x-rays as they transform into uranium. The others (^{241}Pu and ^{243}Pu) undergo beta minus decay and transform into isotopes of americium. The radiation dose from plutonium can be designated as either external (if the material is outside the body) or internal (if it is inside the body). The total radiation dose is the sum of external and internal radiation doses. The external dose from most plutonium isotopes is low because the x- and gamma-rays are of very low branching intensity and energy and the high energy alpha particles travel only very short distances and can only affect the outermost (epidermal) layers of intact skin even when in direct dermal contact. External beta emissions from isotopes such as ^{241}Pu can travel slightly farther and may even penetrate the outer dermal layers, but are generally not of significant health concern unless a beta-emitting plutonium isotope comes into direct contact with the skin. Extreme skin contamination from plutonium-produced alpha and beta radiation, which could potentially occur in accidents or the workplace, might induce dermal and subdermal effects such as erythema, ulceration, or

even tissue necrosis. Internally deposited plutonium, however, possesses the potential to produce significant health effects via transfer of energy from alpha particles to nearby cellular molecules. Once plutonium is internalized, the distribution, retention, and excretion kinetics, paired with the plutonium decay and energy deposition parameters, determine how the radiation dose increases over time.

In radiation biology, the term absorbed dose refers to the amount of energy deposited by radiation per unit mass of material (e.g., tissue), and is expressed in units of rad or gray (Gy) (see Appendix D for a detailed description of principles of ionizing radiation). One Gy is equivalent to 100 rad. Because alpha radiation is more biologically damaging internally than other types of radiation (i.e., x-rays, gamma rays, beta particles), a given absorbed dose (rad or Gy) is multiplied by a radiation weighting factor of 20 for alpha radiation or 1 for x-rays, gamma rays, and beta particles to obtain a quantity that expresses, on a common scale for all ionizing radiation, the biological damage (dose equivalent in units of rem or Sievert [Sv]) to a particular tissue. One Sv is equivalent to 100 rem. The committed dose equivalent is typically the radiation dose to a particular organ or tissue that is received from an intake of radioactive material by an individual during the 50-year period following the intake. The internal dose from plutonium is estimated using the quantity of material entering the body (via inhalation, ingestion, or dermal absorption), the biokinetic parameters for plutonium (distribution, retention, and excretion), the energies and intensities of the various radiations emitted, and the parameters describing the profile of absorbed energy within the body. For example, for a person who inhales a given activity of ^{239}Pu (measured in becquerel [Bq] or curies [Ci]), a certain portion is retained and the body will absorb all of the alpha and beta energy emitted and some of the gamma energy in a pattern reflecting the temporal and spatial (tissue) distribution of the ^{239}Pu (which might be a function of age), the isotope decay rate, the production and decay rates of the progeny radionuclides, and radiation energy absorption factors. Each tissue, therefore, receives a tissue-specific radiation dose. The effective dose reflects the integration of dose over the time interval of interest and a tissue weighting factor scheme based on the relative sensitivities of the tissues and organs. Radiation-induced adverse health effects are related to the extent of molecular damage resulting from both direct ionization of atoms within range of the emitted radiation energy and interaction of radiation-produced free radicals with nearby molecules. Tissue damage occurs when the molecular damage is sufficiently extensive and insufficiently repaired in a timely manner.

Uptake-to-dose conversion factors (dose coefficients) are typically expressed in terms of committed dose equivalent per unit intake of activity (Sv/Bq). Age-specific dose coefficients for isotope-specific inhalation and/or ingestion are available in U.S. EPA Federal Guidance Report Number 11 (EPA 1988b); U.S. EPA Federal Guidance Report Number 13 (EPA 1999) and supplemental CD (EPA 2002);

International Commission on Radiological Protection (ICRP) publications 56 (ICRP 1990), 71 (ICRP 1996a), and 72 (ICRP 1996b); and the ICRP CD-ROM system (ICRP 2001).

3.2 DISCUSSION OF HEALTH EFFECTS OF PLUTONIUM BY ROUTE OF EXPOSURE

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

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

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no

adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

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

3.2.1 Inhalation Exposure

Possible associations between exposure to plutonium and adverse health outcomes have been examined in studies of workers at the U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (e.g., Mayak) and the United Kingdom (e.g., Sellafield). Strengths and weaknesses of each study must be considered in interpreting the overall weight of evidence for plutonium-associated health outcomes in these populations. Studies that have individual subject plutonium dose or exposure measurements and that present exposure- or dose-response analyses are much stronger than those that simply compare risks for a group of exposed subjects with those for a group of unexposed subjects. A common study design has been to construct plutonium worker cohorts based solely on whether the individuals had been monitored for plutonium. However, this strategy may result in inclusion of workers who have been monitored but never experienced an internal plutonium deposition. The magnitude of the doses received in the study population is also an important design factor. In general, studies of populations that experienced relatively small plutonium radiation doses have limited statistical power for detecting plutonium effects; this includes all of the U.S. and U.K. worker studies. Failure to find significant associations between plutonium exposure and/or radiation dose in low-dose studies does not mean that such associations do not exist. In addition to statistical power, biological plausibility of findings must be considered. Effects observed in organs that receive relatively large plutonium radiation doses (e.g., lung, liver, bone) are more credible than effects observed in organs that are likely to have received relatively small plutonium radiation doses and may have been caused by other uncontrolled factors in the study (e.g., other forms of radiation, chemical exposures). Similarly, associations to plutonium exposure are more uncertain when observed effects are limited to tissues that receive relatively small doses of plutonium (i.e., in the absence of effects in tissues that received much higher plutonium radiation doses). Elevated risk in plutonium-exposed workers does not necessarily imply causal association to plutonium. Demonstration of a consistent increase in risk in association with increasing plutonium radiation dose is far stronger evidence of a causal relationship than a simple elevation of risk in an exposed group compared to an unexposed referent group. Common to the interpretation of any epidemiological studies of workers are factors such as the “healthy worker effect"

(e.g., relatively low mortality or morbidity rates in workers because of loss of unhealthy workers from the working population), false positive findings attributable to assessments of multiple outcomes in a single study, and adequate treatment of confounding and co-variables that may affect the measured outcome independently or in association with plutonium radiation dose.

Numerous animal studies are available regarding adverse health effects following inhalation exposure to plutonium compounds; studies were conducted in nonhuman primates, dogs, and rodents. The discussion of animal studies in this profile has primarily focused on the wealth of information that has developed on the toxicology of plutonium in beagle dogs exposed by inhalation. The series of lifetime dog studies, conducted by the Inhalation Toxicology Research Institute (ITRI) and Battelle Pacific Northwest Laboratory (PNL) as a multi-laboratory effort during the 1950s through the 1990s, provide the most complete evaluations of the adverse health effects associated with inhaled plutonium compounds. Dogs were selected as the experimental model for these studies based on their relatively long life span (12–15 years) and physiologic and anatomical features common to dogs and humans (particularly regarding hematopoietic, pulmonary, and skeletal systems) (DOE 1989). Although conducted by two different laboratories, the ITRI and PNL studies used similar experimental protocols and evaluated the same comprehensive toxicological end points, providing an extensive database on the toxicity of inhaled plutonium. Therefore, information provided in the following sections primarily relies on data from the lifetime exposure studies in the ITRI and PNL dogs; results of inhalation studies conducted in rodents and nonhuman primates are briefly reviewed and included as supportive data.

The most widely studied plutonium compound, $^{239}PuO_2$, is only moderately soluble, which results in long-term retention in the lung following inhalation exposure. Other plutonium compounds assessed in lifetime dog studies include $^{238}PuO_2$ (more rapidly cleared from the lung than $^{239}PuO_2$ due to much higher specific activity, which results in fragmentation) and $^{239}Pu(NO_3)_4$ (more chemically soluble than $^{239}PuO_2$). Studies conducted by PNL investigated the effects of single inhalation exposures of adult dogs to $^{238}PuO_2$, $^{239}PuO_2$, or $^{239}Pu(NO_3)_4$. The lifetime exposure studies conducted by ITRI evaluated the effects of single exposures of adult dogs to $^{238}PuO_2$ and $^{239}PuO_2$ of varying particle sizes, single exposures of juvenile and elderly dogs to $^{239}PuO_2$, and repeated exposures of adult dogs to $^{239}PuO_2$ (Table 3-1). An overview of the complete series of lifetime exposure studies conducted by both PNL and ITRI was published by DOE (1989). A substantial amount of health effects data for the Pu-exposed dogs is available. In addition, comprehensive reports were published in the late 1990s for $^{238}PuO_2$-induced health effects in the ITRI (Muggenburg et al. 1996) and PNL (Park et al. 1997) dogs. A comprehensive report has recently been finalized for $^{239}PuO_2$-exposed dogs from the ITRI facility (Muggenburg et al. 2008). At present, available

Table 3-1. Selected Exposure Details from the ITRI and PNL Dog Studies and Conversion Procedures Used to Compare Initial Lung Burden in Common Units of kBq/kg Body Weight

Exposure and conversion information	Study references
$^{238}PuO_2$:	
ITRI evaluated single inhalation exposure of young adult male and female dogs (12–15 months of age) at two AMAD particle sizes, 1.6 and 2.9 μm. Test material was prepared at high calcining temperatures (700 °C). Exposed dogs were assigned to one of six groups, which resulted in median ILBs (range) of 0 (0), 0.36 (0.10–0.69), 1.05 (0.77–1.55), 2.84 (1.85–4.06), 5.99 (4.42–8.42), 11.2 (8.59–15.2), and 23.7 (15.3–45.4) kBq/kg body weight for dogs inhaling 1.6 μm AMAD particles, and 0 (0), 0.47 (0.15–0.77), 1.35 (0.84–1.70), 3.00 (2.39–3.79), 7.02 (4.07–9.37), 12.6 (10.4–15.6), and 25.4 (19.7–43.1) kBq/kg/body weight for dogs inhaling 2.9 μm AMAD particles. Because effects did not appear to depend on particle size, the study authors combined the results from the separate studies.	DOE 1989; Gillett et al. 1988; Hahn et al. 1991a; Muggenburg et al. 1996
PNL evaluated single inhalation exposure of young adult male and female dogs (12–20 months of age). Test material prepared at high calcining temperatures (750 °C). Mean ILBs of 0, 0.13, 0.68, 3.1, 13, 52, and 210 kBq were reported for controls and 6 experimental groups (Park et al. 1997), and were converted to mean ILBs of 0, 0.01, 0.061, 0.28, 1.17, 4.68, and 18.9 kBq/kg body weight by dividing the reported ILBs by the reported median body weight of 11.1 kg at aerosol exposure.	DOE 1978a, 1988a, 1989; Park et al. 1995, 1997; Weller et al. 1995a, 1996
$^{239}PuO_2$:	
ITRI evaluated single inhalation exposure of young adult male and female dogs (12–15 months of age) at three different AMAD particle sizes, 0.75, 1.5, and 3.0 μm. Test material was prepared at high calcining temperatures (700 °C). Because effects did not appear to depend on particle size, the study authors combined the results. Median ILBs (range) of 0 (0), 0.19 (0.026–0.35), 0.63 (0.37–0.96), 1.6 (1.0–2.4), 3.7 (2.6–4.8), 6.3 (5.2–9.3), 14 (10–20), and 30 (21–74) kBq/kg body weight were reported for controls and six experimental groups.	Diel et al. 1992; DOE 1989; Hahn et al. 1999; Muggenburg et al. 1988, 1999
PNL evaluated single inhalation exposure of young adult male and female dogs (12–20 months of age) at an AMAD particle size of 2.3 μm. The test material was prepared at high calcining temperatures (750 °C). Mean ILBs of 0, 0.12, 0.69, 2.7, 11, 41, and 213 kBq were reported for controls and six experimental groups, and were converted to mean ILBs of 0, 0.01, 0.064, 0.25, 1.0, 3.83, 19.9 kBq/kg body weight by dividing the reported ILBs by the reported mean body weight of 10.7 kg at the time of aerosol exposure.	DOE 1988a, 1989; Weller et al. 1995b
ITRI evaluated single and repeated exposure of young adult male and female dogs (12–15 months of age) at an AMAD particle size of 0.75 μm. Repeated exposures were once every 6 months for a total of 20 exposures. A mean ILB of 3.9 kBq/kg was reported for dogs exposed once; the mean total alveolar deposition was 5.3 kBq/kg body weight in the repeatedly-exposed dogs.	Diel et al. 1992; DOE 1989

Table 3-1. Selected Exposure Details from the ITRI and PNL Dog Studies and Conversion Procedures Used to Compare Initial Lung Burden in Common Units of kBq/kg Body Weight

Exposure and conversion information	Study references
ITRI evaluated single exposure of juvenile male and female dogs (3 months of age) at an AMAD particle size of 1.5 µm. The dogs were placed into one of eight groups based on intended ILB, resulting in mean ILBs of 0, 0.018, 0.11, 0.37, 1.1, 2.3, 3.7, 7.0, or 19 kBq/kg body weight.	DOE 1989, 1994b
ITRI evaluated single exposure of aged male and female dogs (7–10 years of age) at an AMAD of 3.0 µm. The dogs were placed into one of five groups based on intended ILB. The reported mean ILBs of 0, 0.033, 0.091, 0.18, and 0.37 µCi/kg body weight were converted to 0, 1.22, 3.37, 6.6, and 13.7 kBq/kg, respectively (1 µCi = 37 kBq).	DOE 1988d, 1989
ITRI evaluated single inhalation exposures of beagle dogs (n=108 exposed and 18 controls for each sex) using three separate particle sizes (0.75, 1.5, and 3.0 µm AMAD with individual particle activities from 0.048 to 7.4 mBq), and four to eight graded exposure levels for each particle size (with median ILBs of 0.16, 0.63, 1.6, 3.7, 6.4, 14, and 29 kBq/kg lung). ILB was measured after allowing time for mucociliary clearance using ^{169}Yb incorporated into the ^{239}Pu particles as a tracer. Animals were followed until death. Information was collected on retention, distribution, respiratory function, and pathology. Data by time after exposure and particle size include percent activity retention, activity distribution and retention in five types of lymph nodes, lymphocyte counts, surviving fraction, lung dose, lung tumor probability, occurrence of radiation pneumonitis and its impact on respiratory function, malignant and benign tumors by organ system and type, causes of death, and competition between pneumonitis and lung cancer, Particle size was converted to activity, with 0.75 and 3.0 µm AMAD particles containing 0.048 and 7.4 mBq of ^{239}Pu, respectively.	Muggenburg et al. 2008
$^{239}Pu(NO_3)_4$:	
PNL evaluated single exposure of young adult male and female dogs (17–22 months of age) at an AMAD particle size of 0.81 µm. Mean ILBs of 0, 0, 2±2; 8±4; 56±17; 295±67; 1,709±639; and 5,445±1,841 nCi were reported for unexposed controls, vehicle controls, and exposed groups 1–6, respectively, and were converted to mean ILBs of 0, 0, 0.0069, 0.030, 0.207, 1.02, 5.91, and 18.83 kBq/kg body weight by converting nCi to kBq (1 nCi = 0.037 kBq), which were then divided by a mean body weight of 10.7 kg (the reported mean body weight for the $^{239}PuO_2$-exposed PNL dogs, which was assumed to represent the $^{239}Pu(NO_3)_4$-exposed PNL dogs as well since body weight data for these dogs were not located in available study reports).	Dagle et al. 1996; DOE 1986b;1988b, 1989, 1994a; Park et al. 1995

µCi = microCurie; AMAD = activity median aerodynamic diameter; ILB = initial lung burden; ITRI = Inhalation Toxicology Research Institute; kBq = kiloBequerel; PNL = Pacific Northwest Laboratory

$^{239}Pu(NO_3)_4$ data from the dog studies consist of interim and annual reports and more recent publications that focus on selected end points of toxicity. The presentation of health effects in the dog studies from ITRI and PNL in this Toxicological Profile for Plutonium focuses primarily on results of the available comprehensive reports and secondarily on results of interim data.

Inhalation exposures in the dog studies were quantified using radiological measurements to estimate initial plutonium burdens (activity or activity-per-body weight or activity-per-organ weight), rather than aerosol concentrations of plutonium. In the ITRI and PNL studies, exposure groups were defined as ranges or group means based on initial plutonium burdens. However, over the 30-year time span of publications, initial plutonium burdens were quantified using several different units (e.g., μCi, μCi/kg lung weight, kBq, kBq/kg body weight, total kBq deposited in the lung); thus, data obtained from a single study may have been reported in several different publications over a span of time during which changes may have been made in conventions for reporting initial lung burdens. The convention of kBq/kg body weight has been selected to express initial lung burden for the ITRI and PNL dog studies summarized in this toxicological profile for plutonium. Table 3-1 summarizes reported initial lung burden data from each of these studies, as well as any additional data used for conversions to the convention of kBq/kg body weight. Selected interim and final reports and all publicly-available comprehensive reports were consulted for relevant exposure and health effects data. It should be noted that for a particular study, various reports may vary slightly in estimated initial lung burdens. In this toxicological profile for plutonium, the most recent publications typically served as the definitive source of initial lung burden data.

As discussed in Section 3.5, Mechanisms of Toxicity, plutonium-induced health effects are considered to be the result of energy deposited by alpha particle emissions in tissues that retain plutonium for extended periods (i.e., lung, bone, liver following inhalation exposure). Similar health effects would be expected from any alpha-emitting source that would result in similar cumulative tissue-specific radiation dose and dose rate.

3.2.1.1 Death

Epidemiological Studies in Humans. Possible associations between exposure to plutonium and mortality have been examined in studies of workers at the U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as wells as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). The most recent findings from these studies are summarized in Table 3-2. Collectively,

Table 3-2. Summary of Human Epidemiology Studies of Health Effects of Plutonium

Reference, study location, period, and study description	Dose measurement[a]	Findings and interpretation
United States:		
Reference: Brown et al. 2004 Location: Denver (Rocky Flats), Colorado Period: 1951–1989 Design: retrospective case control Subjects: workers at Rocky Flats Plant; cases (n=180, 7 females); controls (n=720, 24 females) who also worked at the plant and were matched with cases for age, birth year, and gender Outcome measures: lung cancer mortality Analysis: incidence OR for cumulative internal lung dose, cumulative penetrating dose, period of first hire, and employment years (logistic regression models, adjusted for birth year and smoking)	Internal lung dose (mSv) / Percent 0 / 54 0–100 / 18 >100–400 / 13 >400–644 / 5 >644–900 / 5 >940 / 5 98% internal lung dose from plutonium or inbred ^{241}Am	In full cohort, OR for lung cancer mortality significant at dose strata 400–644 mSv, but was not significantly elevated at higher doses; there was no significant trend with dose. When restricted to subjects employed for 15–25 years, OR was significant at dose strata >644 mSv with significant dose trend; however, there was no evidence of a positive trend for those employed <10 years or ≥25 years. Internal lung dose (mSv) / OR (95% CI) full cohort / OR (95% CI) employed 15–25 years 0 / 1.0 (reference) / 1.0 (reference) 0–100 / 1.42 (0.87–2.33) / 1.14 (0.46–2.86) >100–400 / 1.60 (0.83–3.10) / 2.11 (0.86–5.20) >400–644 / 2.71 (1.20–6.09) / 2.74 (0.92–8.19) >644–900 / 2.30 (0.96–5.53) / 3.20 (1.15–8.94) >940 / 1.48 (0.56–3.89) / 5.04 (1.55–16.40)
Reference: Gilbert et al. 1989b Location: Hanford, Washington Period: 1944–1981 Design: retrospective cohort Subjects: workers at the Hanford plant (n=31,500, 12,600 females) who were hired during the period 1944–1978. Outcome measures: cancer mortality Analysis: trend test for mortality ratios stratified by external radiation dose or internal Pu exposure (adjusted for age, calendar year, sex, and number of years monitored)	Internal Pu exposure (kBq) / Percent <0.074 / 28.7 0.074–1.47 / 30 >1.48 / 1.3	No evidence for statistically significant excess cancer mortality or trend in cancer mortality with external radiation or Pu internal deposition (i.e., all cancers, digestive tract, lung, lymphatic and hematopoietic, prostatic).

Table 3-2. Summary of Human Epidemiology Studies of Health Effects of Plutonium

Reference, study location, period, and study description	Dose measurement[a]	Findings and interpretation
Reference: Newman et al. 2005 Location: Denver, Colorado Period: 1951–1998 Design: retrospective cohort Subjects: male workers at Rocky Flats plant (n=326) hired between 1951 and 1958 with lifetime doses >0.1 Sv; unexposed controls (n=194, 12 females) Outcome measures: lung opacity profusion score (based on most recent x-ray) for assessment of pulmonary fibrosis Analysis: multivariate logistic regression to test association between plutonium radiation dose categories and disease prevalence (covariates: age at x-ray, smoking status, evidence of pleural abnormalities [surrogate for asbestos exposure])	Plutonium lung radiation dose in exposed group: Dose (Sv) / n (percent) 0–28 / 326 0 / 194 (37%) >0–1 / 187 (36%) 1–<5 / 101 (19%) 5–<10 / 22 (4%) ≥10 / 16 (3%)	Significant elevated risk for abnormal lung profusion score in lung dose strata ≥10 Sv: Lung dose (Sv) / OR (95% CI) >0–<1 / 1.5 (0.6–3.8) 1–<5 / 0.9 (0.3–2.6) 5–<10 / 1.7 (0.5–6.6) ≥10 / 5.3 (1.2–23.4)
Reference: Voelz et al. 1997 Location: Los Alamos, New Mexico Period: 1943–1990 Design: retrospective cohort Subjects: adult male workers at Los Alamos National Laboratory exposed to plutonium in 1944–1945 (n=26); controls (n=876) workers not exposed to plutonium Outcome measures: mortality Analysis: incidence rates of exposed group compared to controls (adjusted for age and year of death)	Pu body burden (Bq) mean 970 median 565 range 50–3,180 Pu body dose (mSv) mean 2.08 median 1.25 range 0.1–7.2	SMR and MRR not significantly elevated in plutonium workers (compared to controls): Category / Deaths / SMR (95% CI) / MRR (95% CI) All deaths / 7 / 0.43 (0.17–0.88) / 0.77 (0.36–1.6) All cancers / 3 / 0.75 (0.15–2.18) / 1.5 (0.46–4.9) Lung cancer / 1 / 0.68 (0.01–3.79) / 3.31 (0.44–25) Prostate cancer / 1 / 3.42 (0.04–19.04) / No data Bone cancer / 1 / 96.4 (1.26–536.0) / No data
Reference: Wiggs et al. 1994 Location: Los Alamos, New Mexico Period: 1944–1990 Design: retrospective cohort Subjects: male workers at Los Alamos National Laboratory (n=15,727 employed 1943–1973). Plutonium worker cohort consisted of 3,775 workers ever monitored for plutonium exposure Outcome measures: mortality Analysis: incidence rates for workers with plutonium whole-body deposition ≥74 Bq compared to <74 Bq (adjusted for age and year of death)	Pu body burden (Bq) / n <74 / 3,472 ≥74 / 303	MRR not significantly associated with plutonium body burden (<74 Bq compared to ≥74 Bq): Category / MRR (95% CI) All deaths / 0.89 (0.69–1.14) All cancers / 1.07 (0.67–1.69) Respiratory tract cancer / 1.77 (0.79–3.96) Lung cancers / 1.78 (0.79–3.99) Bone cancer / not reported (n=0) Lympho/hematopoietic cancer / 0.34 (0.05–2.24)

Table 3-2. Summary of Human Epidemiology Studies of Health Effects of Plutonium

Reference, study location, period, and study description	Dose measurement[a]	Findings and interpretation
Reference: Wing et al. 2004 Location: Hanford, Washington Period: 1944–1994 Design: retrospective cohort Subjects: workers at the Hanford plant (n=26,389, 8,145 females) who were hired during the period 1944–1978. Plutonium worker cohort consisted of workers in routine plutonium-associated jobs (n=3,065) or non-routine jobs (n=8,266). Outcome measures: cancer mortality Analysis: multivariate regression to test association between length of employment in jobs with plutonium exposure potential and mortality rate (covariates: age, race, gender, birth date, socioeconomic status, employment status)	Not reported	Workers in the plutonium-associated jobs category had lower death rates from all cancers, cancers of the lung, and "plutonium-cancers" (lung, liver, bone, and connective tissue) than other Hanford workers. Trends for increased mortality and duration of routine plutonium-associated jobs were as follows: Percent increase (± SE) in mortality per year in plutonium jobs (LRT for trend at 1 df; higher value means stronger association with job duration) Non-external deaths: Age <50 years: 0.1±0.9 (0.01); Age ≥50 years: 2.0±1.1 (3.37) All cancers: Age <50 years: -1.5±1.7 (0.79); Age ≥50 years: 2.6±2.0 (1.60) Pu cancers (lung, liver, skeletal, lymphatic): Age <50 years: 0.6±0.05 (0.05); Age ≥50 years: 4.9±3.3 (2.17) Lung cancers: Age <50 years: -1.0±2.7 (0.14); Age ≥50 years: 7.1±3.4 (4.06)
Russia: Reference: Gilbert et al. 2004 Period: 1955–2000 Design: retrospective cohort Subjects: workers at Mayak Production Association (n=21,790, 5,332 female) employed during the period 1948–1972 Outcome measures: lung cancer mortality Analysis: risk per unit of plutonium radiation dose (Poisson regression models, adjusted for age, gender, year of death, age at hire)	Pu lung dose (Gy) / n: <DL: 1,560 (25%) >0–0.2: 3,688 (60%) >0.2–1.0: 688 (11%) >1.0–3.0: 163 (2.6%) >3.0–5.0: 39 (0.6%) >5.0: 55 (0.9%) mean: 0.24 Gy (lung) mean: 1.84 kBq (body)	Cancer mortality risk was linearly related to plutonium radiation dose. Excess relative risk per Gy declined strongly with attained age (Gilbert et al. 2004). Increased ERR for lung cancer mortality in association with increasing lung dose (per Gy attained at age 60 years): Lung dose (Gy) / RR males (95% CI) / RR females (95% CI) >0–0.2: 1.4 (1.0–1.8); 0.91 (<0.91–3.1) >0.2–1.0: 2.4 (1.5–3.6); 16 (6.1–37) >1.0–3.0: 10 (6.3–15) >3.0–5.0: 19 (9.5–35) >1.0–5.0: 15 (3.0–38) >5.0: 33 (14–67); 250 (110–660) ERR per Gy lung dose: 4.7 (3.3–6.7); 19 (9.5–39) ERR per Sv lung dose: 0.23 (0.16–0.33); 0.93 (0.46–1.9) ERR per Gy lung dose (for subjects with smoking data, adjusted for smoking): 3.9 (2.6–5.8); 19 (7.7–51)

Table 3-2. Summary of Human Epidemiology Studies of Health Effects of Plutonium

Reference, study location, period, and study description	Dose measurement[a]	Findings and interpretation
Reference: Gilbert et al. 2000 Period: 1948–1996 Design: retrospective cohort Subjects: workers at Mayak Production Association (n=11,000) hired during the period 1948–1958 Outcome measures: liver cancer mortality Analysis: relative risk for plutonium body burden (general linear regression model adjusted for age, gender, year of death, external radiation)	Pu body burden (kBq) Males 3.78 Females 6.05 Pu liver dose (Gy) Males 0.47 Females 0.88 n=2,207 (monitored)	Significantly increased RR within highest plutonium body burden stratum: Pu body burden (kBq) / RR males (95% CI) / RR females (95% CI) 0–1.48 / 1.0 (reference) / 1.0 (reference) 1.4–7.40 / 0.9 (0.1–3.2) / 7.1 (0.9–59) >7.4 / 9.2 (3.3–23) / 66 (16–452) All workers >7.4 / 17 (8.0, 26)
Reference: Jacob et al. 2005 Period: 1948–1998 Design: retrospective cohort Subjects: male workers at Mayak Production Association (n=5,058) employed during the period 1948–1972 Outcome measures: lung cancer mortality Analysis: excess relative risk per plutonium dose unit (Sv) (mechanistic multistage regression model, adjusted for age and multiplicative or sub-multiplicative interaction with smoking)	Pu lung dose (Sv) mean (range) All plants 3.0 (0–24) Pu production 8.7 (0–81) Radio-chemical 2.5 (0–15) Reactor 0.04 (0–0.40)	Significant ERR for lung cancer mortality in association with plutonium dose (per Sv), adjusted for smoking: Smoking interaction / ERR per Sv (95% CI) Multiplicative / 0.21 (0.15–0.35) Sub-multiplicative / 0.11 (0.08–0.17)
Reference: Koshurnikova et al. 2000 Period: 1948–1996 Design: retrospective cohort Subjects: workers at Mayak Production Association (n=11,000) hired during the period 1948–1958 Outcome measures: bone cancer mortality Analysis: relative risk for plutonium body burden (general linear regression model adjusted for age, gender, year of death, external radiation)	Pu body burden (kBq) Males 3.78 Females 6.05 Pu bone surface dose (Gv) Males 2.99 Females 5.56 n=2,207 (monitored) Bone surface dose from Gilbert et al. (2000)	Significantly increased RR for bone cancer mortality within highest plutonium body burden stratum: Pu body burden (kBq) / RR (95% CI) 0–1.48 / 1.0 (reference) 1.48–7.40 / 0.9 (0.05–5.5) >7.4 / 7.9 (1.6–32)

Table 3-2. Summary of Human Epidemiology Studies of Health Effects of Plutonium

Reference, study location, period, and study description	Dose measurement[a]	Findings and interpretation
Reference: Kreisheimer et al. 2003 Period: 1948–1999 Design: retrospective cohort Subjects: male workers at Mayak Production Association (n=4,212) hired during the period 1948–1958 Outcome measures: lung cancer mortality Analysis: excess relative risk per plutonium dose unit (Gy, Sv) (general linear regression models, adjusted for age and multiplicative interaction with smoking)	Pu lung dose (Gy) Pu production 0.450 Radiochemical 0.140 Reactor Not reported	Significant ERR for lung cancer mortality: ERR unit — ERR (95% CI) ERR per Gy — 4.50 (3.15–6.10) ERR per Sv (assuming α-radiation quality factor=20) — 0.23 (0.16–0.31)
Reference: Shilnikova et al. 2003 Period: 1949–1997 Design: retrospective cohort Subjects: workers at Mayak Production Association (n=21,557, 24.2% female) employed during the period 1948–1972 Outcome measures: cancer mortality Analysis: regression models, (adjusted for age, gender, year of death, age at hire)	Pu body burden 2.9–18.5 kBq Cumulative lung Pu dose: 0.28–1.92 Gy (hired 1948–1954)	Increased risk of plutonium cancers (i.e., lung, liver or skeletal) in association with increased internal exposure ($p<0.001$). Increased risk of leukemia in association in increasing external gamma radiation dose ($p=0.04$), but not for internal exposure to plutonium.
Reference: Tokarskaya et al. 2006 Period: 1972–1999 Design: retrospective case-control Subjects: workers at Mayak Production Association (n=44 cases); controls (n=111) workers not exposed to plutonium matched for year of birth, gender, year of starting work, work assignment Outcome measures: liver cancer morbidity Analysis: OR for plutonium liver dose (Gy) (logistic regression model, adjusted for alcohol consumption, γ-radiation dose)	Quartile — Pu liver dose (Gy) 1st — 0 2nd — 0–0.07 3rd — >0.07–0.54 4th — >0.54–16.9	Significant ORs for liver cancers: Pu liver dose (Gy) — OR (95% CI) All liver cancers 0–2.0 — 1.0 (reference) >2.0–16.9 — 11.3 (3.6–35.2) Hemiangiosarcomas 0–2.0 — 1.0 (reference) >2.0–5.0 — 41.7 (4.6–333) >5.0–16.9 — 62.5 (7.4–500)

Table 3-2. Summary of Human Epidemiology Studies of Health Effects of Plutonium

Reference, study location, period, and study description	Dose measurement[a]	Findings and interpretation
United Kingdom:		
Reference: Carpenter et al. 1998 Period: Before 1976–1988 Design: retrospective cohort Subjects: workers at U.K. nuclear facilities during the period before 1976–1980 (n=40,761, 3,366 females). Plutonium worker cohort consisted of 12,498 workers ever monitored for plutonium exposure Outcome measures: cancer mortality Analysis: mortality incidence rates in workers monitored for plutonium exposure compared to workers not monitored (adjusted for age, gender, year of death, social class)	Not reported	MRR for workers monitored for plutonium were not significant (monitored compared to not monitored): Category — MRR (95% CI) All cancers — 1.01 (0.90–1.13) Lung and bronchus cancer — 1.18 (0.97–1.42) Pleura cancer — 1.97 (0.71–5.49) Liver and gall bladder cancer — 2.00 (0.59–6.38) Bone cancer — 1.01 (0.12–7.35) Trends for all cancers were statistically significant (p<0.05), while those for lung and bronchus cancer were not: Years since first monitored — MRR all cancers* — MRR lung and bronchus cancer <10 — 0.79 — 0.95 10–19 — 0.95 — 1.26 ≥20 — 1.20 — 1.26 Number of years monitored — MRR all cancers* — MRR lung and bronchus cancer <10 — 0.85 — 1.09 10–19 — 0.92 — 0.99 ≥20 — 1.15 — 1.45
Reference: McGeoghegan et al. 2003 Period: 1947–1998 Design: retrospective cohort Subjects: female workers ever employed at Sellafield plant (n=6,376). Plutonium worker cohort consisted of 5,203 workers ever monitored for plutonium exposure Outcome measures: mortality and cancer morbidity Analysis: mortality and morbidity incidence rates in plutonium workers compared to other radiation and non-radiation workers	Pu internal lung radiation dose: Dose (mSv) Mean — 3.45 Median — 1.59 Maximum — 178 5th% — 0.36 95th% — 8.89	Significant (p<0.05) MRR for plutonium workers compared to other radiation workers (CIs not reported) with no significant trends with organ-specific plutonium radiation doses: Category — MRR (*p<0.01; **p<0.05) Mortality All deaths — 2.20* All cancers — 3.30* Breast cancer — 3.77** Circulatory disease — 2.18** Ischemic heart disease — 5.46* Respiratory tract disease — 4.05 Digestive system disease — 0.65 Morbidity Breast cancer — 2.61**

Table 3-2. Summary of Human Epidemiology Studies of Health Effects of Plutonium

Reference, study location, period, and study description	Dose measurement[a]	Findings and interpretation
Reference: Omar et al. 1999 Period: 1947–1992 Design: retrospective cohort Subjects: workers at Sellafield plant (n=14,319, 2,689 females) who were employed at any time during the period 1947–1975; plutonium worker cohort consisted of 5,203 workers ever monitored for plutonium exposure Outcome measures: mortality and cancer morbidity Analysis: mortality and morbidity incidence (1971–1986) in plutonium workers compared to other radiation and non-radiation workers	Cumulative Pu exposure: Exposure (Bq) / Percent 0–250 / 75 >250–500 / 13 >500–750 / 7 >750–1,000 / 2 >1,000 / 3 Pu internal radiation dose (mean) : Tissue / Dose (Sv) Bone surfaces / 3,282 Lungs / 45–896 Liver / 421 Digestive tract / 8 Whole body / 219–355	Significant (*p<0.01; **p<0.05) MRR for plutonium workers compared to other radiation workers (CIs not reported). Significant negative trend for deaths from all cancers with internal plutonium plus external radiation doses (trend tests for internal plutonium doses, alone, were not reported). No other significant dose trends. Category / MRR All cancers / 1.05 Breast cancer / 7.66* Not cancer / 0.98 Cerebrovascular disease / 1.27** Respiratory tract disease / 0.88 Digestive system disease / 0.60**

[a]1 kBq=0.027 μCi; 1Gy=100 rad; 1 Sv=100 rem

CI = confidence interval; df = degrees of freedom; DL = detection limit; ERR = excess relative risk; LRT = likelihood ratio test; MRR = mortality and/or morbidity rate ratio; OR = odds ratio; RR = relative risk; SE = standard error

these studies provide evidence for an association between cancer mortality (bone, liver, lung) and exposure to plutonium. Plutonium dose-response relationships for lung cancer mortality and morbidity have been corroborated in four Mayak studies (Gilbert et al. 2004; Jacob et al. 2005; Kreisheimer et al. 2003; Sokolnikov et al. 2008). Estimated excess relative risk in these four studies (adjusted for smoking) were as follows: (1) 3.9 per Gy (95% CI: 2.6–5.8) in males and 19 per Gy (95% CI: 9.5–39) in females (Gilbert et al. 2004); (2) 7.1 per Gy (95% CI: 4.9–10) in males and 15 per Gy (95% CI: 7.6–29) in females at attained age of 60 years (Sokolnikov et al. 2008); (3) 4.50 per Gy (95% CI: 3.15–6.10) in males (Kreisheimer et al. 2003); and (4) 0.11 per Sv (95% CI: 0.08–0.17) or 0.21 per Sv (95% CI: 0.15–0.35) (Jacob et al. 2005), depending on the smoking-radiation interaction model that was assumed (these estimates per Sv correspond to 2.2 or 4.3 per Gy, respectively, assuming a radiation weighting factor of 20 for α-radiation). The excess relative risk per Gy in Mayak workers declined strongly with attained age (Gilbert et al. 2004).

The risks of mortality and morbidity from bone and liver cancers have also been studied in Mayak workers (Gilbert et al. 2000; Koshurnikova et al. 2000; Shilnikova et al. 2003; Sokolnikov et al. 2008; Tokarskaya et al. 2006). Increasing estimated plutonium body burden was associated with increasing liver cancer mortality, with higher risk in females compared to males. Relative risk for liver cancer for a cohort of males and females was estimated to be 17 (95% CI: 8.0–26) in association with plutonium uptakes >7.4 kBq; however, when stratified by gender, the relative risk estimate for females was 66 (95% CI: 16–45), while for males, it was lower at 9.2 (95% CI: 3.3–23; Gilbert et al. 2000). Risk of bone cancer mortality in this same cohort (n=11,000) was estimated to be 7.9 (95% CI: 1.6–32) in association with plutonium uptakes >7.4 kBq (males and females combined; Koshurnikova et al. 2000). Risks of leukemia mortality in the same cohort were not associated with internal plutonium exposure (Shilnikova et al. 2003). In a case control study of Mayak workers, the odds ratio for liver cancer was 11.3 (95% CI: 3.6–35.2) for subjects who received doses >2.0–5.0 Gy (relative to 0–2.0 Gy), and the odds ratios for hemangiosarcomas were 41.7 per Gy (95% CI: 4.6–333) for the dose group >2.0–5.0 Gy and 62.5 per Gy (95% CI: 7.4–500) for the dose group >5.0–16.9 Gy. Doses were estimated based on periodic urine sampling (Tokarskaya et al. 2006). Sokolnikov et al. (2008) reported averaged-attained age ERRs for liver cancer of 2.6 per Gy (95% CI: 0.7–6.9) for males and 29 per Gy (95% CI: 9.8–95) for females, and averaged-attained age ERRs for bone cancer of 0.76 per Gy (95% CI: <0–5.2) for males and 3.4 per Gy (95% CI: 0.4–20) for females. Elevated risks for bone cancer were observed only for workers with plutonium doses exceeding 10 Gy. For lung and bone cancer, the ERR declined with attained age, and for lung cancer, the ERR declined with age at first plutonium exposure.

Epidemiological studies of cancer mortality and morbidity are described in detail in the discussion of cancer from inhaled plutonium (Section 3.2.1.7).

Studies in Animals.

Exposure of Dogs to $^{238}PuO_2$. Decreased survival of dogs following inhalation of $^{238}PuO_2$ was observed in the ITRI and PNL studies (Muggenburg et al. 1996; Park et al. 1997). In both studies, postexposure survival decreased with increasing initial ^{238}Pu lung burden. In the ITRI study, survival appeared to decrease in dogs exposed to $^{238}PuO_s$ aerosols at a median initial lung burden as low as 0.36 kBq/kg body weight, although it was most apparent at median initial lung burdens ≥1.05 kBq/kg (Muggenburg et al. 1996). At a mean initial lung burden of 23.7 kBq/kg, mean postexposure survival was only 1,316 days (range: 536–1,517 days), whereas mean survival of vehicle-exposed controls was 4,580 days (range: 3,694-5,694 days). In the $^{238}PuO_2$-exposed dogs at PNL, mean initial lung burdens ranged from 0.01 to 18.9 kBq/kg body weight and survival was decreased at all levels, but statistically significantly decreased only at mean initial lung burdens ≥1.17 kBq/kg (Park et al. 1997). Radiation pneumonitis, lung tumors, bone tumors, and liver tumors were competing causes of death in the $^{238}PuO_2$-exposed dogs of both ITRI and PNL (Muggenburg et al. 1996; Park et al. 1997).

Exposures of Dogs to $^{239}PuO_2$. Premature death was also observed in dogs exposed to aerosols of $^{239}PuO_2$. In the ITRI studies, a dose-related decrease in mean survival time was observed, with survival time inversely related to initial lung burden (Hahn et al. 1999; Muggenburg et al. 1999, 2008). Decreased postexposure survival was evident at a median initial lung burden as low as 0.63 kBq/kg. Survival ranged from 152 to 5,941 days in dogs with initial lung burdens between 1 and 10 kBq/kg. At the highest median initial lung burden (29 kBq/kg), postexposure survival times were as short as 105–1,525 days compared to 1,893–6,308 days in aerosol vehicle-exposed controls. In the PNL dogs, survival times were decreased at mean initial lung burdens ≥1 kBq/kg body weight (DOE 1988a; Weller et al. 1995b). Radiation pneumonitis/interstitial fibrosis and lung tumors were the primary cause of premature death in ITRI and PNL dogs highly exposed to $^{239}PuO_2$ aerosols. The first two effects are shown together since the inflammation from radiation pneumonitis is constant due to long-term plutonium retention, and long-term inflammation always resulted in interstitial fibrosis.

Exposures of Dogs to $^{239}Pu(NO_3)_4$. Decreased survival was observed in PNL dogs exposed to aerosols of $^{239}Pu(NO_3)_4$ resulting in initial lung burdens ≥1.02 kBq/kg body weight (DOE 1986b, 1988b; Park et al. 1995). In the highest exposure group (mean initial lung burden 18.83 kBq/kg), death due to radiation

pneumonitis was noted as early as 14 months postexposure (DOE 1988b). Radiation pneumonitis was the primary cause of early deaths. Lung tumors and bone tumors were the primary causes of death among dogs that either did not develop radiation pneumonitis or survived the condition (Park et al. 1995).

Exposure of Other Laboratory Animal Species. Decreased survival has been observed in rats exposed to $^{239}PuO_2$ (Lundgren et al. 1995; Métivier et al. 1986; Oghiso and Yamada 2003a; Oghiso et al. 1994b, 1998; Sanders and Lundgren 1995; Sanders et al. 1976, 1988a, 1988b, 1993b), mice (Lundgren et al. 1987), hamsters (Lundgren et al. 1983; Sanders 1977), and baboons (Metivier et al. 1974, 1978b). In these animal species, death was usually caused by radiation pneumonitis accompanied by edema, fibrosis, and other signs of respiratory damage. Three Cynomolgus monkeys died at 155, 188, and 718 days, respectively, after aerosol exposure to $^{239}Pu(NO_3)_4$ at levels projected to produce an initial total lung burden of 40 kBq (1.1 μCi); each was diagnosed with radiation pneumonitis (Brooks et al. 1992).

The highest NOAEL values and all reliable LOAEL values for deaths in each species and duration category are recorded in Table 3-3.

All reliable LOAEL values for death in dogs and nonhuman primates exposed to aerosols of plutonium are recorded in Table 3-3 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding dermal/ocular effects in humans or animals after inhalation exposure to plutonium.

Respiratory Effects.

Epidemiological Studies in Humans. Possible associations between exposure to plutonium and respiratory tract disease have been examined in studies of workers at U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). The most recent findings from these studies are summarized in Table 3-2. Study outcomes for mortality from lung or respiratory tract disease (e.g., cancer and other causes) are described in Section 3.2.1.1 (Brown et al. 2004; Carpenter et al. 1998; Gilbert et al. 1989b, 2004; Jacob et al. 2005; Kreisheimer et al. 2003; McGeoghegan et al. 2003; Omar et al. 1999; Wiggs et al. 1994; Wing et al. 2004). Collectively, these studies have not found statistically significant

Table 3-3 Levels of Significant Exposure to Plutonium - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (kBq/kg)	LOAEL Less Serious (kBq/kg)	LOAEL Serious (kBq/kg)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Monkey (Cynomolgus)	once				8 M (fatal radiation pneumonitis)	Brooks et al. 1992 239Pu(NO3)4	
2	Monkey (Rhesus)	once				11.7 M (fatal radiation pneumonitis)	LaBauve et al. 1980 239PuO2	
3	Dog (Beagle)	once				1 (decreased survival)	DOE 1988a 239PuO2	Group mean ILB.
4	Dog (Beagle)	once				5.91 (fatal radiation pneumonitis)	DOE 1988b 239Pu(NO3)4	Group mean ILB.
5	Dog (Beagle)	once				1.6 (fatal radiation pneumonitis)	Hahn et al. 1999 239PuO2	Group median ILB.
6	Dog (Beagle)	once				0.77 (markedly decreased survival)	Muggenburg et al. 1996 238PuO2	Group median ILB.
7	Dog (Beagle)	Once				1.6 (fatal radiation pneumonitis)	Muggenburg et al. 2008 239PuO2	Group median ILB.
						0.63 (decreased survival)		

Table 3-3 Levels of Significant Exposure to Plutonium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (kBq/kg)	LOAEL Less Serious (kBq/kg)	LOAEL Serious (kBq/kg)	Reference Chemical Form	Comments
8	Dog (Beagle)	once				1.02 (decreased survival at 9 years; 55% compared to 90% in controls)	Park et al. 1995 239Pu(NO3)4	Group median ILB.
9	Dog (Beagle)	once 10-30 min				1 (significantly decreased survival)	Park et al. 1997 238PuO2	Group mean ILB.
Systemic								
10	Monkey (Cynomolgus)	once	Resp	1.9 M	4.8 M (pulmonary lesions consisting of interstitial fibrosis and alveolar epithelial proliferation)		Brooks et al. 1992 239Pu(NO3)4	
			Hemato	19 M				
11	Dog (Beagle)	once	Hemato	1.02	5.91 (significantly decreased lymphocyte, neutrophil, total leukocyte counts)		DOE 1988b 239Pu(NO3)4	Group mean ILB.

Table 3-3 Levels of Significant Exposure to Plutonium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (kBq/kg)	LOAEL Less Serious (kBq/kg)		LOAEL Serious (kBq/kg)		Reference Chemical Form	Comments
12	Dog (Beagle)	once	Resp				8.3	(fatal radiation pneumonitis)	Muggenburg et al. 1996 238PuO2	Lowest individual ILB resulting in fatal radiation pneumonitis. Group median ILB for hemato and hepatic effects.
			Hemato		1	(decreased lymphocyte count)				
			Hepatic		5	(increased serum liver enzymes: ALP, ALT)				
13	Dog (Beagle)	Once	Resp	0.63			1.6	(fatal radiation pneumonitis)	Muggenburg et al. 2008 239PuO2	Group median ILB
			Hemato	1.6	3.7	(significantly decreased lymphocyte count)				
14	Dog (Beagle)	once	Hepatic	0.0069	0.028	(significantly increased severity of adenomatous hyperplasia)			Park et al. 1995 239Pu(NO3)4	Group mean ILB.

Table 3-3 Levels of Significant Exposure to Plutonium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (kBq/kg)	LOAEL Less Serious (kBq/kg)		LOAEL Serious (kBq/kg)		Reference Chemical Form	Comments
15	Dog (Beagle)	once 10-30 min	Resp		0.28	(chronic radiation pneumonitis)			Park et al. 1997 238PuO2	Group mean ILB for respiratory, hemato and hepatic effects.
			Hemato		0.28	(lymphopenia)				
			Musc/skel	0.28	1	(radiation osteodystrophy)				
			Hepatic		0.28	(increased serum liver ALT and ALP)				
16	Dog (Beagle)	once	Hemato	0.075	1.18	(intermittent lymphopenia)			Weller et al. 1995b 239PuO2	Mean ILB for nonlymphopenic dogs.
Cancer										
17	Dog (Beagle)	once					0.25	(CEL: lung tumors)	DOE 1988a 239PuO2	Based on group mean ILB and fatal lung tumors.
18	Dog	once					0.19	(CEL: bone tumors)	DOE 1994a 239Pu(NO3)4	Group mean ILB.
19	Dog (Beagle)	once					0.4 0.3	(CEL: bone tumors) (CEL: lung, liver tumors)	Muggenburg et al. 1996 238PuO2	Lowest ILB at which tumors were detected.
20	Dog (Beagle)	Once					0.63	(CEL: lung tumors)	Muggenburg et al. 2008 239PuO2	Group median ILB

Table 3-3 Levels of Significant Exposure to Plutonium - Inhalation (continued)

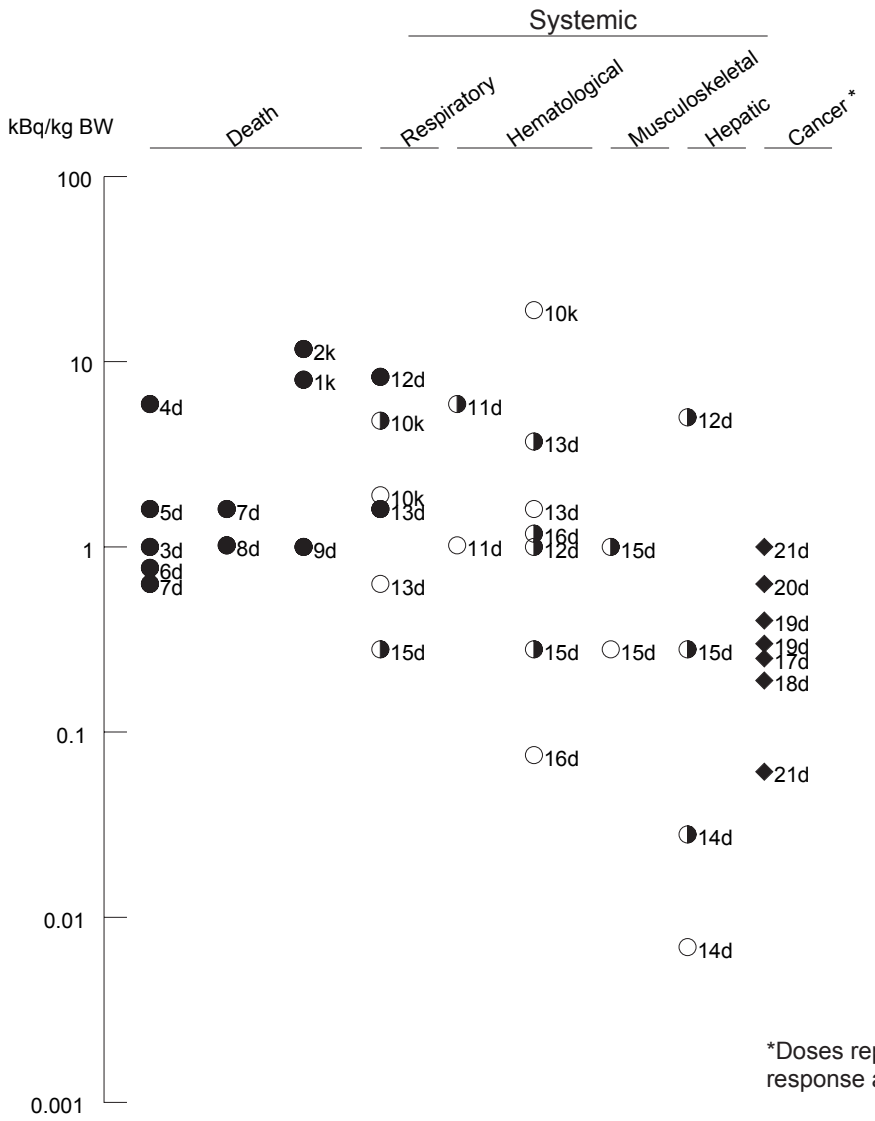
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (kBq/kg)	LOAEL			Reference Chemical Form	Comments
					Less Serious (kBq/kg)	Serious (kBq/kg)			
21	Dog (Beagle)	once 10-30 min				1	(CEL: bone tumors)	Park et al. 1997 238PuO2	Group mean ILB.
						0.061	(CEL: lung tumors)		

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

ALP = alkaline phosphatase; ALT = alanine aminotransferase; BW = body weight; CEL = cancer effect level; Hemato = hematological; ILB = initial lung burden; kBq/kg BW = initial lung burden in kilobecquerel/kilogram body weight; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory

Figure 3-1 Levels of Significant Exposure to Plutonium - Inhalation

Acute (≤14 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

associations between mortality rates from noncancer respiratory tract diseases and exposure to plutonium among workers at these facilities.

Possible associations between exposure to plutonium and pulmonary fibrosis was examined in a cohort of workers (n=326) at Rocky Flats (Newman et al. 2005). The study assessed lung interstitial abnormalities from the most recent available x-rays in relation to estimated lung equivalent doses from plutonium. Estimated lung equivalent doses ranged from 0 to 28 Sv (approximately 73% <1 Sv). The odds ratio (OR) (adjusted for age, smoking status, and evidence from pleural abnormalities from possible asbestos exposure) was significant for the dose group with lung equivalent doses ≥10 Sv (OR 5.3, 95% CI: 1.2–23.4). The report of Newman et al. (2005) was based on scoring radiographs for the severity of chest abnormalities consistent with fibrosis, and did not include information regarding a possible association between these lung abnormalities and clinical symptoms of disease.

Studies in Animals. Radiation pneumonitis has been observed following plutonium (primarily insoluble) aerosol exposure of dogs, nonhuman primates (monkeys and baboons), and rodents. As discussed in Section 3.2.1.1, radiation pneumonitis was identified as primary, major contributing, or incidental cause of death in some dogs and nonhuman primates that inhaled $^{238}PuO_2$, $^{239}PuO_2$, or $^{239}Pu(NO_3)_4$ aerosols.

Muggenburg et al. (2008) studied the effect of plutonium ILB and radiation dose on radiation pneumonitis in beagles as part of a plutonium lifespan composite study. The relationship between pneumonitis induction and the cause of death was reported to be a function of the plutonium ILB, the resulting cumulative radiation dose, and the particle size to some extent. Increased ILB and plutonium dose rate were associated with the fraction of animals with radiation pneumonitis as primary, major contributing, or incidental cause of death. A trend was observed for the induction of radiation pneumonitis at lower ILBs in the 0.75 and 1.5 μm AMAD groups than in the 3 μm AMAD group. At radiation doses sufficient to produce radiation pneumonitis, the resulting inflammation was a chronic symptom due to long-term retention of $^{239}PuO_2$ in the lung. As a result, $^{239}PuO_2$-induced radiation pneumonitis was always associated with pulmonary fibrosis. The radiation pneumonitis/pulmonary fibrosis progressively impaired lung function, including alveolar-capillary gas exchange, resulting in increases in respiratory rate, minute volume, arterial CO_2 pressure, and lung stiffness, along with decreases in tidal volume and arterial O_2 pressure. Symptoms in order of decreasing frequency were tachypnea, increased breath sounds, body weight loss, anorexia, dyspnea, cyanosis, bradycardia, and discharge from the nose, eyes, or mouth. Increasing radiation dose and dose rate corresponded to

progressively shorter times to onset of symptoms and increased severity of effects (Muggenburg et al. 2008).

Results of inhalation toxicity studies in dogs show that the clinical course of radiation pneumonitis is similar following exposure to $^{238}PuO_2$ or $^{239}PuO_2$. The typical initial presenting symptom of radiation pneumonitis is tachypnea (increased number of breaths per minute) with radiological evidence of pulmonary interstitial infiltrate. Histopathological findings include interstitial pneumonia with alveolar epithelial hyperplasia, vasculitis, inflammatory cells infiltration, and pulmonary fibrosis (Muggenburg et al. 1996, 1999, 2008; Park et al. 1997). Results of the ITRI and PNL studies indicate that radiation pneumonitis in the $^{239}PuO_2$-exposed dogs occurred at lower initial lung burdens and had a shorter time to onset of symptoms (Muggenburg et al. 2008) compared to that observed in $^{238}PuO_2$- or $^{239}Pu(NO_3)_4$-exposed dogs. This observation is consistent with toxicokinetic differences observed for inhaled plutonium compounds, showing that inhaled $^{239}PuO_2$ is cleared from the lung more slowly than $^{238}PuO_2$ and $^{239}Pu(NO_3)_4$ (see Section 3.4, Toxicokinetics).

Exposure of Dogs to $^{238}PuO_2$. In the ITRI $^{238}PuO_2$ dog studies, the first symptom of radiation pneumonitis (tachypnea) was observed at approximately 600 days after initial exposure (Muggenburg et al. 1996). Pulmonary function tests performed periodically over several years on a subgroup of dogs with radiation pneumonitis (mean initial lung burden 28 kBq/kg) showed progressive changes in lung function including decreased dynamic lung compliance, decreased CO diffusing capacity, increased alveolar-arterial pO_2, pulmonary edema (a near terminal event), and decreased arterial pO_2 (terminal event). Pulmonary interstitial or septal fibrosis was observed at necropsy in all dogs with radiation pneumonitis; severity was dose-related. Radiation pneumonitis was the primary cause of death in eight dogs with initial lung burdens of 8.3–45 kBq/kg (Muggenburg et al. 1996). Similar observations were reported in the PNL studies on $^{238}PuO_2$, with chronic radiation pneumonitis observed in dogs with initial lung burdens ≥0.28 kBq/kg (Park et al. 1997).

Exposure of Dogs to $^{239}PuO_2$. Chronic radiation pneumonitis also was observed in the ITRI and PNL dogs exposed to $^{239}PuO_2$ aerosols. In the ITRI studies, tachypnea was first observed in cases of nonfatal radiation pneumonitis approximately 1 year after exposure (Muggenburg et al. 1988). Morphological changes to the lung included alveolar epithelial hyperplasia and interstitial fibrosis (Muggenburg et al. 2008). Radiation pneumonitis was observed in dogs dying from 0.3 to 11.7 years after inhaling $^{239}PuO_2$, with the time to death inversely related to initial lung burden (Hahn et al. 1999; Muggenburg et al. 1999, 2008). The lowest initial lung burden causing fatal radiation pneumonitis was 1.0 kBq/kg (Muggenburg

et al. 1999, 2008). The time to death from radiation pneumonitis was not different in ITRI dogs administered a single exposure (initial lung burden of 3.9 kBq/kg) or repeated exposures (7–10 semi-annual exposures for a mean total lung burden of 5.3 kBq/kg) (Diel et al. 1992). Death due to radiation pneumonitis was observed in $^{239}PuO_2$-exposed PNL dogs at mean initial lung burdens ≥1 kBq/kg (DOE 1988a; Weller et al. 1995b). Histopathologic changes to lungs included interstitial and subpleural fibrosis, alveolar hyperplasia, and squamous metaplasia. Radiation pneumonitis and lung cancer were competing causes of death in dogs that inhaled $^{239}PuO_2$. The frequencies of both radiation pneumonitis and lung cancer were the same in dogs receiving an average ILB of 3.7 kBq/kg from $^{239}PuO_2$. At higher doses, radiation pneumonitis occurred more frequently to the point that dogs died without signs of cancer at an average ILB of 29 kBq/kg. At lower doses, cancer occurred more frequently and radiation pneumonitis was not observed at average ILBs ≤0.63 kBq/kg (Muggenburg et al. 2008). In the ITRI dogs, radiation pneumonitis occurred at similar initial lung burdens whether the dogs were exposed as juveniles, young adults, or elderly adults (DOE 1988d, 1989, 1994b; Hahn et al. 1999; Muggenburg et al. 1999). Radiation pneumonitis-induced death occurred earlier in the dogs exposed as elderly adults than in the dogs exposed as young adults (DOE 1988d).

Exposure of Dogs to $^{239}Pu(NO_3)_4$. Radiation pneumonitis was the primary cause of death in all five dogs that died early following exposure to $^{239}Pu(NO_3)_4$ aerosols at levels resulting in a mean initial lung burden of 18.83 kBq/kg; death was noted as early as 14-months postexposure (DOE 1988b; Park et al. 1995). Data on the time to onset and clinical progression of disease or histopathologic findings were not reported.

Exposure of Other Laboratory Animal Species. Baboons that inhaled $^{239}PuO_2$ displayed a pattern of respiratory disease similar to that observed in dogs. Radiation pneumonitis-induced mortality was observed in one baboon within 400 days following exposure to $^{239}PuO_2$ that resulted in an estimated initial lung burden of 28.5 kBq/kg body weight (Metivier et al. 1974, 1978b). Higher initial lung burdens resulted in earlier death from radiation pneumonitis accompanied by pulmonary edema. Radiation pneumonitis and pulmonary fibrosis were also reported in Rhesus monkeys at initial lung burdens of 14.8 or 26.64 kBq/kg (LaBauve et al. 1980). Dose-related increased severity of radiation pneumonitis and pulmonary interstitial fibrosis were observed in Cynomolgus monkeys exposed to $^{239}Pu(NO_3)_4$ at levels resulting in initial total lung burdens ≥4.8 kBq/kg (based on reported initial lung burdens and mean body weight) (Brooks et al. 1992). Monkeys with the highest initial lung burdens exhibited extensive alveolar septal fibrosis and zonal pleural fibrosis accompanied by lymphocytic infiltrates and epithelial hyperplasia of alveolar lining cells. Radiation pneumonitis and pulmonary fibrosis have also been

observed in rats, mice, and hamsters that inhaled $^{239}PuO_2$ (DOE 1986d; Lundgren et al. 1983, 1987, 1995; Oghiso et al. 1994b; Sanders 1977; Sanders and Mahaffey 1979).

The highest NOAEL values and all reliable LOAEL values for respiratory effects in dogs and nonhuman primates exposed to aerosols of plutonium are recorded in Table 3-3 and plotted in Figure 3-1.

Cardiovascular Effects.

Epidemiological Studies in Humans. Possible associations between exposure to plutonium and cardiovascular disease have been examined in studies of workers at production and/or processing facilities in the United Kingdom (Sellafield) (McGeoghegan et al. 2003; Omar et al. 1999). These studies are summarized in Table 3-2 and study outcomes for mortality from cardiovascular disease are described in Section 3.2.1.1. Omar et al. (1999) compared mortality rates between plutonium workers and other radiation workers within a cohort of Sellafield workers and found that the mortality rate ratios were significantly elevated for cerebrovascular disease (1.27, $p<0.05$) in a cohort of Sellafield workers. The cumulative internal uptakes of plutonium in the cohort were estimated to range from 0 to 12 kBq, with approximately 75% of the cohort having cumulative uptakes ≤250 Bq. McGeoghegan et al. (2003) compared mortality rates between plutonium workers and other radiation workers within a cohort of Sellafield workers and found that morality rate ratios for plutonium workers were significantly elevated for deaths from circulatory disease (2.18, $p<0.05$) and ischemic heart disease (4.46, $p<0.01$).

Studies in Animals. No significant changes in cardiovascular function were seen in the ITRI dogs exposed to $^{239}PuO_2$ at initial lung burdens up to and including those resulting in radiation pneumonitis; observed right ventricular hypertrophy was most likely a compensatory response to decreased respiratory function (Diel et al. 1992; Muggenburg et al. 1999).

Gastrointestinal Effects. Possible associations between exposure to plutonium and mortality from diseases of the gastrointestinal tract have been examined in studies of workers at plutonium production and/or processing facilities in the United Kingdom (Sellafield) (McGeoghegan et al. 2003; Omar et al. 1999). These studies are summarized in Table 3-2 and study outcomes for mortality are described in Section 3.2.1.1. Collectively, these studies have not found statistically significant associations between mortality rates from diseases of the digestive tract and exposure to plutonium among workers at these facilities.

No reports were located regarding gastrointestinal effects in animals exposed to plutonium aerosols.

Hematological Effects. Possible associations between exposure to plutonium and mortality from hematopoietic diseases have been examined in studies of workers at plutonium production and/or processing facilities in the United States (Rocky Flats) (Wiggs et al. 1994) and the United Kingdom (Sellafield) (McGeoghegan et al. 2003; Omar et al. 1999). These studies are summarized in Table 3-2 and study outcomes for mortality are described in Section 3.2.1.1. Collectively, these studies have not found statistically significant associations between mortality rates from diseases of blood or blood-forming organs and exposure to plutonium among workers at these facilities.

Studies in Animals. Inhalation exposure of dogs to plutonium compounds produced adverse hematological effects, specifically decreased numbers of lymphocytes, neutrophils, and leukocytes. Primary hematological effects of inhaled $^{238}PuO_2$ and $^{239}Pu(NO_3)_4$ were lymphopenia and neutropenia. In contrast, lymphopenia was the only hematological effect of inhaled $^{239}PuO_2$. The lymphopenia was considered the result of lymphocytes being irradiated as they passed through plutonium-containing pulmonary lymph nodes. Effects were not observed on other blood cell types, perhaps the result of the small fraction of $^{239}PuO_2$ that translocated to bone or bone marrow (Muggenburg et al. 2008). No fatal cancers of the hematopoietic system were reported in studies of dogs or monkeys exposed to plutonium. Effects of plutonium compounds on functions of circulating immunological cells are discussed in Section 3.2.1.2, Immunological and Lymphoreticular Effects.

Exposure of Dogs to $^{238}PuO_2$. Lymphopenia and neutropenia were observed in dogs exposed to $^{238}PuO_2$. In the ITRI dogs, dose-dependent decreases in lymphocyte and neutrophil counts occurred during the first year following exposure at initial lung burdens equal to 1 kBq/kg (Muggenburg et al. 1996). Similar results were observed in the PNL dogs, although decreased lymphocyte counts were observed at a lower initial lung burden (≥0.28 kBq/kg) than decreased neutrophil counts (≥4.68 kBq/kg) (Park et al. 1997).

Exposure of Dogs to $^{239}PuO_2$. Lymphopenia was both the first biological effect to be observed and the primary hematological effect observed in dogs exposed to $^{239}PuO_2$, although leukopenia, and transient neutropenia have also been reported. Chronic lymphopenia developed during the first year of exposure in the ITRI dogs with initial lung burdens ≥3.7 kBq/kg (Muggenburg et al. 1999, 2008). In the PNL dogs, transient lymphopenia occurred at initial lung burdens ≥0.064 kBq/kg and transient and persistent lymphopenia was noted at initial lung burdens ≥0.25 kBq/kg (Weller et al. 1995b). The time of occurrence for significant lymphopenia was inversely related to dose (112 days, 180 days, 1 year, or up to

5 years for respective average initial lung burdens of 29, 14, 6.4, and 3.7 kBq/kg). Although the lymphocyte counts returned to normal after 5 years for some of these animals, all experienced a shortening of life. No changes in red blood cell counts were observed through year 7 other than a compensatory increase in animals with pneumonitis or pulmonary fibrosis. In addition to lymphopenia, plutonium accumulated in the pulmonary lymph nodes of the $^{239}PuO_2$-exposed dogs. This resulted initially in corticomedullary lymphoid atrophy and fibrosis in the hilar areas, especially in the trachiobronchial region, and progressed to relatively complete atrophy and focal scarring (Muggenburg et al. 2008). Repeated inhalation exposure to $^{239}PuO_2$ produced lymphopenia in dogs with total lung burden of 5.3 kBq/kg (Diel et al. 1992).

Other hematological effects observed in dogs exposed to $^{239}PuO_2$ aerosols include transient neutropenia, leukopenia, and erythrocytosis. Transient neutropenia developed 4 months after exposure to $^{239}PuO_2$ in the ITRI dogs with initial lung burdens ≥8.4 kBq/kg, although the duration of the effect was not reported (Weller et al. 1995b). A reduction in total leukocytes was also observed in the PNL dogs at the "higher" (not otherwise specified) initial lung burden levels (Park et al. 1997). Erythrocytosis, secondary to decreased diffusing capacity of the lungs due to radiation pneumonitis, was reported in the $^{239}PuO_2$-exposed ITRI dogs (Muggenburg et al. 1999, 2008). Erythrocyte counts in were not affected in the $^{239}PuO_2$-exposed PNL dogs (DOE 1988a).

Exposure of Dogs to $^{239}Pu(NO_3)$. In PNL dogs exposed to inhaled $^{239}Pu(NO_3)_4$, hematological effects were the first exposure-related effect observed. Lymphopenia, leukopenia, and neutropenia occurred 4 weeks after exposures resulting in initial lung burdens ≥5.91 kBq/kg (DOE 1988b). Leukopenia was characterized by decreased numbers of neutrophils, lymphocytes, monocytes, and eosinophils.

Exposure of Other Laboratory Animal Species. Lymphopenia was noted in Rhesus monkeys exposed to $^{239}PuO_2$ aerosols, but initial lung burdens resulting in this effect were not specified (LaBauve et al. 1980). Total leukocyte count (in the absence of lymphopenia and neutropenia) was decreased in Cynomolgus monkeys exposed to $^{239}Pu(NO_3)_4$, but the initial lung burdens at which the effect was noted were not specified (Brooks et al. 1992).

The highest NOAEL values and all reliable LOAEL values for hematological effects in each species and duration category are recorded in Table 3-3.

The highest NOAEL values and all reliable LOAEL values for hematological effects in dogs and nonhuman primates exposed to aerosols of plutonium are recorded in Table 3-3 and plotted in Figure 3-1.

Musculoskeletal Effects.

Epidemiological Studies in Humans. Possible associations between exposure to plutonium and mortality from bone disease (e.g., bone cancer) and other musculoskeletal diseases have been examined in studies of workers at U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). The most recent findings from these studies are summarized in Table 3-2. Study outcomes for mortality (e.g., bone cancer) are described in Section 3.2.1.1 (Carpenter et al. 1998; Koshurnikova et al. 2000; McGeoghegan et al. 2003; Omar et al. 1999; Wiggs et al. 1994; Wing et al. 2004). Collectively, these studies have not found statistically significant associations between mortality rates for noncancer bone or musculoskeletal disease and exposure to plutonium among workers at these facilities (McGeoghegan et al. 2003; Omar et al. 1999; Wiggs et al. 1994).

Studies in Animals. Radiation osteodystrophy, characterized by peritrabecular fibrosis, osteosclerosis, and osteoporosis, was observed on necropsy in ITRI and PNL dogs exposed to $^{238}PuO_2$ aerosols (Hahn et al. 1991a; Muggenburg et al. 1996; Park et al. 1997). Although osteodystrophy in the $^{238}PuO_2$-exposed ITRI dogs was often associated with bone tumors, it also occurred in the absence of bone tumors (Hahn et al. 1991a; Muggenburg et al. 1996). In the $^{238}PuO_2$-exposed PNL dogs, radiation osteodystrophy was observed at initial lung burdens ≥1.17 kBq/kg (Park et al. 1997). The incidence and severity of osteodystrophy was dose-related and necrotic osteoblasts and empty lacunae near endosteal surfaces were observed at high (not otherwise specified) initial lung burdens (Park et al. 1997). Radiation osteodystrophy has also been reported in dogs exposed to $^{239}Pu(NO_3)_4$ aerosols (DOE 1986b, 1989).

Information on plutonium-induced bone tumors is reviewed in Section 3.2.1.7, Cancer.

The highest NOAEL values and all reliable LOAEL values for musculoskeletal effects in each species and duration category are recorded in Table 3-3.

The highest NOAEL values and all reliable LOAEL values for musculoskeletal effects in dogs and nonhuman primates exposed to aerosols of plutonium are recorded in Table 3-3 and plotted in Figure 3-1.

Hepatic Effects.

Epidemiological Studies in Humans. Possible associations between exposure to plutonium and mortality from liver disease (e.g., liver cancer) have been examined in studies of workers at U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). The most recent findings from these studies are summarized in Table 3-2. Study outcomes for mortality (e.g., liver cancer) are described in Section 3.2.1.1 (Carpenter et al. 1998; Gilbert et al. 1989b, 2000; McGeoghegan et al. 2003; Omar et al. 1999; Wiggs et al. 1994; Wing et al. 2004). Collectively, these studies have not found statistically significant associations between mortality rates for noncancer liver disease and exposure to plutonium among workers at these facilities (McGeoghegan et al. 2003; Omar et al. 1999; Wiggs et al. 1994). Studies of liver cancer morbidity among Sellafield and Mayak workers are described in Table 3-2 and in greater detail in Section 3.2.1.7 (McGeoghegan et al. 2003; Omar et al. 1999; Tokarskaya et al. 2006).

Studies in Animals. Adverse effects on the liver have been observed in dogs exposed to aerosols of plutonium. Elevated serum liver enzymes and non-neoplastic liver lesions were noted in dogs exposed to $^{238}PuO_2$ and $^{239}Pu(NO_3)_4$, and non-neoplastic liver lesions have been observed in dogs exposed to $^{239}PuO_2$. In addition, bile duct hyperplasia was observed in dogs treated with $^{238}PuO_2$ and $^{239}Pu(NO_3)_4$. Although elevated liver enzymes and non-neoplastic liver lesions indicate are indicative of plutonium-induced hepatotoxicity, clinical signs of liver dysfunction (i.e., ascites, icterus, clotting disorders) have not been observed (Park et al. 1997; Weller et al. 1995b). Information on plutonium-induced liver tumors is reviewed in Section 3.2.1.2, Cancer.

Exposure of Dogs to $^{238}PuO_2$. Elevated serum alkaline phosphatase (ALP) and alanine aminotransferase (ALT) was observed in $^{238}PuO_2$-exposed ITRI and PNL dogs over the entire range of initial lung burdens (≥0.36 kBq/kg) (Muggenburg et al. 1996; Park et al. 1997; Weller et al. 1995b). The increased enzyme activity exhibited a biphasic (early and late effects) response that was dependent on time and exposure level (Park et al. 1997; Weller et al. 1995a). The time to occurrence was inversely related to initial lung burden, with elevations observed by 6–8 years postexposure in dogs with initial lung burden of 1 kBq/kg and in 4–6 years postexposure in dogs with higher initial lung burdens (≥5 kBq/kg) (Muggenburg et al. 1996). The most common non-neoplastic liver lesion was nodular hyperplasia (or adenomatous hyperplasia), followed by vacuolar degeneration (Muggenburg et al. 1996). Periportal fibrosis and biliary fibrosis were also observed in $^{238}PuO_2$-exposed dogs (Gillett et al. 1988).

Exposure of Dogs to $^{239}PuO_2$. Centrilobular congestion and vacuolization were observed in dogs that inhaled $^{239}PuO_2$ (initial lung burden ≥1 kBq/kg), although no consistent changes in serum liver enzymes were seen (DOE 1988a).

Exposure of Dogs to $^{239}Pu(NO_3)_4$. Serum liver enzymes ALP and glutamic pyruvic transaminase (GPT) were significantly elevated In PNL dogs that inhaled $^{239}Pu(NO_3)_4$, at levels resulting in initial lung burdens ≥0.19 kBq/kg (DOE 1988b, 1994a; Park et al. 1995). Bile duct hyperplasia was reported in controls and plutonium-exposed dogs and did not appear to exhibit dose-related increased incidence or severity (Dagle et al. 1996). However, the severity of observed nodular hyperplasia was significantly higher in dogs with mean initial lung burdens ranging from 0.028 to 1.02 kBq/kg (Dagle et al. 1996).

Exposure of Other Laboratory Animal Species. Degenerative liver lesions (hepatic degeneration, necrosis, fibrosis, and amyloidosis) were reported in Syrian hamsters exposed to $^{239}PuO_2$ (once or repeatedly every other month for a total of seven doses over 12 months) at a target ^{239}Pu lung burden of 1.8 kBq/hamster; it was noted that the lesions observed in these hamsters were typical of those usually seen in aged Syrian hamsters (Lundgren et al. 1983).

The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and duration category are recorded in Table 3-3.

The highest NOAEL values and all reliable LOAEL values for hepatic effects in dogs and nonhuman primates exposed to aerosols of plutonium are recorded in Table 3-3 and plotted in Figure 3-1.

Renal Effects. Possible associations between exposure to plutonium and mortality from diseases of the kidney and genitourinary tract have been examined in studies of workers at plutonium production and/or processing facilities in the United States (Rocky Flats) (Wiggs et al. 1994) and the United Kingdom (Sellafield) (McGeoghegan et al. 2003; Omar et al. 1999). These studies are summarized in Table 3-2 and study outcomes for mortality are described in Section 3.2.1.1. Collectively, these studies have not found significant associations between mortality rates from kidney or genitourinary tract disease and exposure to plutonium among workers at these facilities.

Endocrine Effects.

Epidemiological Studies in Humans. Possible associations between exposure to plutonium and mortality from endocrine disorders have been examined in studies of workers at plutonium production and/or processing facilities in the United Kingdom (Sellafield) (McGeoghegan et al. 2003; Omar et al. 1999). These studies are summarized in Table 3-2 and study outcomes for mortality are described in Section 3.2.1.1. Collectively, these studies have not found significant associations between mortality rates from endocrine disorders and exposures to plutonium among workers at these facilities.

Studies in Animals. Hypoadrenocorticism was reported in $^{238}PuO_2$-exposed PNL dogs (n=6) with individual initial lung burdens in the range of 1–25 kBq/kg body weight and was considered the cause of death in 3 of the 6 dogs (Park et al. 1997). The time to detection of hypoadrenocorticism ranged from 1,263 to 4,616 days after exposure; physical symptoms included depression, weakness, dehydration, bradycardia, and anorexia. Laboratory findings in affected animals (hemoconcentration, altered serum Na:K ratio, hypochloremia, hypoglycemia, metabolic acidosis, and hypercalcemia) were consistent with adrenal cortical insufficiency. Cardiovascular changes (bradycardia and other cardiac arrhythmias) were consistent with hypoadrenocorticism-induced hypokalemia. Histopathological findings included bilateral adrenal cortex atrophy with capsular thickening and fibrosis, and mononuclear cell infiltration. Results of ACTH response tests indicated that hypoadrenocorticism resulted from adrenal cortical insufficiency rather than from altered pituitary function. Based on the presence of anti-adrenal antibodies in serum, hypoadrenocorticism may have resulted from an autoimmune disorder caused by radiation damage to the lymphatic system (Park et al. 1997).

3.2.1.3 Immunological and Lymphoreticular Effects

Epidemiological Studies in Humans. Possible associations between exposure to plutonium and mortality from immunological or lymphoreticular diseases have been examined in studies of workers at plutonium production and/or processing facilities in the United States (Rocky Flats) (Wiggs et al. 1994) and the United Kingdom (Sellafield) (McGeoghegan et al. 2003; Omar et al. 1999). These studies are summarized in Table 3-2 and study outcomes for mortality are described in Section 3.2.1.1. Collectively, these studies have not found statistically significant associations between mortality rates from diseases of the immunological or lymphoreticular systems and exposures to plutonium among workers at these facilities.

Studies in Animals. As discussed in detail in Section 3.4, Toxicokinetics, inhaled plutonium compounds are translocated to tracheobronchial lymph nodes, resulting in a high tissue concentration of plutonium and sclerotic atrophy of lymph nodes. Exposure of lymphocytes in plutonium-laden tracheobronchial lymph nodes is considered the probable cause of lymphopenia in the plutonium-exposed dogs (Ragan et al. 1976). Effects of inhaled plutonium on the number lymphocytes circulating in blood are reviewed in Section 3.2.1.2, Hematological Effects.

Histopathologic lesions of lymph nodes, particularly tracheobronchial lymph nodes, have been observed following exposure to $^{238}PuO_2$, $^{239}PuO_2$, or $^{239}Pu(NO_3)_4$. Fibrosis and loss of lung-associated and mediastinal lymph nodes were observed in the $^{238}PuO_2$-exposed ITRI dogs with the highest initial lung burdens, although specific levels resulting in this effect were not specified (Muggenburg et al. 1996). Severity of non-neoplastic lesions in $^{238}PuO_2$-exposed PNL dogs was related to dose, progressing from lymphoid atrophy of medullary cords at an initial lung burden of 0.061 kBq/kg to significant lymph node atrophy with hypocellular scar tissue replacing lymphoid tissue at higher (not otherwise specified) initial lung burdens (Park et al. 1997). Similar dose-related atrophy and fibrosis of lung-associated, mediastinal, sternal, and hepatic lymph nodes were observed in dogs exposed to $^{239}PuO_2$ (DOE 1988a; Muggenburg et al. 1999, 2008). Sclerotic lymph nodes were observed in the groups of $^{239}Pu(NO_3)_4$-exposed PNL dogs with mean initial lung burdens ≥5.9 kBq/kg, but lymph node lesions in these dogs were considered less severe than those observed in $^{238}PuO_s$- or $^{239}PuO_2$-exposed dogs (DOE 1986b, 1989).

Results of studies on immunological function indicate that inhalation exposure to $^{239}PuO_2$ impairs T-cell response to antigens, as indicated by decreased response to antigen (DOE 1978a). Davila et al. (1992) detected accelerated aging of the T-cell response to mitogenic stimulation in dogs that had been exposed to $^{239}PuO_2$ 10 years earlier at levels resulting in mean initial lung burdens ≥6.5 kBq (0.61 kBq/kg, assuming a body weight of 10.7 kg at time of $^{239}PuO_2$ aerosol exposure). Other reports of $^{239}PuO_2$-induced effects from plutonium exposure include decreases in pulmonary alveolar macrophages in mice (Moores et al. 1986) and depressed antibody-forming cells in hamsters (Bice et al. 1979).

The highest NOAEL values and all reliable LOAEL values for immunological and lymphoreticular effects in each species and duration category are recorded in Table 3-3.

3.2.1.4 Neurological Effects

Possible associations between exposure to plutonium and mortality from brain or neurological diseases have been examined in studies of workers at plutonium production and/or processing facilities in the United States (Rocky Flats) (Wiggs et al. 1994) and the United Kingdom (Sellafield) (McGeoghegan et al. 2003; Omar et al. 1999). These studies are summarized in Table 3-2 and study outcomes for mortality are described in Section 3.2.1.1. Collectively, these studies have not found statistically significant associations between mortality rates from diseases of the central or peripheral nervous systems and exposures to plutonium among workers at these facilities.

3.2.1.5 Reproductive Effects

Possible associations between exposure to plutonium and mortality from diseases of the genitourinary tract and diseases of pregnancy have been examined in studies of workers at plutonium production and/or processing facilities in the United States (Rocky Flats) (Wiggs et al. 1994) and the United Kingdom (Sellafield) (McGeoghegan et al. 2003; Omar et al. 1999). These studies are summarized in Table 3-2 and study outcomes for mortality are described in Section 3.2.1.1. Collectively, these studies have not found statistically significant associations between mortality rates from genitourinary tract disease or diseases of pregnancy and exposures to plutonium among workers at these facilities.

No studies were located regarding reproductive effects in animals following inhalation exposure to plutonium compounds.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to plutonium compounds.

3.2.1.7 Cancer

Epidemiological Studies in Humans. Possible associations between exposure to plutonium and cancer mortality and morbidity have been examined in studies of workers at the U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). The most recent findings from these studies are summarized in Table 3-2. Compared to studies of U.K. and U.S. facilities, the Mayak cohorts had relatively high

exposures to plutonium (i.e., mean body burdens ranging from 0.09 to 9.2 kBq, with individual exposures as high as 470 kBq (Krahenbuhl et al. 2005). Collectively, the Mayak studies provide evidence for an association between cancer mortality and exposure to plutonium. Plutonium dose-response relationships for lung cancer mortality have been corroborated in three Mayak studies (Gilbert et al. 2004; Jacob et al. 2005; Kreisheimer et al. 2003). Studies of U.K. and U.S. facilities have examined cohorts of workers who had substantially lower estimated plutonium exposures and corresponding internal radiation doses than the Mayak cohorts (e.g., Sellafield: body burdens ≤1 kBq in 97% of the assessed workers [Omar et al. 1999]; Los Alamos: mean body burden 0.970 kBq, range: 0.05–3.18 kBq [Voelz et al. 1997]). Although a significantly higher incidence of cancer mortality in certain groups of plutonium workers has been found in some studies, higher cancer incidence and/or risks for tissues that received the highest plutonium radiation doses (i.e., lung, liver, bone) have not been found, making causal connections of these outcomes to plutonium exposure more uncertain (Brown et al. 2004; Carpenter et al. 1998; Gilbert et al. 1989b; McGeoghegan et al. 2003; Omar et al. 1999; Wing et al. 2004).

Mayak Production Association Workers. Studies of mortality of plutonium workers at Russian facilities are summarized in Table 3-2 (Gilbert et al. 2000, 2004; Jacob et al. 2005; Koshurnikova et al. 2000; Kreisheimer et al. 2003; Sokolnikov et al. 2008). The total Mayak cohort includes approximately 22,000 workers; plutonium monitoring data exist on approximately 28% of subjects (Gilbert et al. 2004). However, reliability of the monitoring data varies across subjects, which introduces uncertainty into stratification of the cohort by estimated plutonium body burden or internal radiation absorbed dose (i.e., Gy) or effective dose equivalents (i.e., Sv). These data yielded estimates of mean plutonium body burdens in the full cohort that ranged from 0.9 to 9.2 kBq (Krahenbuhl et al. 2005). The mean body burden, based on data considered to be the most reliable, was 9.2 kBq (range: 0–469 kBq, n=805). In an earlier analysis of the Mayak monitoring data, Gilbert et al. (2004) and Shilnikova et al. (2003) estimated body burdens and lung radiation doses for various categories of employment (e.g., dates, jobs, work conditions, monitoring and autopsy data) and exposure. The estimated job category mean body burdens ranged from 0.45 to 17.8 kBq, and the corresponding internal absorbed doses to the lung ranged from 0.016 to 2.91 Gy. The corresponding effective dose equivalents are 0.32 and 58 Sv (assuming a radiation weighting factor of 20 for α-radiation). The mean body burden for the monitored fraction of the cohort (n=6,193) was 1.84 kBq, and the corresponding internal lung absorbed dose was 0.24 Gy (Gilbert et al. 2004). Sokolnikov et al. (2008) applied recently improved individual dose estimates to 5,572 of the Mayak workers with confirmed plutonium exposure and estimated that the mean plutonium dose to the lung was 0.19 Gy (0.14 Gy for males and 0.29 Gy for females).

Collectively, the Mayak studies provide evidence for increased risk of cancer mortality (bone, liver, lung) in association with increased internal plutonium-derived radiation dose and/or body burden, with approximately 4-fold higher risks in females compared to males. Four studies estimated lung cancer mortality risk among Mayak workers and yielded similar estimates of excess relative risk per Gy of internal lung dose. Gilbert et al. (2004) estimated the excess lung cancer mortality risk (per Gy attained at age 60 years) for essentially the entire cohort of Mayak workers (n=21,790) to be approximately 4.7 per Gy (95% CI: 3.3–6.7) in males, and 19 per Gy (95% CI: 9.5–39) in females. Adjustment for smoking, based on risk estimates in subgroups for which smoking data were available, decreased these estimates only slightly: males, 3.9 per Gy (95% CI: 2.6–5.8); and females, 19 (95% CI: 7.7–51). Cancer mortality risk was linearly related to plutonium radiation dose. Excess relative risk per Gy declined strongly with attained age (Gilbert et al. 2004). Kreisheimer et al. (2003) examined lung cancer mortality risk for a subset of male Mayak workers (n=4,212) and estimated smoking-adjusted excess relative risk to be 4.50 per Gy (95% CI: 3.15–6.10). Jacob et al. (2005) used a mechanistic (i.e., multi-stage physiological) model to estimate smoking-adjusted lung cancer mortality risk in a similar cohort (n=5,058) and found the excess relative risk to be 0.11 per Sv (95% CI: 0.08–0.17); the corresponding estimate in units of absorbed radiation dose would be 2.2 per Gy (assuming a radiation weighting factor of 20 for α-radiation). An alternative model that treated smoking as a multiplicative risk factor (rather than additive), yielded an estimated excess relative risk of 0.21 per Sv (95% CI: 0.15–0.35), which corresponds to approximately 4.3 per Gy, very close to the estimates from Gilbert et al. (2004) and Kreisheimer et al. (2003). Sokolnikov et al. (2008) estimated ERRs of 7.1 per Gy (95% CI: 4.9–10) in males and 15 per Gy (95% CI: 7.6–29) in females at attained age of 60 years among 5,572 of the Mayak workers with confirmed plutonium exposure. A significant dose-response was noted and lung cancer risk was reasonably described by a linear function. The ERR declined with attained age and age at first plutonium exposure.

Risks of mortality and morbidity from bone and liver cancers have also been studied in Mayak workers (Gilbert et al. 2000; Koshurnikova et al. 2000; Shilnikova et al. 2003; Sokolnikov et al. 2008; Tokarskaya et al. 2006). Increasing estimated plutonium body burden was associated with increasing cancer mortality, with higher risk in females compared to males. Gilbert et al. (2000) examined liver cancer mortality in a cohort of Mayak workers (n=11,000). Mean plutonium body burdens for the cohort were estimated to have been 3.78 kBq in males and 6.05 kBq in females. The corresponding absorbed radiation doses to liver were 0.47 Gy in males and 0.88 Gy in females. A model in which liver cancer risk was treated as a quadratic function of plutonium body burden achieved better fit to the data than a linear model. Relative risk for liver cancer for the entire cohort was estimated to be 17 (95% CI: 8.0–26)

in association with plutonium body burdens >7.4 kBq; however, when stratified by gender, the relative risk estimate for females was 66 (95% CI: 16–45) and higher than for males (9.2; 95% CI: 3.3–23). Risk of bone cancer mortality in this same cohort (n=11,000) was estimated to be 7.9 (95% CI: 1.6–32) in association with plutonium body burdens >7.4 kBq for males and females combined (Koshurnikova et al. 2000). Risks of leukemia mortality, in the same cohort, were not associated with internal plutonium exposure (Shilnikova et al. 2003). Liver cancer risk was examined in a case-control study of Mayak workers (Tokarskaya et al. 2006). The case group consisted of histologically-confirmed cases of malignant liver tumors (n=44) diagnosed during the period 1972–1999. These were matched to members of a control group (n=111) for years of birth, gender, years of hire, and job assignments. Estimated absorbed radiation doses to the liver from plutonium ranged from 0 to 16.9 Gy (the 4th quartile range was 0.54–16.9 Gy). When stratified by absorbed radiation dose to the liver, the odds ratio for liver cancer was 11.3 (95% CI: 3.6–35.2) for subjects who experienced >2.0–5.0 Gy (relative to 0–2.0 Gy). Odds ratios for hemangiosarcomas were 41.7 (95% CI: 4.6–333) for the dose group >2.0–5.0 Gy, and 62.5 (95% CI: 7.4–500) for the dose group >5.0–16.9 Gy. Sokolnikov et al. (2008) reported averaged-attained age ERRs for liver cancer of 2.6 per Gy (95% CI: 0.7–6.9) for males and 29 per Gy (95% CI: 9.8–95) for females, and averaged-attained age ERRs for bone cancer of 0.76 per Gy (95% CI: <0–5.2) for males and 3.4 per Gy (95% CI: 0.4–20) for females. Elevated risks for bone cancer were observed only for workers with plutonium doses exceeding 10 Gy. For lung and bone cancer, the ERR declined with attained age, and for lung cancer, the ERR declined with age at first plutonium exposure.

U.K. Atomic Energy Authority and Atomic Weapons Establishment Workers. *S*tudies of mortality of plutonium workers at U.K. facilities are summarized in Table 3-2 (Carpenter et al. 1998; McGeoghegan et al. 2003; Omar et al. 1999). Although several studies have examined mortality rates in workers at the Sellafield nuclear facility (Douglas et al. 1994; McGeoghegan et al. 2003; Omar et al. 1999; Smith and Douglas 1986), the McGeoghegan et al. (2003) and Omar et al. (1999) studies attempted to estimate risks in association with plutonium exposures, as opposed to radiation exposures, in general. Omar et al. (1999) identified a cohort of plutonium workers as a subset (n=5,203) of workers who had been monitored at any time for exposure to plutonium (e.g., urinalysis). An analysis of monitoring data on these subjects provided estimates of internal uptakes of plutonium (Omar et al. 1999). Cumulative internal uptakes were estimated to range from 0 to 12 kBq, with approximately 75% of the cohort having cumulative uptakes ≤250 Bq. Cumulative radiation dose equivalents for plutonium were estimated to be approximately 3,280 Sv for bone surfaces, 44.5–896 Sv for lung, and 421 Sv for liver; however, analyses of dose trends were of the combined dose equivalents from plutonium and external radiation. In a comparison of mortality rates for plutonium workers compared to other radiation workers (i.e., those

never monitored for plutonium exposure), mortality rate ratios were not significant for deaths from cancer (1.05, all causes of cancer) or all causes other than cancer (0.98). Mortality rate ratios significantly decreased in association with increasing effective dose equivalents for plutonium and external radiation combined (trends for plutonium doses were not reported). However, when stratified by specific causes of death, mortality rate ratios were not significantly elevated ($p \geq 0.05$) for the tissues that received the highest plutonium radiation doses (lung, 1.12; liver, 0.85; bone, 0.00), nor were there significant positive trends with radiation dose (external plus internal plutonium dose). The mortality rate ratio was significantly elevated for breast cancer (7.66, $p<0.01$) and cerebrovascular disease (1.27, $p<0.05$). McGeoghegan et al. (2003) examined cancer mortality in a cohort of female Sellafield workers (n=6,376), from which a subset (n=837) of women who had been monitored for plutonium exposure was identified as plutonium workers. This cohort overlapped considerably with that studied by Omar et al. 1999). Effective dose equivalents to the lung from plutonium were estimated to have ranged up to 178 mSv (mean: 3.45 mSv, 5^{th}–95^{th} percentile range: 0.36–8.89 mSv). Comparisons of mortality rates between plutonium workers and other radiation workers yielded significantly elevated mortality rate ratios for all deaths (2.20, $p<0.01$), all cancers (3.30, $p<0.01$), breast cancer (3.77, $p<0.05$), circulatory disease (2.18, $p<0.05$), and ischemic heart disease (4.46, $p<0.01$). Mortality rate ratios were not elevated for cancers in tissues that received the highest plutonium radiation doses (lung, 2.36; bone; 0.00; digestive organs including liver, 3.90). Excess relative risks (per Sv) were estimated for external radiation, but not for plutonium, and were not statistically significant. Collectively, the Omar et al. (1999) and McGeoghegan et al. (2003) studies did not find elevated mortality rate ratios for the tissues that received the highest plutonium radiation doses among plutonium workers compared to other radiation workers (lung, liver, bone), and did not find significant positive trends in cancer mortality or incidence in these tissues with plutonium radiation dose. Although both studies found elevated mortality rate ratios in other selected organ categories (e.g., breast cancer), the associations between these outcomes and plutonium exposure are more uncertain, given the negative findings for lung, liver, or bone, and that other tissues, such as breast, received a much smaller radiation dose. The findings for all cancers and breast cancer may also have been influenced by the relatively low standardized mortality ratios (<100) for these end points in the other radiation workers (the comparison cohort to the plutonium workers), indicative of a "healthy worker effect", that was not evident in the plutonium worker cohort.

Carpenter et al. (1998) examined cancer mortality in workers at U.K. nuclear facilities (n=40,761) from which a subset (n=12,498), who had been monitored for plutonium exposure, was identified as plutonium workers. Plutonium exposures (i.e., Bq) or doses (i.e., Gy, Sv) were not included in this analysis; however, the number of years since first monitored or the total number of years monitored were

considered as surrogates for duration of plutonium exposures. Mortality rates for plutonium workers were not significantly elevated when compared to workers who were never monitored for radiation exposure (to any nuclide). However, when stratified by number of years since monitored or by number of years monitored, significant trends were found for increasing mortality rate ratios (monitored compared to never monitored) for all cancers ($p<0.05$) in association with increasing years of monitoring.

U.S. Nuclear Facilities (Hanford, Los Alamos, Rocky Flats). Lung cancer mortality in plutonium workers employed at the Rocky Flats nuclear weapons plant has been examined in a case-control study (Brown et al. 2004). Lung cancer cases (n=180) were employed at the Rocky Flats facility for at least 6 months during the period 1952–1989, when plutonium pits were fabricated at the facility. The control group (n=720) consisted of Rocky Flats workers who were matched with cases for age, birth, year, and gender. Internal lung radiation doses in the cohort derived primarily from exposures to ^{239}Pu, ^{240}Pu, ^{241}Pu, ^{241}Am, and ^{238}U; however, 98% of the internal effective dose equivalents in cases (96% in controls) were estimated to have come from Pu and ^{241}Am (inbred from ^{241}Pu). Estimated effective dose equivalents for internal α-radiation (cases plus controls) ranged from 0 (54%) to >940 mSv (5%). In the full cohort, the odds ratio for lung cancer mortality was significant for the internal lung dose strata 400–644 mSv, but was not significantly elevated at higher doses; there was no significant trend with dose (2.71, 95% CI: 1.20–6.09); the odds ratios were <1 for most dose categories for persons employed for <15 or >25 years. When the analysis was restricted to workers employed at the facility for 15–25 years, a significant trend was evident for increasing odds ratio in association with increasing internal lung effective dose equivalents; however, there was no evidence of a positive trend for those employed for <10 or ≥25 years.

Some of the highest exposures to plutonium at Los Alamos occurred during the period 1944–1945 (i.e., Manhattan Project) when occupational safety procedures for handling of plutonium were not as complex or well-regulated as more recent procedures (Hempelmann et al. 1973). A small cohort of adult males (n=26) who worked at the Los Alamos facility at that time have been followed and assessed for health effects (Hempelmann et al. 1973; Voelz and Lawrence 1991; Voelz et al. 1997). Based on urine monitoring (up to 1994) and/or postmortem tissue analyses, plutonium body burdens ranged from 50 to 3,180 Bq (median: 565 Bq), and effective dose equivalents ranged from 0.2 to 7.2 Sv (median: 1.25 Sv; Voelz et al. 1997). Mortality in the group was compared to that in a group of workers (n=876) employed at Los Alamos during the same period who had no history or evidence of exposure to plutonium (Voelz et al. 1997). At the time of the study (1994), seven deaths had occurred; three from cancer (bone, lung, prostrate), two from diseases of the circulatory system, one from respiratory disease, and one from external causes. The single bone cancer death greatly exceeded expected numbers (0.01 deaths;

standardized mortality ratio [SMR]=96; 95% CI: 1.26–536). Similarly the lower 95% confidence limit on the mortality rate ratio for bone cancer was >1. Standard mortality ratios and mortality rate ratios for other deaths were not statistically significant.

A larger cohort study was examined for cancer mortality in Los Alamos workers (n=15,527 males) employed at the facility during the period 1943–1973 (Wiggs et al. 1994). From this larger cohort, a subset (n=3,775) had been monitored for plutonium exposure and, on that basis, were identified as plutonium workers in the study. Mortality incidence rates for plutonium workers who were estimated to have internal plutonium depositions ≥74 Bq (n=303) were compared to workers with depositions <74 Bq (n=3,472). Cancer mortality rate ratios were not statistically significant (e.g., all cancers, cancers of the respiratory tract or lung, bone, or lymphopoietic and hematopoietic systems).

Workers at the Hanford plutonium production and processing facility have been examined for possible associations between cancer mortality and exposure to ionizing radiation (Gilbert et al. 1989b; Wing and Richardson 2005; Wing et al. 2004). Gilbert et al. (1989b) examined mortality in association with external radiation exposure and internal plutonium among workers at the Hanford plant. From the total cohort of workers (n=31,500), a subset of workers who had confirmed plutonium depositions (n=457) were identified. The cohort was stratified into exposure categories based internal depositions relative the maximum permissible body burden (MPBB) at that time (1,480 Bq): no evidence of deposition, deposition <5% of MPBB (<74 Bq), or deposition ≥5% of MPBB. Approximately 30% of the confirmed depositions were between 5 and 99% of the MPBB (74–1,465 Bq) and 1.3% were ≥100% of the MPBB. The study found no evidence for statistically significant excess cancer mortality or trends in cancer mortality with external radiation or Pu internal deposition (i.e., for all cancers, or cancers of the digestive tract, lung, lymphatic and hematopoietic tissues, or prostate). Wing et al. (2004) examined mortality in association with duration of engagement in plutonium-associated jobs as a surrogate for plutonium exposure or dose estimates. From the total cohort of workers (n=26,389), subsets of workers who had activities in routine plutonium-associated jobs (n=3,065) or nonroutine jobs (n=8,266) were identified (of these, only 377 had confirmed systemic plutonium deposition). Workers in the plutonium-associated jobs category had lower death rates from all cancers, cancers of the lung, and “plutonium-cancers” (lung, liver, bone, and connective tissue) than other Hanford workers. However, a significant trend for increased mortality from nonexternal causes of death with increasing duration at routine plutonium-associated jobs was observed (1.1% increase in mortality per year, standard error [SE]=0.06). When stratified by age, the trend was stronger among workers ≥50 years of age (2.0±1.1% per year), compared to ages <50 years (0.1±0.9% per year). The strongest trend was for lung cancer (7.1±3.4% per year).

Studies in Animals. Consistent with findings from human epidemiological studies, results of animal studies show that tissue location of plutonium-induced cancer is compound dependent. Compound-related differences in cancer location reflect differences in distribution of plutonium following inhalation; a significant amount of plutonium from the relatively soluble $^{238}PuO_2$ and $^{239}Pu(NO_3)_4$ compounds is distributed to bone and liver. In contrast, the relatively insoluble $^{239}PuO_2$ is primarily retained within the lungs and associated lymph nodes (DOE 1987f, 1988a), with approximately 10, <1, 0.2, and 0.002% relocating to liver, skeleton, spleen, and kidney, respectively (Muggenburg et al. 2008) (see Section 3.4, Toxicokinetics). Experiments in the ITRI and PNL dogs provide the most extensive database on radiation-induced cancer following inhalation exposure to plutonium. Information on plutonium-induced cancer as a primary cause of death is reviewed in Section 3.2.1.1.

In addition, Muggenburg et al. (2008) provided evidence against the "hot particle" theory, which hypothesized that larger particles with higher activity and less uniform distribution might be more likely to cause cancer than smaller, more uniformly dispersed particles. The authors exposed dogs to three uniform sizes of plutonium particles (0.75, 1.5, and 3.0 μm AMAD, representing activities spanning more than 2 orders of magnitude from 0.048 to 7.7 mBq) and conducted a composite lifespan study. They found that smaller and more uniformly distributed particles have the same or greater potential to produce neoplasms than less uniformly distributed larger particles.

Exposure of Dogs to $^{238}PuO_2$. Bone tumors (predominantly osteosarcomas) were the primary cause of cancer deaths in dogs exposed once to $^{238}PuO_2$ aerosols; lung tumor incidences were also relatively high in these dogs and liver tumors appeared to be a contributing cause of death in a few $^{238}PuO_2$-exposed dogs (Muggenburg et al. 1996; Park et al. 1997). In the ITRI study (Muggenburg et al. 1996), initial ^{238}Pu lung burdens ranged from 0.15 to 43.1 kBq/kg. Incidences of bone, lung, and liver tumors as the cause of death were 93/144, 36/144, and 2/144 dogs, respectively. The tumors appeared beginning at about 3 years postexposure; liver tumors appeared later than bone and lung tumors. In the PNL study (Park et al. 1997), mean initial ^{238}Pu lung burdens ranged from 0.01 to 18.9 kBq/kg. Incidences of bone, lung, and liver tumors were 34/116 (29%), 31/116 (27%), and 8/116 (7%), respectively. More deaths were due to bone tumors than lung tumors, although the average cumulative alpha radiation dose to the lung was higher than that to the skeleton. Bone tumors occurred more frequently in the axial skeleton than in the appendicular skeleton (Park et al. 1997). One of 20 control dogs was euthanized due to lung tumors and 1 control dog had a nonfatal liver tumor. Most lung tumors in the $^{238}PuO_2$-exposed ITRI and PNL dogs were located in peripheral lung, rather than central airways, and the majority were classified as

bronchoalveolar carcinomas and papillary adenocarcinomas (Muggenburg et al. 1996; Park et al. 1997). No single histopathological type of liver tumor was identified as the most frequent. Bile duct tumors were also observed in the $^{238}PuO_2$-exposed ITRI and PNL dogs (Muggenburg et al. 1996; Park et al. 1997).

Exposure of Dogs to $^{239}PuO_2$. In contrast to the high incidences of bone tumors in the dogs exposed to $^{238}PuO_2$ or $^{239}Pu(NO_3)_4$ aerosols, cancer deaths in dogs exposed to aerosols of the relatively insoluble $^{239}PuO_2$ were predominantly associated with lung tumors, as reported in a 20-year lifespan composite study (Muggenburg et al. 2008). The study included 18 control dogs and 108 $^{239}PuO_2$-exposed dogs per sex, including seven dose groups with average ILBs of 0.16, 0.63, 1.6, 3.7, 6.4, 14, and 29 kBq/kg lung. A total of 125 of the $^{239}PuO_2$-exposed dogs developed primary lung tumors and died between days 1,086 and 6,123 after receiving radiation lung doses between 1.7 and 80 Gy. The lowest absorbed dose for radiation pneumonitis in the dogs was in excess of 10-fold higher than that reported for humans by Newman et al. (2005).

Most of the lung cancers were papillary adenocarcinomas (n=70) followed by bronchiolo-alveolar carcinomas (n=40) and adenosquamous carcinomas (n=22). The frequency of lung cancer occurrence exceeded that of radiation pneumonitis at the lower doses, but radiation pneumonitis dominated at doses above an ILB of 3.7 mBq/kg; there was insufficient time for cancer development at ILBs >14 kBq/kg (Muggenburg et al. 2008). Earlier and shorter studies reported bronchiolo-alveolar carcinoma as the most frequently identified cancer type. (DOE 1987f, 1988a, 1990a; Hahn et al. 1999; Weller et al. 1995b). At exposure levels used in those studies, surviving dogs were at high risk for lung tumors. In the dog study performed at PNL (DOE 1988a, 1990a; Weller et al. 1995b), death due at least in part to lung tumors was noted in 52/116 plutonium-exposed dogs versus 4/20 control dogs.

Among the various studies, few dogs died from tumors of the bone, liver, or kidney where the respective radiation doses to those organ systems were approximately 2, 4, or 5 orders of magnitude lower than that to the lungs. Although up to 10 and 1% of the plutonium deposited in the lung relocated to liver and skeleton, respectively, tumor incidences in liver and skeleton of plutonium-exposed were not significantly different from those of controls (Muggenburg et al. 2008). Although bone tumors were reported as a primary cause of death in three PNL dogs from the two lowest exposure groups (mean ILBs of 0.01 or 0.064 kBq/kg (DOE 1988a), they were not observed in dogs with higher ILBs and may not have been $^{239}PuO_2$-induced. Death due to radiation pneumonitis in dogs with higher ILBs would be expected to preclude late-developing lung tumors or tumors in organs where significantly lower radiation doses would

make them relatively unlikely to occur. Time-to-death in dogs with primary lung tumors ranged from 1,086 days for a bronchioloalveolar carcinoma at 1.7 Gy to 6,123 days for a squamous cell carcinoma at 80 Gy. Neither bone nor liver tumors were reported in the $^{239}PuO_2$-exposed ITRI dogs (Hahn et al. 1999; Muggenburg et al. 2008).

Exposure of Dogs to $^{239}Pu(NO_3)_4$. The pattern of tumor development in PNL dogs exposed to $^{239}Pu(NO_3)_4$ was similar to that of dogs exposed to $^{238}PuO_2$, with tumors observed in lung, bone, and liver (principally of bile-duct epithelium) (Dagle et al. 1996; DOE 1988b, 1994a). Bone tumors were the main cause of death in the exposure groups with mean initial lung burdens of 1.02 and 5.91 kBq/kg, exposure levels at which incidences of dogs with bone tumors were 10/20 and17/20, respectively (DOE 1994a). Three of 20 dogs in the next lower exposure group (initial lung burden of 0.19 kBq/kg) also exhibited bone tumors. No bone tumors were observed in the lowest exposure groups (mean initial lung burdens of 0.028 or 0.0069 kBq/kg) or control dogs. Bone tumors were found in axial and appendicular skeleton and primarily consisted of osteogenic sarcomas arising from endosteal surfaces (DOE 1994a). In an interim report (DOE 1988b), lung tumors were a main cause of early death in 2/20, 6/20, and 11/20 dogs in the groups with mean initial lung burdens of 0.19, 1.02, and 5.91 kBq/kg, respectively. Final lung tumor incidences were not located in available reports of $^{239}Pu(NO_3)_4$-exposed PNL dogs. Incidences of liver tumors were 1/20, 0/20, 3/20, 3/20, 3/20, 5/20, and 0/20 in unexposed controls, vehicle controls, and low-to-high exposure groups (mean initial body burdens of 0.0069, 0.030, 0.19, 1.02, and 5.91 kBq/kg), respectively (DOE 1994a). At the highest exposure level, early deaths from other causes may have precluded the development of liver tumors.

Exposure of Other Laboratory Animal Species. Lung tumors have been associated with exposure to $^{239}PuO_2$ aerosols in rats (Dudoignon et al. 2001, 2003; Herbert et al. 1993; Lundgren et al. 1995; Oghiso and Yamada 2003a; Oghiso et al. 1994b, 1998; Sanders and Lundgren 1995; Sanders and Mahaffey 1979; Sanders et al. 1988a, 1988b, 1993b), mice (Lundgren et al. 1987), and primates (Hahn et al. 1984; Metivier et al. 1974). Two of 32 baboons developed lung tumors following exposure to $^{239}PuO_2$ aerosols at levels resulting in initial ^{239}Pu lung burdens ranging from 10.6 to 267 kBq/kg lung (Metivier et al. 1974). Lung tumors have also been reported in rats exposed to $^{238}PuO_2$ aerosols (Sanders et al. 1977).

Hamsters appear to be resistant to lung tumor induction following inhalation of plutonium. No statistically significant increases in tumor incidence occurred in lifetime studies of Syrian hamsters exposed once or repeatedly (seven exposures during 12 months) to $^{238}PuO_2$ or $^{239}PuO_2$ aerosols at levels resulting in initial or reestablished ^{238}Pu or ^{239}Pu lung burdens ranging from 52 to 130 kBq/kg (Sanders

1977). Hamsters were also resistant to radiation-induced lung cancer following exposure to other alpha-emitting radionuclides, such as radon and radon daughters (Agency for Toxic Substances and Disease Registry/EPA 1990).

All cancer effect levels (CELs) for dogs and nonhuman primates exposed to aerosols of plutonium compounds are recorded in Table 3-3 and plotted in Figure 3-1.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death or lifespan shortening in humans after oral exposure to plutonium.

In neonatal rats, given a single $1.2x10^4$ kBq ^{238}Pu /kg dose (as plutonium citrate) by gavage, 45% mortality was observed by 2 weeks postexposure; no deaths were reported following dosing at 3.7 kBq/kg (Fritsch et al. 1987).

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, hematological, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans or animals after oral exposure to plutonium.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to plutonium.

Gastrointestinal effects were observed in neonatal rats following oral administration of ^{238}Pu/kg (as plutonium citrate) by gavage (Fritsch et al. 1987). Mild hypertrophy of the crypts of the small intestine, which form the secretions of the small intestine, was observed in the rats receiving a 5,300 kBq ^{238}Pu/kg dose. Total disappearance of epithelial cells and crypts, combined with intestinal hemorrhaging, was observed in rats that received 17,400 kBq ^{238}Pu /kg (Fritsch et al. 1987). Increased neutrophils were noted on the surface epithelium and superficial cellular layers of the large intestine in adult rats given 155 μCi $^{238}PuO_2$/kg (5,740 kBq/kg) (Sullivan et al. 1960). This effect was noted at 3 (but not 6) days postexposure.

No studies were located regarding the following health effects in humans or animals after oral exposure to plutonium:

3.2.2.3 Immunological and Lymphoreticular Effects

3.2.2.4 Neurological Effects

3.2.2.5 Reproductive Effects

3.2.2.6 Developmental Effects

3.2.2.7 Cancer

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death or the shortening of lifespan in humans or animals after dermal exposure to plutonium.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans or animals after dermal exposure to plutonium.

No studies were located regarding the following health effects in humans or animals following dermal exposure to plutonium:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

Numerous health effects studies are available for plutonium-injected animals. Results of the injection studies support the findings from the inhalation studies. For example, bone and liver tumors were observed in dogs exposed to aerosols of $^{238}PuO_2$ or $^{239}Pu(NO_3)_4$ that resulted in toxicologically significant

systemic distribution of plutonium (see Section 3.2.1). Similarly, bone and liver tumors were associated with intravenous injection of ^{239}Pu (as plutonium citrate) in dogs (Lloyd et al. 1993, 1995a, 1999a, 1999b; Taylor et al. 1991). Detected plutonium levels in testes and ovaries of mice intravenously injected with ^{239}Pu (as the citrate) provide suggestive evidence that internalized plutonium could result in the irradiation of germ cells (Green et al. 1976, 1977). However, Brooks et al. (1979) noted the lack of significantly increased frequency of chromosomal aberrations in spermatogonia of rodents following intravenous injection of ^{239}Pu (as the citrate) at levels high enough to induce marked life shortening and increased cancer incidence. Collectively, these results indicate that irradiation from internalized plutonium is not of particular reproductive toxicity concern.

Because adequate information is available regarding health effects in animals following inhalation exposure to aerosols of plutonium compounds that resulted in toxicologically significant levels of internalized plutonium, the results of the injection studies are not presented in detail in this toxicological profile for plutonium.

3.3 GENOTOXICITY

Abundant information is available regarding the genotoxicity of ionizing radiation (refer to the Toxicological Profile for Ionizing Radiation for a detailed discussion of the genotoxic effects of various forms of ionizing radiation). The genotoxicity of alpha radiation from plutonium sources has been investigated in various groups of plutonium workers, as well as *in vivo* animal studies and a variety of *in vitro* test systems. Tables 3-4 and 3-5 present the results of *in vivo* and *in vitro* genotoxicity studies, respectively.

Although epidemiological studies do not provide conclusive evidence that plutonium produces genetic damage in humans, results of some studies provide suggestive evidence of dose-related increases in chromosomal aberrations in plutonium workers with measurable internalized plutonium. For example, Livingston et al. (2006) examined relationships between external radiation dose, internal radiation dose, and frequencies of chromosomal aberrations and micronuclei in peripheral blood lymphocytes of a group of 30 retired plutonium workers with dosimetrically-estimated internal and external radiation doses >0.5 Sv, another 17 workers with predominantly external radiation doses <0.1 Sv, and 21 control subjects with no history of occupational radiation exposure. Frequency of chromosomal aberrations was positively correlated with the bone marrow dose (alpha radiation from internalized plutonium; 168 mSv

Table 3-4. Genotoxicity of Plutonium *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian systems:			
Human (peripheral blood lymphocytes)	Chromosomal aberrations	+	Schofield 1980
Human (peripheral blood lymphocytes)	Chromosomal aberrations	(+)	Brandom et al. 1990; Hande et al. 2003, 2005; IAEA 1979; Livingston et al. 2006; Mitchell et al. 2004; Okladnikova et al. 2005; Tawn et al. 1985; Whitehouse et al. 1998
Human (whole blood)	Chromosomal aberrations	–	Hempelmann et al. 1973; Voelz et al. 1979
Monkey (peripheral blood lymphocytes)	Chromosomal aberrations	+	Brooks et al. 1992; LaBauve et al. 1980
Mouse (testes)	Chromosomal aberrations	+	Beechey et al. 1975; Generoso et al. 1985; Pomerantseva et al. 1989
Mouse (testes)	Chromosomal aberrations	–	Brooks et al. 1979; Searle et al. 1976
Mouse (bone marrow)	Chromosomal aberrations	+	Svoboda et al. 1987
Chinese hamster (testes)	Chromosomal aberrations	–	Brooks et al. 1979
Chinese hamster (liver cells)	Chromosomal aberrations	+	IAEA 1976b, 1976e
Chinese hamster (blood cells)	Chromosomal aberrations	+	DOE 1976
Syrian hamster (lung cells)	Chromosomal aberrations	+	Stroud 1977
Mouse (pulmonary alveolar macrophages)	Micronuclei	+	Talbot et al. 1986, 1989
Mouse (male germ cells)	Dominant lethal	+	IAEA 1976k; Lüning et al. 1976; Pomerantseva et al. 1989
Mouse (male germ cells)	Dominant lethal	–	Searle et al. 1976
Mouse (ovaries)	Dominant lethal	(+)	Searle et al. 1982

– = negative result; + = positive result; (+) = positive or marginal result

Table 3-5. Genotoxicity of Plutonium *In Vitro*

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Mammalian cells:				
Human (peripheral blood lymphocytes)	Chromosomal aberrations	No data	+	Purrott et al. 1980
Human (lymphoblastic cell line)	Chromosomal aberrations	No data	+	DOE 1980h
Mouse (10T1/2, 3T3 cells)	Chromosomal aberrations	No data	+	Nagasawa et al. 1990a
Mouse (bone marrow)	Chromosomal aberrations	No data	+	Kadhim et al. 1992
Chinese hamster (M3-1 cells)	Chromosomal aberrations	No data	+	Welleweerd et al. 1984
Chinese hamster (V79 cells)	Chromosomal aberrations	No data	+	Griffin et al. 1994
Chinese hamster (ovary K-1 cells)	Chromosomal aberrations	No data	+	Nagasawa et al. 1990b
Human (peripheral blood lymphocytes)	Sister chromatid exchanges	No data	+	Aghamohammadi et al. 1988
Mouse (10T1/2, 3T3 cells)	Sister chromatid exchanges	No data	+	Nagasawa et al. 1990a
Chinese hamster (ovary cells)	Sister chromatid exchanges	No data	+	Nagasawa and Little 1992; Nagasawa et al. 1990b
Human (peripheral blood lymphocytes)	Micronuclei	No data	+	Bilbao et al. 1989
Human (embryonic skin fibroblasts)	Gene mutation	No data	+	Chen et al. 1984
Chinese hamster (ovary cell line)	Gene mutation	No data	+	Barnhart and Cox 1979; DOE 1980h
Chinese hamster (V79-4 cells)	Gene mutation	No data	+	Thacker et al. 1982
Chinese hamster (V79-4 cells)	DNA double-strand breaks	No data	+	Jenner et al. 1993
Chinese hamster (V79-379A lung fibroblasts)	DNA double-strand breaks	No data	+	Fox and McNally 1990
Chinese hamster (V79-379A cells)	DNA damage	No data	+	Prise et al. 1987
Mouse-rat (hybrid cell line)	Reduction in radio-resistance	No data	+	Robertson and Raju 1980
Prokaryotic organisms:				
Salmonella typhimurium (TA100, TA98, TA1535, TA1537, TA1538, TA2420, TA2421)	Gene mutation	No data	–	DOE 1980h

— = negative result; + = positive result

median dose to the bone marrow), but not with the external radiation dose. Frequency of micronuclei did not differ significantly among the three study groups.

Significantly increased frequencies of symmetrical and asymmetrical chromosomal aberrations were reported among workers at the Sellafield (United Kingdom) plutonium facility with internalized plutonium in excess of 20% of the maximum permissible body burden (Tawn et al. 1985). Frequencies of symmetrical aberrations were significantly higher at retesting 10 years later, although no significant external radiation exposure had occurred during the 10-year interim (Whitehouse et al. 1998). This finding is consistent with the hypothesis that internally-deposited plutonium irradiates hemopoietic precursor cells (Whitehouse et al. 1998).

Internal plutonium dose-related increased frequencies in chromosomal aberrations have also been reported in peripheral blood lymphocytes of plutonium workers with estimated plutonium body burdens as high as 15.5 kBq from exposure at the Mayak plutonium facilities in Russia (Hande et al. 2003, 2005; Mitchell et al. 2004; Okladnikova et al. 2005). The increased frequencies of chromosomal aberrations in the Mayak workers persisted many years following the cessation of exposure (Hande et al. 2003, 2005; Mitchell et al. 2004).

Significantly increased frequencies of chromosomal aberrations were observed among Rocky Flats (Colorado) plutonium workers with internal plutonium burdens >740 Bq (Brandom et al. 1990; IAEA 1979). Conversely, among Manhattan Project plutonium workers followed for up to 32 years, no apparent correlation was found between the frequency of chromosomal aberrations and plutonium body burdens in the range of 0.185–15.4 kBq (Hempelmann et al. 1973; Voelz et al. 1979).

Open wounds represent a significant route through which plutonium workers might be exposed to plutonium alpha particles. Chromosomal aberrations were observed in lymphocytes among eight plutonium workers in the United Kingdom occupationally exposed to plutonium with the primary routes of exposure through wounds, punctures, or abrasions (estimated plutonium body burdens from 0.78 to 1.5 kBq). In exposed individuals, the number of dicentric aberrations averaged 5 per 500 cells, while the natural population background frequency of this aberration is 1 per 4,000 cells (Schofield 1980; Schofield et al. 1974).

Results of *in vivo* genotoxicity studies in laboratory animals consistently reveal alpha radiation-induced dose-related increases in the frequency of chromosomal aberrations following internalization of

plutonium. Chromosomal aberrations were observed in monkeys and hamsters following inhalation exposure to plutonium. Increases in chromosomal aberrations in blood lymphocytes were seen in immature Rhesus monkeys exposed to $^{239}PuO_2$ at concentrations resulting in initial lung burdens of 1.9–19 kBq ^{239}Pu/kg body weight (LaBauve et al. 1980) and Cynomolgus monkeys exposed to $^{239}Pu(NO_3)_4$ at a concentration resulting in a projected initial lung burden of 40 kBq (Brooks et al. 1992), but not at lower levels. Dose-related increases in the frequency of chromosomal aberrations were observed in Chinese hamster blood cells 30 days after exposure of the animals at aerosol concentrations resulting in deposition of 370–9600 kBq ^{239}Pu/g of lung tissue (DOE 1976). Increases in chromosomal aberrations in bone marrow cells were observed in mice following intravenous injection of ^{239}Pu (as the citrate) at 13 kBq ^{239}Pu/kg body weight (Svoboda et al. 1987). The highest incidence of these mutations was observed in the early days postinjection. Increased frequency of chromosomal aberrations was observed in liver tissue of Chinese hamsters intravenously given ^{239}Pu or ^{238}Pu (as the citrate or the dioxide) to achieve levels ranging from 0.026 to 0.74 kBq ^{239}Pu or ^{238}Pu/g of liver tissue (DOE 1976) or 74 kBq ^{239}Pu/kg body weight (IAEA 1976b). The frequency of aberrations was much higher in hamsters exposed by intravenous injection to ^{239}Pu or ^{238}Pu (as the citrate) than in hamsters exposed to $^{239}PuO_2$ or $^{238}PuO_2$ (IAEA 1976a, 1976b). Stroud (1977) reported significantly increased frequency of chromosomal aberrations in lung cells of Syrian hamsters following inhalation exposure to $^{238}PuO_2$-ZrO_2 particles at a level resulting in initial ^{238}Pu lung burden of approximately 5.2 kBq.

The induction of micronuclei in pulmonary alveolar macrophages (PAM) was noted in mice exposed to $^{238}PuO_2$ or $^{239}Pu\ O_2$ aerosols under exposure conditions that resulted in mean initial lung deposits of approximately 550 and 580 Bq, respectively (approximately 22 and 24 Bq/kg body weight, respectively) (Talbot et al. 1989). Micronuclei in PAM of control mice averaged <0.1%, whereas peak incidences of micronuclei in the $^{238}PuO_2$- and $^{239}PuO_2$-exposed mice reached 3 and 5%, respectively, at 21 days postexposure.

Increased frequency of chromosomal aberrations have been observed in spermatogonia of rodents following parenteral administration of plutonium compounds at activity levels much higher than those known to cause marked life shortening and increased cancer incidence. Markedly increased frequencies of chromosomal aberrations were observed in spermatogonia of mice receiving a single intraperitoneal injection of $^{238}Pu(NO_3)_4$ at ^{238}Pu activity levels ≥231 kBq/kg body weight (Pomerantseva et al. 1989). Increased frequency of reciprocal translocations in spermatogonia was observed in male mice 6–18 weeks after intravenous injection of ^{239}Pu (as the citrate) at 370 kBq ^{239}Pu/kg body weight (Beechey et al. 1975). An increase in the frequency of heritable translocations was also observed in spermatogonia of male mice

intravenously injected with ^{239}Pu (as the citrate) at 370 kBq ^{239}Pu/kg body weight (Generoso et al. 1985). The frequency of translocations increased as a function of time and dose. However, induction of reciprocal translocations was not significant in male mice intravenously injected with 150 kBq ^{239}Pu/kg body weight (Searle et al. 1976). No statistically significant increases in the incidence of chromosomal aberrations per spermatogonia cell were observed in mice or hamsters following intravenous administration of ^{239}Pu (as the citrate) at activity levels (ranging from 22 to 74 kBq ^{239}Pu/kg body weight) high enough to induce marked life shortening and increased cancer incidence (Brooks et al. 1979).

Dominant lethality has been observed in plutonium-exposed mice. Fetal intrauterine death occurred in female mice mated with male mice that had received ^{239}Pu (as the citrate) at levels ranging from 3.7 or 18.5 kBq 4 weeks prior to mating (IAEA 1976k; Lüning et al. 1976). The effects of the dominant lethal mutations were also observed when untreated females were mated with male mice from the F_1 generation. Exposure of male mice to higher doses of ^{239}Pu resulted in sterility 12 weeks postexposure (IAEA 1976k; Lüning et al. 1976). Pomerantseva et al. (1989) reported the induction of dominant lethal mutations in male mice that had been administered single intraperitoneal injection of $^{239}Pu(NO_3)_4$ at levels ≥0.925 kBq/g body weight 2–22 weeks prior to mating; males receiving 1.85 kBq/g body weight became sterile 9 weeks postinjection. Exposure of female mice to plutonium also resulted in dominant lethal mutations (Searle et al. 1982). Intravenous injection of female mice with ^{239}Pu (as the citrate) at 740 kBq ^{239}Pu/kg body weight resulted in marked oocyte killing and subsequently reduced number of mice which became pregnant, compared with the controls. Both pre- and postimplantation dominant lethals were induced when mating occurred at long periods (12 weeks) after intravenous exposure to plutonium.

Consistently positive genotoxicity results have been reported in various test systems exposed to the alpha radiation from plutonium compounds *in vitro* (see Table 3-5). Chromosomal aberrations were reported in human peripheral blood lymphocytes and lymphoblasts (DOE 1980h; Purrott et al. 1980); bone marrow and 10T1/2, 3T3 cells from mice (Kadhim et al. 1992; Nagasawa et al. 1990a); and M3-1, V79, and ovary K-1 cells from Chinese hamsters (Griffin et al. 1994; Nagasawa et al. 1990b; Welleweerd et al. 1984). Sister chromatid exchanges were noted in plutonium-exposed human peripheral blood lymphocytes (Aghamohammadi et al. 1988), mouse 10T1/2, 3T3 cells (Nagasawa et al. 1990a), and Chinese hamster ovary cells (Nagasawa and Little 1992; Nagasawa et al. 1990b). Bilbao et al. (1989) reported plutonium-induced micronuclei in human peripheral blood lymphocytes. Other positive genotoxicity results include gene mutation in human and hamster cell lines (Barnhart and Cox 1979; Chen et al. 1984; DOE 1980h; Thacker et al. 1982), DNA double-strand breaks in Chinese hamster V79-4 and V79-379A cells (Fox and McNally 1990; Jenner et al. 1993), DNA damage in Chinese hamster V79379A cells (Prise et al. 1987),

and reduction in radio-resistance in mouse-rat (hybrid) cell line (Robertson and Raju 1980). Results were negative for plutonium-induced gene mutation in several strains of *Salmonella typhimurium* (DOE 1980h).

3.4 TOXICOKINETICS

Studies of the toxicokinetics of plutonium have focused on two general classes of compounds: highly insoluble compounds (e.g., PuO_2) and soluble compounds (e.g., $Pu[NO_3]_4$, plutonium citrate complexes). However, factors other than solubility affect the behavior of plutonium in biological systems. These include: (1) hydrolysis reactions at physiological pH that yield highly insoluble polymers from soluble Pu(IV); (2) particle size, which affects deposition characteristics in the respiratory tract and absorption rates from the lung and gastrointestinal tract; (3) firing temperature at which the PuO_2 was formed, which may affect particle surface characteristics and susceptibility to physical transformation reactions that increase mobility and absorption; and (4) isotope specific activity, which can affect the intensity of radiation of the particles and rates of radiolytic fragmentation of particles in tissues. These various factors give rise to toxicokinetics of the various plutonium compounds that are not easily distinguished solely on the basis of water solubility. The toxicokinetics of inhaled $^{238}PuO_2$ is distinctly different from that of inhaled $^{239}PuO_2$ having a similar particle size range (>1 μm). Inhaled $^{238}PuO_2$ that deposits in the lung is much more rapidly absorbed and distributed to liver and skeleton (predominantly) compared to $^{239}PuO_2$. As a result, deposition of similar initial lung burdens of the two isotopes will result in long-term (e.g., chronic) radiation doses to liver and skeleton (i.e., bone and marrow) that are higher, and lung doses that are lower, following exposures to $^{238}PuO_2$ compared to $^{239}PuO_2$. The consequences of these different radiation doses are distinct patterns of health effects that have been observed in controlled lifetime studies in animals, with more prominent lung effects following exposures to $^{239}PuO_2$.and more prominent effects on bone, marrow, and liver following exposures to $^{238}PuO_2$ (see Section 3.2.1). The kinetics, distribution, and health outcomes of inhaled $^{239}Pu(NO_3)_4$ are similar to those of $^{238}PuO_2$.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Evidence for absorption of inhaled plutonium in humans derives from several types of measurements: (1) measurements of fecal and urinary excretion of plutonium following occupational inhalation exposures (Carbaugh and La Bone 2003; DOE 1985k, 1991c; James et al. 2003; Kathren and McInroy 1991; Kurihara et al. 2002; McInroy et al. 1991; Voelz et al. 1979; Woodhouse and Shaw 1998);

(2) postmortem plutonium levels in tissues of workers exposed to airborne plutonium (Filipy and Kathren 1996; Filipy et al. 1994; Hahn et al. 2003, 2004; Kathren and McInroy 1991; Khokhryakov et al. 2005; McInroy et al. 1989, 1991; Romanov et al. 2003; Voelz et al. 1997); (3) *in vivo* chest radiation measurements (^{241}Am) following occupational exposures to airborne ^{241}Pu (Carbaugh and La Bone 2003; DOE 1991c); and (4) experimental studies in which *in vivo* blood, urine, and organ x-ray emission were measured in subjects who inhaled ^{237}Pu nitrate (Etherington et al. 2003; Hodgson et al. 2003).

Inhaled plutonium particles that deposit in the respiratory tract are subject to three general distribution processes: (1) bronchial and tracheal mucociliary transport to the gastrointestinal tract; (2) transport to thoracic lymph nodes (e.g., lung, tracheobronchial, mediastinal); or (3) absorption by blood and/or lymph and transfer to other tissues (e.g., bone, liver). The above processes apply to all forms of deposited plutonium, although the relative contributions of each pathway and rates associated with each pathway vary with the physical characteristics (e.g., particle size), chemical form (degree of water solubility), and radiological characteristics (e.g., specific activity). The various processes that contribute to the elimination of plutonium from the respiratory tract give rise to multi-phasic lung retention kinetics. In most studies of lung retention, at least two kinetic components are evident. The faster phase is thought to be contributed by relatively rapid mechanical clearance mechanisms (e.g., mucociliary transport) and absorption to blood of soluble or relatively rapidly dissolved insoluble material deposited in the lung. The slower phase is contributed by the transformation and dissolution and/or mechanical clearance (e.g., phagocytic) of highly insoluble particles.

Etherington et al. (2003) measured plutonium kinetics in two adult subjects who inhaled an aerosol of $^{237+244}Pu(NO_3)_4$ (activity median aerodynamic diameter [AMAD]=1.1 μm; geometric standard deviation [GSD]=1.2). Lung, liver, and urine plutonium levels were estimated from K x-ray emission from the decay of ^{237}Pu; blood plutonium levels were measured by mass spectrometry of ^{244}Pu. Initial lung burdens were estimated to be 8 kBq ^{237}Pu and 35 ng ^{244}Pu. Lung retention half-times, estimated from observations made up to 120 days following the exposure, were 1.6–3.0 days (20%) for the fast phase, and 280–430 days (80%) for the slow phase. Longer-term observations of lung retention kinetics are available from studies of accidental inhalation exposures to plutonium oxide containing ^{241}Pu (Carbaugh and La Bone 2003; DOE 1991c). In these studies, lung plutonium burdens were inferred from measurements of external radiation emitted by ^{241}Am, a gamma-emitting daughter of ^{241}Pu. Estimated lung retention half-times for 10 subjects ranged from 14 to 80 years.

The relatively long retention kinetics of inhaled plutonium particles in the lung is thought to reflect, in part, rates of physical transformation and dissolution of the particles. Various estimates have been made for these rates, based on modeling of data on urinary excretion and tissue burdens of plutonium following inhalation exposures (James et al. 2003; Khokhryakov et al. 2005). Based on an analysis of data from 535 autopsies of plutonium workers, particle dissolution half-times were estimated to range from approximately 5–6 years, for exposures to highly insoluble plutonium oxides, to 1–2 years for exposures to more soluble forms (e.g., plutonium nitrate; Khokhryakov et al. 2005). James et al. (2003) estimated the lung dissolution half-time to be approximately 7 years in a subject who inhaled PuO_2 ceramic particles.

Absorption of inhaled PuO_2 has been studied in various nonhuman primate species (Brooks et al. 1992; LaBauve et al. 1980; Lataillade et al. 1995; Metivier et al. 1974, 1978b; Stanley et al. 1982). Observed lung retention kinetics were biphasic. The slow-phase retention half-time in baboons exposed to $^{238}PuO_2$ (count median aerodynamic diameter [CMAD]=2.1 μm±1.3 standard deviation [SD]) was estimated to be approximately 400 days (range: 200–600 days), based on measurements made during the first 30–170 days after exposure (Metivier et al. 1974); however with longer observation periods (>200–300 days), the half-time was estimated to be approximately 1,000 days (Metivier et al. 1978b). Lataillade et al. (1995) estimated the lung retention half-time in baboons that inhaled an aerosol of an industrial PuO_2 (AMAD=1.9 μm± 1.7 SD) consisting primarily of ^{239}Pu and ^{240}Pu (≈94 w%, 0.2 w% ^{238}Pu); the estimated half-time was approximately 66 days, for an observation period of 180 days. Slow-phase lung retention half-times measured in Cynomolgus monkeys exposed to an aerosol of $^{239}PuO_2$ (AMAD=1.6 μm; GSD=1.6) ranged from 300 to 1,800 days (LaBauve et al. 1980). In Rhesus monkeys exposed to $^{239}PuO_2$ from industrial ball milling processes (AMAD=1.5 μg±1.6 SE), the slow-phase lung retention half-time was estimated to be approximately 300 days (Stanley et al. 1982). Lung plutonium burdens have also been measured at various times in Cynomolgus monkeys exposed to aerosols of $^{239}Pu(NO_3)_4$ (AMAD=06 μm; GSD=2.1); based on these data, the slow-phase retention half-time was approximately 200–300 days (Brooks et al. 1992).

Numerous studies have examined the lung deposition and kinetics of absorption of inhaled plutonium in dogs (Bair et al. 1962b; Dagle et al. 1996; Guilmette et al. 1984, 1987; Mewhinney and Diel 1983; Muggenburg et al. 1996; Park et al. 1997). Inhaled aerosols of $^{238}PuO_2$ were more rapidly cleared from the lung than aerosols of $^{239}PuO_2$ of similar particle size distributions (Guilmette et al. 1984; Park et al. 1997). This difference has been attributed to radiolytic fragmentation of particles in the lung, resulting in more enhanced particle dissolution and absorption from the lung (Mewhinney and Diel 1983). Lung

retention half-times following exposure of young adult beagles to aerosols of $^{239}PuO_2$ (AMAD=1.6 μm±1.2 SD) were 86 days (32%) and 1,386 days (Guilmette et al. 1984). In comparison, lung retention half-times following exposure of young adult beagles to aerosols of $^{238}PuO_2$ (AMAD=1.8 μm±1.9 SD) were 174 days (84%) and 908 days (Park et al. 1997). The corresponding times to achieve 50% of initial lung burdens are approximately 500 days for exposure to $^{239}PuO_2$ and 250 days for exposure to $^{238}PuO_2$ (Park et al. 1997). Mewhinney and Diel (1983) analyzed data on lung retention in beagles exposed to $^{238}PuO_2$ of various particle sizes (AMAD 0.7, 1.7, 2.7 μm) in order to estimate fragmentation rates of the deposited particles. Estimated fragmentation rates appeared to increase with time after exposure and particle size. Corresponding fragmentation half-times at 100 days postexposure were 100–250 days and, at 500 days postexposure were 50–120 days. Particle size (AMAD 0.7–2.7 μm) had little effect on long-term lung retention (Mewhinney and Diel 1983). In beagles, short-term (i.e., <1 month) lung retention of inhaled $^{239}PuO_2$ was influenced by aerosol particle size distribution, with faster clearance from the lung as particle size decreased (Bair et al. 1962b). Long-term lung retention in beagles is also influenced by particle size. In beagles that were exposed to $^{239}PuO_2$, the slow phase lung retention half-times were 700 days (90%, AMAD=0.9 μm±1.4 SD), 1,400 days (68%, AMAD=1.6 μm±1.2 SD), and 1,800 days (78%, AMAD=2.8 μm±1.2 SD) (Guilmette et al. 1984). The method used to produce PuO_2 also appears to affect the absorption of inhaled PuO_2. Oxides produced at high temperature (i.e., high-fired, e.g., 1,000 °C) had longer lung retention than oxides produced at low temperature (i.e., low-fired, e.g., 350 °C) (Bair et al. 1973).

Inhaled aerosols of $^{238}Pu(NO_3)_4$ are also more rapidly cleared from the lung than aerosols of $^{239}Pu(NO_3)_4$ (Dagle et al. 1983, 1996). In beagles, this difference was most pronounced in the first 30 days postexposure, during which approximately 80% of the initial lung burden from $^{238}Pu(NO_3)_4$ was cleared compared to approximately 40% from $^{239}Pu(NO_3)_4$. Retention half-times were similar (≈130–150 days) for the two isotopes, for observations extending from 30 days to 1 year.

3.4.1.2 Oral Exposure

Absorption of plutonium accumulated in shellfish (mollusks) has been studied in humans. Adult subjects ingested winkles (six males, two females) or cockles (five males, one female) containing $^{239,240}Pu$ that were collected from marine waters near the British Nuclear Fuels facility at Sellafield, Cumbria (Hunt 1998; Hunt et al. 1986, 1990). The range of the ingested activity of $^{239+240}Pu$ was 6–16 Bq. Serial 24-hour urine samples were collected from each subject for up to 7 days after they ingested the mollusks. The fraction of the activity absorbed was estimated as the ratio of the observed cumulative urinary

excretion of $^{239+240}$Pu to that of the excretion predicted to occur if absorption had been complete. The latter was predicted using kinetic models of excretion of absorbed plutonium (Durbin 1972; Talbot et al. 1987, 1993). The reported mean absorption fraction was $1.7x10^{-4}$ (range: $0.2x10^{-4}$–$4.9x10^{-4}$) for subjects who ingested winkles. The estimated mean absorption fraction for subjects who ingested cockles was $3.4x10^{-4}$ (range up to $7x10^{-4}$) based on the kinetic model of Durbin (1972), which predicts approximately 1.1% of the body burden eliminated in 7 days, or $1.9x10^{-4}$ (range up to $3.9x10^{-4}$), based on the kinetic model of Talbot et al. (1987, 1993), which predicts approximately 2% of the body burden eliminated in 7 days.

Gastrointestinal absorption was also measured in three adult male volunteers following ingestion of a plutonium citrate solution along with food (Popplewell et al. 1994). Based on comparisons between measured urinary plutonium excretion for 8 or 9 days postingestion and similar assessments following intravenous injection of plutonium citrate 6 months later, calculated fractional absorption of ingested plutonium ranged from $2x10^{-4}$ to $9x10^{-4}$.

The gastrointestinal absorption fraction has also been estimated in human populations, based on analyses of inhalation and ingestion intakes, biological monitoring of plutonium excretion in urine or measurements of body burdens at autopsy. These estimates rely on model-based assumptions regarding the deposition of inhaled plutonium and the absorption fraction for plutonium deposited in the respiratory tract. Sun and Meinhold (1997) conducted an analysis of data on 34 residents of Rongelap Island who were exposed to plutonium fallout during and following the nuclear bomb detonations in the Marshall Islands. Based on measurements of urinary plutonium excretion and assumptions regarding the deposition and absorption of inhaled plutonium, the gastrointestinal absorption fraction (for diet and soil, combined) was estimated to be approximately $4.2x10^{-4}$ (range: $1.7x10^{-4}$–$7.1x10^{-4}$). Mussalo-Rauhamaa et al. (1984) conducted an analysis of plutonium body burdens in Finnish Lapps and, along with estimates of inhalation and dietary intake of plutonium (primarily from consumption of reindeer), and assumptions regarding elimination rate of plutonium, estimated the gastrointestinal absorption fraction to range from approximately $8x10^{-4}$ to $9x10^{-4}$.

The gastrointestinal absorption of plutonium has been studied in nonhuman primates, dogs, and a variety of rodent species. Most of these studies have estimated absorbed plutonium as the sum of the plutonium burden in major tissue depots (e.g., liver and skeleton), plus the plutonium excreted in urine. Double isotope techniques have also been used to estimate the gastrointestinal absorption of plutonium in nonhuman primates (USNRC 1992). In this study, ^{239}Pu(VI) bicarbonate was administered orally and

^{236}Pu(VI) bicarbonate (or ^{238}Pu) was administered intravenously to baboons and the gastrointestinal absorption fraction was estimated from the retention ratios for the two isotope ratios in tissues and cumulative excretion ratio in urine. Absorption was estimated to be 0.22% of the oral dose in fasted baboons and 0.011% in fed baboons. Gastrointestinal absorption of plutonium was measured in adult marmosets that received single gavage doses of either ^{239}Pu citrate or ^{239}Pu citrate added to powdered potato, and was based on levels of activity measured in tissues (mainly liver and skeleton) following sacrifice (Ham et al. 1994). Absorption was approximately 0.24% of the dose when administered as plutonium citrate and 0.14% of the dose when administered in potato powder.

In addition to the above studies conducted in nonhuman primates, gastrointestinal absorption of plutonium, in various isotopic and chemical forms, has been measured in pigs, dogs, and various rodent species. Results from these studies support the following general conclusions regarding factors that affect absorption: (1) in general, absorption of plutonium citrate tends to be greater than nitrate, which is greater than plutonium oxide (PuO_2) (Sullivan 1980a); (2) most estimates of absorption of plutonium citrate and nitrate in adult animals are <0.1% of the dose; (3) fasting tends to increase absorption (Bhattacharyya et al. 1986; USNRC 1992); (4) absorption is 10–1,000 times greater in neonates compared to adults, depending on the animal species and chemical form of plutonium (Sullivan 1980a, 1980b; Sullivan and Gorham 1983; Sullivan et al. 1985); (5) iron deficiency increases absorption in juvenile rats and administration of ferric iron (Fe^{3+}) to iron-deficient rats decreases absorption (Sullivan and Ruemmler 1988); and (6) absorption of plutonium in surface dusts (e.g., bomb test sites) in guinea pigs was <0.001% of the dose (Harrison et al. 1994).

3.4.1.3 Dermal Exposure

Occupational accidents have resulted in dermal exposures and/or penetration of plutonium into skin wounds and subsequent systemic absorption of plutonium (McInroy et al. 1989; Woodhouse and Shaw 1998). In one case, postmortem measurements of ^{239}Pu levels in tissues, measured 17 years following the incident, showed that liver contained approximately 41% of the body burden and skeleton contained 49% of the body burden (McInroy et al. 1989). Woodhouse and Shaw (1998) reported urinary excretion of plutonium during 20–30-year periods following various wound-related exposures to PuO_2 (oxalate), $Pu(NO_3)_4$, or plutonium metal. Systemic absorption of ^{239}Pu was estimated to have been approximately 0.001%. Plutonium absorption through the intact human palmar skin was estimated to have been 0.0002%/hour when applied as the nitrate (10 µg Pu) in a 0.4 N nitric acid solution for 8 hours (Langham

1959) and approximately 0.001%/hour following contamination of finger skin with $Pu(NO_3)_4$ in 9% HCl (Lister et al. 1963).

Studies conducted in rodents have shown that dermal absorption of plutonium is accelerated when plutonium is applied to the skin in an acid medium and increases with severity of acid burns (ICRP 1986). Plutonium has been found to migrate down hair follicles (AEC 1955) and into sweat and sebaceous glands (AEC 1970b).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Information on the general pattern of distribution of absorbed plutonium in humans is available from direct measurements of plutonium in human autopsy tissues. Such measurements generally reflect the long-term distribution pattern, in some cases being heavily influenced by discrete exposure events that occurred years before death. Although some uncertainty exists regarding the relative contributions of inhalation and oral exposures to the tissue distributions observed in the autopsy studies (in particular, those of general populations), the finding of substantial amounts of plutonium in thoracic lymph nodes is considered to be indicative of inhalation exposures to insoluble plutonium compounds.

Much more detailed information on the extra-respiratory distribution of inhaled plutonium derives from numerous studies that have been conducted in animals, including nonhuman primates, dogs, and various rodent species. The dog studies are of particular relevance to our understanding of the toxicology of inhaled plutonium. Beginning in the early 1950s, the U.S. government initiated several life-span studies of the toxicology of inhaled plutonium in beagles (DOE 1989). The results of these studies form part of the basis for our understanding of the toxicity and carcinogenicity of inhaled plutonium (see Section 3.2).

Organ Distribution of Absorbed Plutonium in Humans. Information on tissue distribution of plutonium in humans has come from the analysis of plutonium levels in postmortem tissue samples. Postmortem studies have included workers exposed occupationally (Filipy and Ford 1997; Filipy and Kathren 1996; Filipy et al. 1994; James et al. 2003; McInroy et al. 1989, 1991; Suslova et al. 2002), as well as studies of the populations from the general public (Bunzl and Kracke 1983; Ibrahim et al. 2002; Kawamura and Tanaka 1983; Mussalo et al. 1981; Mussalo-Rauhamma et al. 1984; Nelson et al. 1993; Popplewell et al. 1985; Singh and Wrenn 1983; Yamamoto et al. 2008a). Collectively, these studies have shown that approximately 95% of the systemic (i.e., absorbed) plutonium burden is found in skeleton (≈45%), liver

(≈45%), and skeletal muscle (≈5%). A substantial fraction of the total body burden (e.g., 20–70%) has also been found in the respiratory tract (including associated lymph nodes) in workers who experienced inhalation exposures (James et al. 2003; McInroy et al. 1989). Autopsy studies of subjects from the general public have found respiratory tract plutonium burdens ranging from approximately 3 to 6% of the combined burdens of respiratory tract, liver and skeleton (Ibrahim et al. 2002; Kawamura and Tanaka 1983; Singh and Wrenn 1983). Yamamoto et al. (2008a) also evaluated the activity ratios of $^{240}Pu/^{239}Pu$ in autopsy samples from individuals surrounding the Semipalatinsk Nuclear Test Site in the former Soviet Union. They determined that both isotopes were present at highest concentrations in liver followed by lungs and kidney, and that the isotopic ratios ranged from 0.088 to 0.207, which were consistent with values obtained elsewhere from exposure to atomic weapons fallout.

The highest concentrations of absorbed plutonium are usually found in liver, bone, and spleen (Filipy and Ford 1997; Filipy et al. 1994; McInroy et al. 1991; Yamamoto et al. 2008a). However, concentrations of plutonium in the respiratory tract and associated lymph nodes can exceed that of other tissues when exposures occur from inhalation (McInroy et al. 1991; Singh and Wrenn 1983). Skeletal:liver concentration ratios measured in tissues from deceased plutonium workers ranged from approximately 0.05 to 1 (Filipy and Kathren 1996). Tissue:liver concentration ratios in a deceased plutonium worker were as follows: tracheobronchial lymph node [TBLN], 100; lung, 2.6; pituitary, 1.1; skeleton, 0.23; spleen, 0.22; and other soft tissues <0.2 (McInroy et al. 1991). An analysis of tissue plutonium levels in a group of deceased plutonium workers (n=69–137) found the following soft tissue:liver concentration ratios: skeleton (0.2) and spleen (0.05–0.08); ratios for other tissues were <0.05 (Filipy and Ford 1997; Filipy et al. 1994).

The above estimates reflect measurements made at autopsy and not initial distributions of absorbed plutonium or redistribution of plutonium over time. Although processes involved in the distribution, initial deposition, and redistribution of absorbed plutonium are not clearly defined, available human and animal data collectively provide some insight. Inhaled plutonium that has entered the blood appears to be largely bound to transferrin and becomes associated with iron-binding proteins such as ferritin and lipofuscin upon entering hepatocytes (Stevens et al. 1968; Stover 1968a; Suslova et al. 2002; Taylor et al. 1991). Based on regression analysis of autopsy data from Mayak workers, approximately 50 and 38% of the plutonium entering the blood from the lung initially deposited in the liver and skeleton, respectively (Suslova et al. 2002). Liver retention decreased linearly from 50% at the beginning of exposure to 42% at 25 years postexposure, during which time skeletal deposition increased from 38 to 50%. This redistribution of approximately 8% of the total systemic content from liver to skeleton during the 25-year

postexposure period represents a translocation rate of approximately 0.32% per year. Redistribution of plutonium from other soft tissue is expected to contribute to increased skeletal content over time as well. Considerable effort and progress has been made in developing models that simulate the distribution and elimination kinetics of absorbed plutonium. These models are described in greater detail in Section 3.4.5.

Organ Distribution of Absorbed Plutonium in Animals. Numerous studies conducted in various animal models, including nonhuman primates, rodents, and dogs, provide additional evidence for distribution of absorbed plutonium to thoracic lymph nodes, liver, and skeleton, following inhalation exposures to plutonium aerosols (Bair et al. 1962b, 1966; Buldakov et al. 1972; Dagle et al. 1986; Guilmette et al. 1984; Lataillade et al. 1995; Mewhinney and Diel 1983; Morin et al. 1972; Muggenburg et al. 2008; Nenot et al. 1972; Park et al. 1972; Sanders 1973; Sanders and Mahaffey 1979; Sanders et al. 1977). These observations are consistent with the larger body of observations of the distribution of plutonium following parenteral administration of plutonium compounds (Bair et al. 1973; DOE 1989; Vaughan et al. 1973).

Studies conducted in animals have also shown that particle size and physical and chemical form of inhaled plutonium influence both the kinetics and patterns of tissue distribution of plutonium. Muggenburg et al. (2008) showed that, for monodisperse particles of 0.75, 1.5, or 3.0 μm AMAD, the smallest particles were most rapidly removed from the lungs during the first few hundred days. Thereafter, removal of the larger particles was more rapid than that of the smaller particles; this trend persisted past 6,000 days. The rate of particle distribution from the lung was greatest to the skeleton followed by liver and spleen. Activity (as percent ILB) in the skeleton increased to 1% at 6,000 days. Activity in the liver reached 10% at 1,500 days and slowly decreased thereafter. Activity in the spleen reached 0.2% at 1500 days and likewise slowly decreased afterward. Activity in the kidney initially reached 0.002% and then slowly decreased. In general, exposures to more insoluble forms of Pu (e.g., PuO_2) result in distribution (percent of ILB) of plutonium from the lungs to thoracic lymph nodes comparable to that of the liver and greater compared to that of more soluble Pu(IV) complexes (e.g., citrate, nitrate) (Bair et al. 1966, 1973; DOE 1988b, 1989; Morin et al. 1972; Muggenburg et al. 2008; Park et al. 1972). The highest concentrations of plutonium in lymph nodes were observed initially in thoracic lymph nodes. Levels in selected lymph nodes increased to 10% ILB after 500 days (thoracic lymph nodes), 10% ILB at 6,000 days (mediastinal lymph nodes), 1% ILB at 2,000 days (hepatic lymph nodes), 0.1% ILB at 6,000 days (sternal lymph nodes), and 0.01% ILB at 300 days (retropharyngeal lymph nodes) (Muggenburg et al. 2008). Whereas plutonium concentrations in the thoracic lymph nodes of $^{239}PuO_2$-exposed dogs remain high during lifetime observation, Mewhinney and Diel (1983)

demonstrated that the concentrations in the thoracic lymph nodes of $^{238}PuO_2$-exposed dogs rapidly increased to peak levels (approximately 10% of the initial lung burden) within the first year postexposure, then declined to <5% of the initial lung burden during the next 3 years. This difference in retention of plutonium by the thoracic lymph nodes is thought to result from radiation fragmentation and subsequent dissolution of the resulting smaller ^{238}Pu particles, lymphatic transport to systemic circulation, and subsequent deposition principally in liver and skeleton (Mewhinney and Diel 1983). The method used to produce PuO_2 also appears to affect the distribution of inhaled plutonium oxide. Distribution to thoracic lymph nodes, bone, and liver was greater when exposure was to chemically prepared oxides or to air-oxidized or low-fired plutonium compared to the high-fired forms (Bair et al. 1973; Sanders and Mahaffey 1979).

Distribution of PuO_2 from the respiratory tract and associated lymph nodes is affected by the size of the particles initially deposited in the lung. Larger particle sizes (e.g., 2–4 μm MMD) deposited in the alveolar region of the lung undergo less extensive mucociliary transport to the gastrointestinal tract and more extensive transfer into bronchial lymph nodes (Bair et al. 1962b, 1973; Guilmette et al. 1984). On the other hand, transfer to extra-respiratory tissues is augmented with decreasing particle size (e.g., <2 μm mass median diameter [MMD]) (Bair et al. 1973; DOE 1989). Plutonium deposited in lung from exposure to $^{238}PuO_2$ or $^{239}Pu(NO_3)_4$ is rapidly and more extensively distributed to extra-respiratory tissues than is $^{239}PuO_2$ (Dagle et al. 1983, 1996; Guilmette et al. 1984; Park et al. 1997). For example, 1,000 days after beagles were exposed to aerosols of similarly sized particles of $^{238}PuO_2$ or $^{239}PuO_2$, liver and skeletal burdens (fraction of initial lung burden) were approximately 100 times higher in dogs exposed to $^{238}PuO_2$, and lung burdens were approximately 3–5 times higher in dogs exposed to $^{239}PuO_2$ (Guilmette et al. 1984; Park et al. 1997). The isotope effect is thought to result from the relatively high specific activity of ^{238}Pu, which contributes to radiolytic fragmentation of Pu-containing particles in lung and lymph nodes, augmenting transport and distribution to lymph and blood (Bair et al. 1973; Diel and Mewhinney 1983). The distribution kinetics of inhaled $^{239}Pu(NO_3)_4$ more closely resemble those of $^{238}PuO_2$ than $^{239}PuO_2$ (Dagle et al. 1983, 1996; Park et al. 1995).

Distribution of inhaled $^{239}PuO_2$ to bone is influenced by age. In immature dogs, a 5-fold increase in distribution to the bone was seen compared to that in young adult dogs (DOE 1986c). These observations are consistent with similar observations made following parenteral administration of Pu(IV) (Bruenger et al. 1991a) and reflect higher bone turn-over in juveniles (see *Distribution within Bone*).

Maternal-fetal Transfer of Plutonium. Absorbed maternal plutonium can be transferred to the placenta and fetus (Lund and Tkatchev 1996; Prosser et al. 1994; Russell et al. 2003). Analyses of plutonium concentration in the placenta from a live birth that occurred 12 years following a work-related accidental inhalation exposure to plutonium found concentration ratios for placenta:maternal (estimated maternal body burden per kg body weight) of 0.16–0.27 (Russell et al. 2003). Analyses of plutonium in a sample of aborted fetuses from the general public found fetal:maternal concentration ratios to be <0.2 (Prosser et al. 1994). Studies in which animals received parenteral injections of plutonium (in most cases, as plutonium citrate) confirm that absorbed plutonium can be transferred to the fetus (Green et al. 1979; Kubota et al. 1993; Morgan et al. 1992; Paquet et al. 1998; Russell et al. 2003; Weiss and Walburg 1978). This distribution pathway would be expected after inhalation exposure. In baboons, fetal:maternal whole body concentration varied with the period of gestation at which the parenteral injection of plutonium occurred and were highest when plutonium was administered during early gestation: day 22, fetal:maternal=4; day 38, fetal:maternal=0.13; and day 106, fetal:maternal=0.04 (Russell et al. 2003, attributed to Andrew et al. 1977). A similar pattern has been observed in other animal species, and is thought to reflect distribution and dilution of plutonium initially transferred to the fetal-placental unit, as fetal growth progresses. A larger fraction of an administered maternal dose of plutonium is transferred to fetal-placental tissues during late pregnancy. In baboons that received a single intravenous injection of plutonium citrate during the 5th month of pregnancy, approximately 3–4% of the activity was transferred to the fetus within 7 days postadministration (Paquet et al. 1998). The fetal:maternal whole-body concentration ratio was approximately 1.3 and the tissue distribution in the fetus was similar to that observed in adult animals, with the skeleton and liver accounting for most of the plutonium activity in the fetal body. Fetal-placental burden was approximately 1% of the administered plutonium dose in guinea pigs, mice, and rats that received an injection of plutonium citrate during late pregnancy (Kubota et al. 1993; Morgan et al. 1991). Maternal-fetal transfer of plutonium, administered as an intravenous injection of plutonium citrate on day 16 of pregnancy was dose-dependent in mice, and ranged from approximately 5% of the dose following administration of 0.1 μCi/kg (3.7 kBq/kg) to approximately 1% following administration of 27 μCi/kg (100 kBq/kg; Weiss and Walburg 1978). The highest concentrations of plutonium in the fetal-placental unit are found in the yolk sac; however, as organogenesis progresses, plutonium is also found in other tissues, with the largest fraction of the fetal burden in liver and bone (Green et al. 1979; Kubota et al. 1993; Morgan et al. 1991; Paquet et al. 1998).

3.4.2.2 Oral Exposure

Studies of the distribution of plutonium in humans exposed to plutonium solely through the ingestion pathway have not been reported. Studies conducted in nonhuman primates, dogs, and various rodent species have shown that plutonium absorbed from the gastrointestinal tract is distributed predominantly (≈90%) to liver and skeleton. A study conducted in fasted adult baboons (n=4) found that, 46 days after a single gavage dose of ^{239}Pu(VI) carbonate, approximately 90% of total body burden was in the skeleton and liver, and that the skeletal:liver plutonium ratio (total burden) was approximately 1.2 (range: 0.7–1.7; USNRC 1992). Skeletal:liver ratios ranging from 1 to 4 have been observed in dogs, following oral exposures to plutonium bicarbonate and nitrate (Sullivan 1980a; Sullivan and Gorham 1983; Toohey et al. 1984), and values ranging from 1 to 8 have been observed in rats and mice (Sullivan et al. 1985).

3.4.2.3 Dermal Exposure

Occupational accidents have resulted in dermal exposures and/or penetration of plutonium into skin wounds and subsequent systemic absorption of plutonium (McInroy et al. 1989; Woodhouse and Shaw 1998). In one case involving a plutonium-contaminated finger wound, postmortem measurements of ^{239}Pu levels in tissues, measured 17 years following the incident, showed that 41 and 49% of the body burden were contained in the liver and skeleton, respectively; another 6.6% was associated with muscle tissue (McInroy et al. 1989). In a similar case of a plutonium-contaminated left finger wound (Popplewell and Ham 1989), postmortem measurements taken 18 years postaccident revealed a total estimated plutonium body burden of 2.4 kBq. The left arm axillary lymph nodes accounted for approximately 76% of the total body burden; other sites of deposition included skeleton (13%), left hand (5.5%), liver (4.5%), and left arm flesh (1%).

3.4.2.4 Other Routes of Exposure

Plutonium tissue distributions (postmortem) have been measured following intravenous injection of Pu(IV) citrate into subjects suffering from chronic disorders (Langham et al. 1980). Various analyses and summaries of these data have been published (AEC 1971; Durbin 1972; Kathren 2004; Leggett 1985). Postmortem tissue plutonium measurements for seven subjects have been reported; data for five of the subjects were obtained 1 year following exposure, data for the other two subjects were obtained 7 or 21 years after exposure. Approximately 66% of the injected dose was found in skeleton (most of which appeared to be associated with bone marrow) and 20–40% in liver (Langham et al. 1980).

Postmortem plutonium tissue distributions were also measured in healthy subjects receiving a single intravenous injection of ^{237}Pu(IV) citrate (Newton et al. 1998; Warner et al. 1994). As much as 73% of the injected ^{237}Pu dose was found in the liver at 7–230 days postinjection; approximately half of the liver ^{237}Pu concentration was achieved within the first 2 days postinjection (Newton et al. 1998). Early gonadal uptake of ^{237}Pu in four healthy males was in excess of 0.05%; mean retention between 30 and 86 days postinjection was approximately 0.015% (Warner et al. 1994).

Distribution of plutonium following intravenous injection of plutonium has been studied in nonhuman primates, dogs, and rodents (e.g., Bair et al. 1973; Bruenger et al. 1991a; Durbin et al. 1972, 1997; Guilmette et al. 1978; Polig 1989; Polig et al. 2000; USNRC 1992).

3.4.3 Metabolism

Plutonium metabolism in physiological systems consists, primarily, of hydrolytic reactions and formation of complexes with protein and nonprotein ligands. Plutonium can exist in oxidation states III–VI in solution; however, under most (if not all) physiological conditions, the predominant state is Pu(IV) (Gorden et al. 2003). At neutral pH, Pu(IV) ion rapidly undergoes hydrolysis to monomeric and insoluble polymeric plutonium hydroxides (e.g., $nPu[OH]_4$) (Taylor 1973). Pu(IV) forms complexes with a variety of physiological proteins, including albumin, globulins (e.g., transferrin), ferritin, and various low molecular weight proteins (Gorden et al. 2003; Lehmann et al. 1983; Stevens et al. 1968; Stover et al. 1968a; Taylor 1973). The dissociation constant of Pu(IV)-transferrin complex has not been measured; however, the complex appears to be less stable than Fe(III)-transferrin complex ($K_d \approx 10^{-22}$ M) (Aisen and Listowsky 1980; Turner and Taylor 1968). As a result, binding of Fe(III) to transferrin can influence the degree of binding of Pu(IV). Excess iron results in reduced binding of plutonium to transferrin (Turner and Taylor 1968). Plutonium also forms complexes with nonprotein ligands, polycarboxylates (e.g., citrate, lactate). The stability constants for the mono- and di-citrate complexes are approximately 10^{15} and 10^{30} M, respectively (Taylor 1973).

3.4.4 Elimination and Excretion

Kinetics of elimination of absorbed plutonium reflect relatively long retention times of plutonium in liver (half-time >9 years) and skeleton (half-time >20 years; ICRP 1994a, 1996a, 2001) (Leggett 1985), the dominant sites of accumulation of absorbed plutonium. Analyses of data on excretion and tissue burdens of plutonium in humans have contributed to the development of mechanistic models of plutonium kinetics (see Section 3.4.5). These models predict observed multi-phasic elimination kinetics, reflecting the

variation in kinetics and relative sizes of the major tissue depots for plutonium, with the half-time for the dominant kinetic process estimated to be 50–100 years (ICRP 1972, 1979, 1994a; Khokhryakov et al. 2002; Leggett 1985). This general pattern of multi-phasic elimination with a dominant slow phase would be expected to apply to absorbed plutonium regardless of the route of exposure. However, with inhalation exposure, additional processes influence the elimination kinetics, including physical transformation and dissolution of particles deposited in the lung, which can provide a source of replenishment of plutonium to blood and other tissues (see Section 3.4.1.1).

3.4.4.1 Inhalation Exposure

Following inhalation exposure to PuO_2, plutonium is excreted in feces and urine (DOE 1991c; Khokhryakov et al. 2004; Kurihara et al. 2002; Voelz et al. 1979). Excretion in feces peaks within 2–5 days following exposure, reflecting bronchial and tracheal mucociliary transport of deposited plutonium particles to the gastrointestinal tract (Kurihara et al. 2002); however, it persists for years after cessation of exposure (DOE 1991c; Khokhryakov et al. 2004; Voelz et al. 1979). In observations made on retired plutonium workers (n=19, ≥40 years following retirement), the median value for fecal:urine excretion ratio was 0.57 (GSD: 1.12; mean=0.83±0.73 SD) (Khokhryakov et al. 2004). Observations made at earlier times yielded higher ratios, indicating a gradual decline in the ratio with time. Group mean fecal:urine ratios in 345 workers (2–30 years postexposure) ranged from approximately 0.7 to 1.4 and were similar for oxides and nitrates (Khokhryakov et al. 2004). Voelz et al. (1979) determined a median fecal:urine ratio of 0.30 for 12 former workers in the United States.

Kinetics of urinary excretion of inhaled plutonium reflect the kinetics of dissolution and absorption of plutonium particles deposited in the lung (half-times 1–20 years) and the relatively long retention times of plutonium in liver (half-time >9 years) and skeleton (half-time >20 years) (ICRP 1994a, 1996a). Following inhalation exposure to $^{238}PuO_2$ ceramic particles, plutonium was not detected in urine until 123 days after exposure and peak excretion rates occurred approximately 1,000 days following exposure (James et al. 2003). The delay in observed urinary excretion is thought to reflect, in part, the relatively slow dissolution kinetics of the particles (half-time ≈7 years) (James et al. 2003). Over longer periods of time following exposure, urinary excretion of plutonium exhibits multi-phasic kinetics, with declining rates over time (Kathren and McInroy 1991; Suslova et al. 2006; Woodhouse and Shaw 1998). Repeated measurements of urinary plutonium excretion in 6 workers who experienced inhalation exposures to aerosols of plutonium nitrate showed that excretion rate declined with a mean half-time of 12 years (95% CI: 10–16 years), when measured at times 1,000–9,000 days postexposure (Woodhouse and Shaw

1998). Suslova et al. (2006) measured urinary plutonium excretion and terminal body burdens in 187 healthy plutonium workers. When expressed as a fraction of terminal body burden (measured at autopsy), the mean excretion rate was $1.5x10^{-5}$ d^{-1} (GSD=1.78); this corresponds to a urinary elimination half-time of approximately 127 years. The excretion rates were higher in workers who died of malignancies, cardiovascular or respiratory tract disease ($2.1x10^{-5}$ d^{-1}, half-time: 90 years), or liver disease ($2.6x10^{-5}$ d^{-1}, half-time: 73 years). Excretion rates among workers exposed primarily to more soluble forms of plutonium (e.g., plutonium nitrate; $1.4x10^{-5}$ d^{-1}, half-time: 136 years) were approximately twice those of workers exposed primarily to plutonium metal and oxides ($0.7x10^{-5}$ d^{-1}, half-time: 271 years). Kathren and McInroy (1991) analyzed data on urinary excretion of plutonium and postmortem tissue levels in five plutonium workers (four of whom were exposed to plutonium by the inhalation route) and concluded that body burdens were consistent with biphasic urinary elimination kinetics with approximate half-times of 40 and 100 years. Etherington et al. (2003) measured urinary and blood plutonium kinetics in two adult subjects who inhaled an aerosol of $^{237+244}Pu(NO_3)_4$ (AMAD=1.1 μm; GSD=1.2). Urinary clearance (expressed as a fraction of blood plutonium burden excreted per day) ranged from 0.03 to 0.1 d^{-1} during the first 30 days following exposure (corresponding half-times are 7–23 days). Medical follow-up studies have been conducted on persons exposed to plutonium during work related to the Manhattan Project (Voelz and Lawrence 1991; Voelz et al. 1979, 1985, 1997). Leggett (1985) reported an analysis of a subset of 12 subjects (Voelz et al. 1979), 30 years following the conclusion of the exposure period, and estimated urinary and fecal clearance (fraction of blood burden) to be 0.06 and 0.024 d^{-1}, respectively (corresponding half-times are approximately 12 and 29 days).

Studies conducted with nonhuman primates have confirmed that the relatively slow excretion and elimination kinetics of inhaled plutonium arise from long retention times in lung, liver, and skeleton (Brooks et al. 1992; LaBauve et al. 1980; Lataillade et al. 1995; Metivier et al. 1978b; Stanley et al. 1982). Studies conducted in dogs (i.e., beagles) have shown that lung retention is a greater contributor to slow elimination of $^{239}PuO_2$ than it is for $^{238}PuO_2$, $^{238}Pu(NO_3)_4$, or $^{239}Pu(NO_3)_4$, which are more rapidly absorbed and distributed to the liver and skeleton. In beagles, during the first few days following inhalation exposure to PuO_2 or $Pu(NO_3)_4$, fecal excretion is the dominant excretory pathway, reflecting mucociliary clearance of deposited plutonium to the gastrointestinal tract where the absorbed fraction is relatively low (e.g., <1%). Following this period of relatively rapid clearance of plutonium from the respiratory tract, fecal excretion declines and urinary excretion makes a larger contribution to elimination of the body burden, equaling or exceeding fecal excretion (Bair et al. 1973; Mewhinney and Diel 1983). However, both fecal and urinary excretion rates (percent of body burden/day) decline over time and vary

with different chemical and physical forms and isotopes of plutonium. Bair et al. (1973) compared urinary excretion kinetics during the first 100 days following exposures of beagles to $^{239}PuO_2$ (MMD 1–5 μm), $^{239}PuO_2$ (MMD 0.1 μm), $^{238}PuO_2$ (MMD 0.1 μm), or $^{239}Pu(NO_3)_4$ (MMD 0.12 μm). Urinary excretion of plutonium (per cent of body burden, 50–100 days postexposure) following exposure to $^{239}PuO_2$ (MMD 1–5 μm) was slower (≈5–10x10^{-5}% body burden/day) than following exposure to $^{239}PuO_2$ (MMD 0.1 μm; ≈1x10^{-3}% body burden/day), $^{238}PuO_2$ (≈2–3x10^{-3}% body burden/day) or $^{239}Pu(NO_3)_4$ (≈1–2x10^{-2}% body burden/day).

3.4.4.2 Oral Exposure

Enhanced urinary excretion of $^{239+240}Pu$ was observed in humans during 7 days following ingestion of mollusks containing $^{239+240}Pu$ (Hunt 1998; Hunt et al. 1986, 1990). Excretion of plutonium in urine was also observed in the first 24 hours following an oral dose of ^{236}Pu(VI) bicarbonate (or ^{239}Pu(VI) bicarbonate) administered to baboons (USNRC 1992). Priest et al. (1999) observed urinary excretion of plutonium in a human who ingested plutonium-contaminated sediments. Studies conducted in dogs and various rodent species have shown that following ingestion, absorbed plutonium is excreted in urine (Sullivan 1980a; Sullivan et al. 1985).

3.4.4.3 Dermal Exposure

Occupational accidents have resulted in dermal exposures and/or penetration of plutonium into skin wounds and subsequent systemic absorption of plutonium (McInroy et al. 1989; Woodhouse and Shaw 1998). In one case, postmortem measurements of ^{239}Pu levels in tissues, measured 17 years following the incident, showed that liver contained approximately 41% of the body burden and skeleton contained 49% of the body burden (McInroy et al. 1989). Woodhouse and Shaw (1998) reported urinary excretion of plutonium during 20–30-year periods following various wound-related exposures to PuO_2 (oxalate), $Pu(NO_3)_4$, or plutonium metal. Slow-phase urinary excretion half-times for six subjects ranged from 17 to 34 years.

3.4.4.4 Other Routes of Exposure

Plutonium excretion and tissue distributions (postmortem) have been measured following intravenous injection of Pu(IV) citrate (Langham et al. 1980; Talbot et al. 1997). Various analyses and summaries of the data from Langham et al. (1980) have been published (AEC 1971; Durbin 1972; Kathren 2004; Leggett 1985). Postmortem tissue plutonium measurements for seven subjects have been reported; data

for five of the subjects were obtained 1 year following exposure and data for the other two subjects were obtained 7 or 21 years after exposure. Whole-body retention half-times ranged from 84 to 175 years (mean: 118 years). Retention of plutonium in blood exhibited multi-phasic kinetics, with the fastest phase (52% of clearance) having a half-time of approximately 20 minutes, and the slowest phase (0.4% of clearance) having a half-time of approximately 80 days. The corresponding time to half of the initial blood burden was approximately 1 hour. Fecal excretion was the dominant pathway for excretion during the first 30 days following exposure, after which urinary excretion exceeded fecal excretion (Leggett 1985). Urinary and fecal excretion rates (fraction of blood burden excreted/day) were approximately 0.08 and 0.07 during the period 19–24 days postexposure; corresponding half-times are approximately 8–9 days (Leggett 1985).

Urinary excretion of plutonium has also been monitored in healthy volunteers following intravenous injection of ^{237}Pu (as the citrate) with a short half-life (45.66 days) compared to 24,100 years for ^{239}Pu. Mean 24-hour urinary excretion of ^{237}Pu ranged from 0.8 to 1.4% following intravenous injection of Pu(IV) citrate into 10 healthy subjects (4 males, 6 females); retention was generally greater in women than men (Talbot et al. 1997). Results of a similar study of two healthy male volunteers indicated 2.0–2.4% urinary excretion during 21 days postinjection (Talbot et al. 1993).

Excretion of plutonium following intravenous injection of plutonium has been studied in nonhuman primates, dogs, and rodents (e.g., Bair et al. 1973; Bruenger et al. 1991a; Durbin et al. 1972, 1997; Guilmette et al. 1978; Polig 1989; Polig et al. 2000; USNRC 1992).

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

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

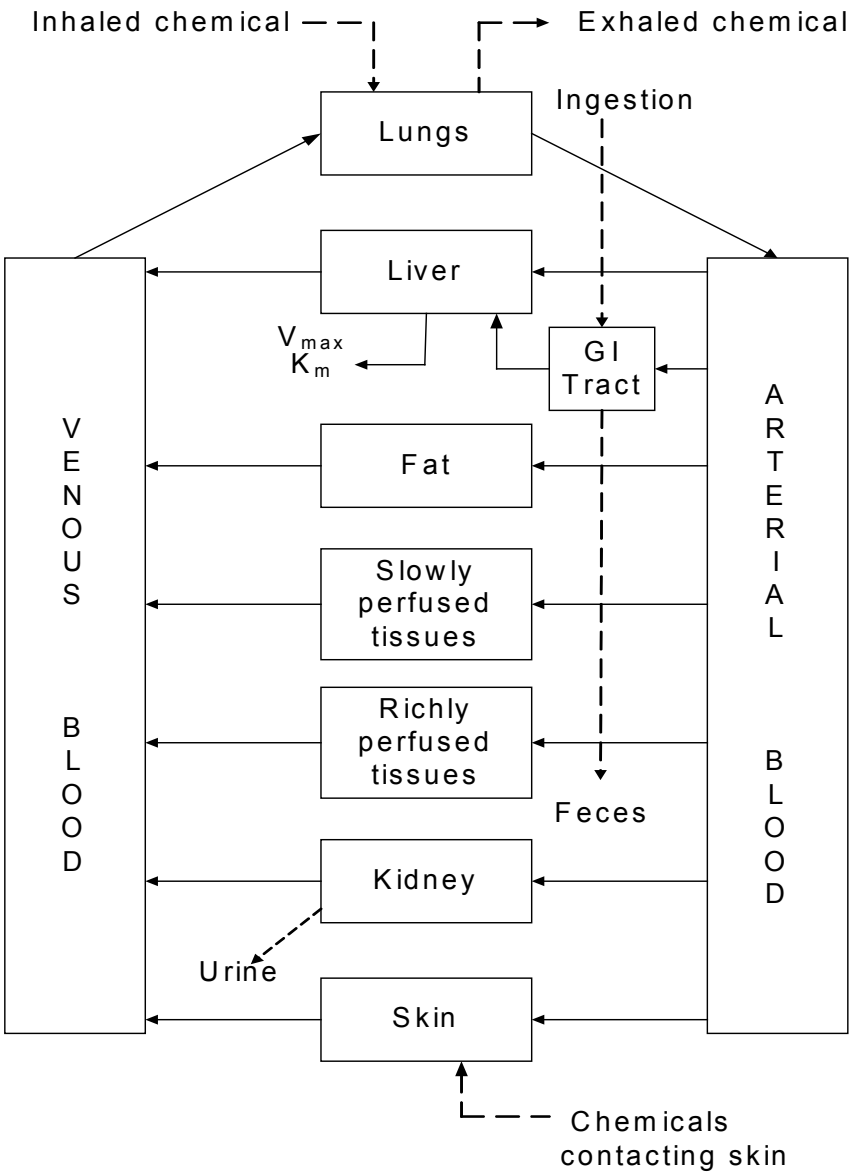
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety; and (2) the target tissue dose and observed responses (Andersen and Krishnan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

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

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-2 shows a conceptualized representation of a PBPK model. Figures 3-3–3-8 show models for radionuclides in general or specifically for plutonium.

Figure 3-2. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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

Source: adapted from Krishnan and Andersen 1994

For radionuclides, the PBPK model is replaced with a set of sophisticated physiologically based biokinetic (PBBK) models for inhalation, ingestion, and submersion. These were developed to accomplish virtually the same end as the PBPK models above, while integrating additional parameters (for radioactive decay, particle and photon transport, and compound-specific factors). Goals are to facilitate interpreting chest monitoring and bioassay data, assessing risk, and calculating radiation doses to a variety of tissues throughout the body. The standard for these models has been set by the ICRP and their models receive international support and acceptance. ICRP periodically considers newer science in a type of weight of evidence approach toward improving the state of knowledge and reducing uncertainties associated with applying the model to any given radionuclide. ICRP publications also allow for the use of situation- and individual-specific data to reduce the overall uncertainty in the results. Even though there may be conflicting data for some parameters, such as absorption factors, one can use conservative values and still reach conclusions on whether the dose is below recommended limits. One of the strengths of the ICRP model is that it permits the use of experimentally determined material-specific absorption parameter values rather than requiring the use of those provided for default types. If the material of interest does not have absorption parameter values that correspond to those in the model (e.g., Type F, M, or S), the difference can have a profound effect on the assessment of intake and dose from bioassay measurements. This has been discussed in National Radiological Protection Board (NRPB) published reports on uranium (NRPB 2002).

The ICRP (1994b, 1996a) developed a Human Respiratory Tract Model for Radiological Protection, which contains respiratory tract deposition and clearance compartmental models for inhalation exposure that may be applied to particulate aerosols of plutonium compounds. The ICRP (1986, 1990) has a biokinetic model for human oral exposure that applies to plutonium. The National Council on Radiation Protection and Measurements (NCRP) has also developed a respiratory tract model for inhaled radionuclides (NCRP 1997). At this time, the NCRP recommends the use of the ICRP model for calculating exposures for radiation workers and the general public. Readers interested in this topic are referred to NCRP Report No. 125; Deposition, Retention and Dosimetry of Inhaled Radioactive Substances (NCRP 1997). In the appendix to the report, NCRP provides the animal testing clearance data and equations fitting the data that supported the development of the human model for plutonium.

Models of the pharmacokinetics of plutonium have been developed for humans (ICRP 1972, 1986, 1994a; Khokhryakov et al. 1994, 2000, 2005; Leggett 1985; Leggett et al. 2005), dogs (Mewhinney and Diel 1983; Polig et al. 2000), rats (Durbin et al. 1972), and mice (Durbin et al. 1997). Models of plutonium

pharmacokinetics in humans that are currently being used for predicting internal exposures and radiation doses are described below.

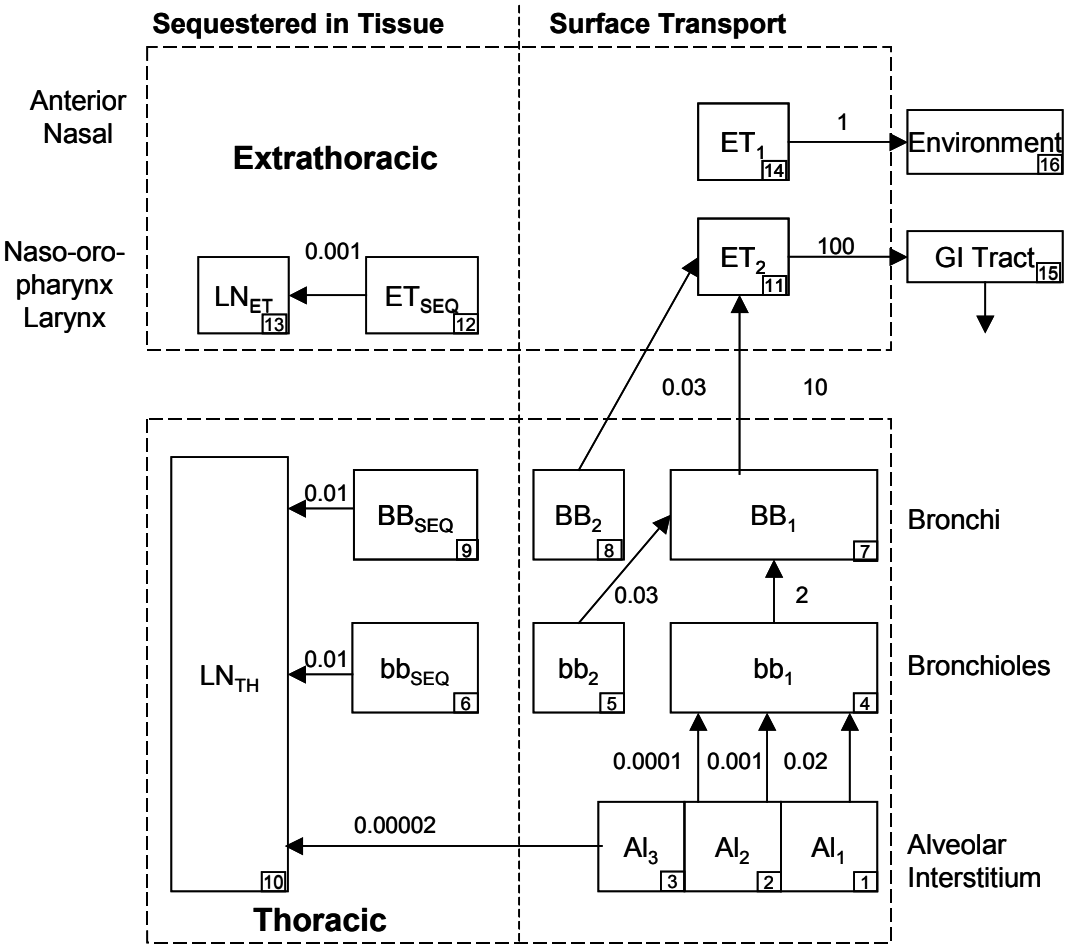
Human Respiratory Tract Model for Radiological Protection (ICRP 1994b)

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

The ICRP deposition model estimates the fraction of inhaled material initially retained in each compartment (see Figure 3-3). The model was developed with five compartments: (1) the anterior nasal passages (ET_1); (2) all other extrathoracic airways (ET_2) (posterior nasal passages, the naso- and oropharynx, and the larynx); (3) the bronchi (BB); (4) the bronchioles (bb); and (5) the alveolar interstitium (AI). Particles deposited in each of the regions may be removed and redistributed either upward into the respiratory tree or to the lymphatic system and blood by different particle removal mechanisms.

For extrathoracic deposition of particles, the model uses measured airway diameters and experimental data, where deposition is related to particle size and airflow parameters, and scales deposition for women and children from adult male data. Similar to the extrathoracic region, experimental data served as the basis for lung (bronchi, bronchioles, and alveoli) aerosol transport and deposition. A theoretical model of gas transport and particle deposition was used to interpret data and to predict deposition for compartments and subpopulations other than adult males. Table 3-6 provides reference respiratory values for the general Caucasian population during various intensities of physical exertion.

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



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

Source: ICRP 1994b

Table 3-6. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity

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

B = ventilation rate; f_R = respiration frequency; NA = not applicable; V_T = tidal volume

Source: See Annex B (ICRP 1994b) for data from which these reference values were derived.

Deposition of inhaled gases and vapors is modeled as a partitioning process that depends on the physiological parameters noted above as well as the solubility and reactivity of a compound in the respiratory tract (see Figure 3-4). The ICRP (1994b) model defines three categories of solubility and reactivity: SR-0, SR-1, and SR-2:

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

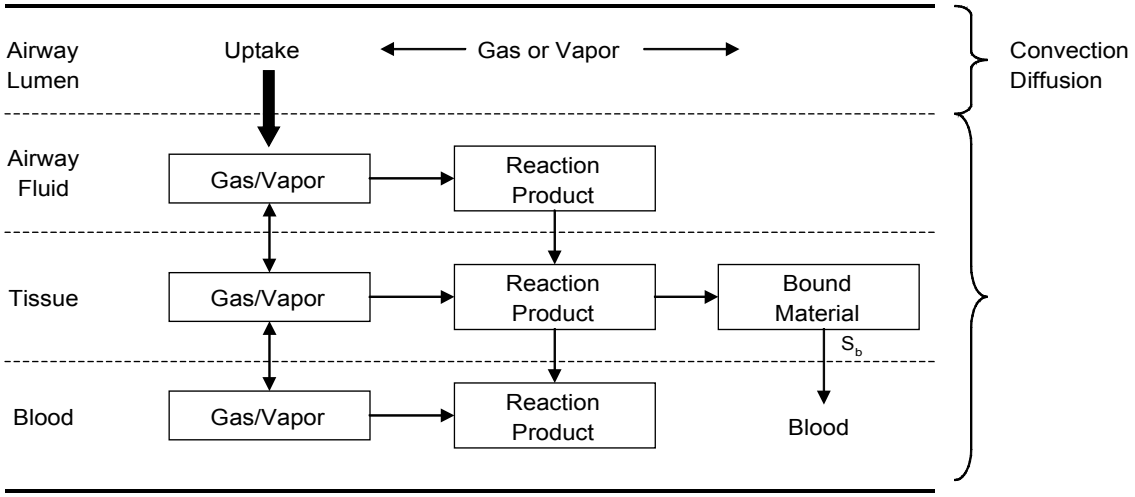
- Type SR-1 compounds include soluble or reactive gases and vapors which are expected to be taken up by the respiratory tract tissues and may deposit in any or all of the regions of the respiratory tract, depending on the dynamics of the airways and properties of the surface mucous and airway tissues, as well as the solubility and reactivity of the compound.

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

Respiratory Tract Clearance. This portion of the model identifies the principal clearance pathways within the respiratory tract. The model was developed to predict the retention of various radioactive materials. The compartmental model represents particle deposition and time-dependent particle transport in the respiratory tract (see Figure 3-3) with reference values presented in Table 3-7 (A,B). This table provides clearance rates, expressed as a fraction per day and also as half-time (Part A), and deposition fractions (Part B) for each compartment for insoluble particles. ICRP (1994b) also developed modifying factors for some of the parameters, such as age, smoking, and disease status. Parameters of the clearance model are based on human evidence for the most part, although particle retention in airway walls is based on experimental data from animal experiments.

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

Figure 3-4. Reaction of Gases or Vapors at Various Levels of the Gas-Blood Interface



Source: ICRP 1994b

Table 3-7. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part A

Clearance rates for insoluble particles				
Pathway	From	To	Rate (d^{-1})	Half-life[a]
$m_{1,4}$	AI_1	bb_1	0.02	35 days
$m_{2,4}$	AI_2	bb_1	0.001	700 days
$m_{3,4}$	AI_3	bb_1	$1x10^{-4}$	7,000 days
$m_{3,10}$	AI_3	LN_{TH}	$2x10^{-5}$	No data
$m_{4,7}$	bb_1	BB_1	2	8 hours
$m_{5,7}$	bb_2	BB_1	0.03	23 days
$m_{6,10}$	bb_{seq}	LN_{TH}	0.01	70 days
$m_{7,11}$	BB_1	ET_2	10	100 minutes
$m_{8,11}$	BB_2	ET_2	0.03	23 days
$m_{9,10}$	BB_{seq}	LN_{TH}	0.01	70 days
$m_{11,15}$	ET_2	GI tract	100	10 minutes
$m_{12,13}$	ET_{seq}	LN_{ET}	0.001	700 days
$m_{14,16}$	ET_1	Environment	1	17 hours

Table 3-7. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part B

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

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

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

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

where

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

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

Source: ICRP 1994b

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

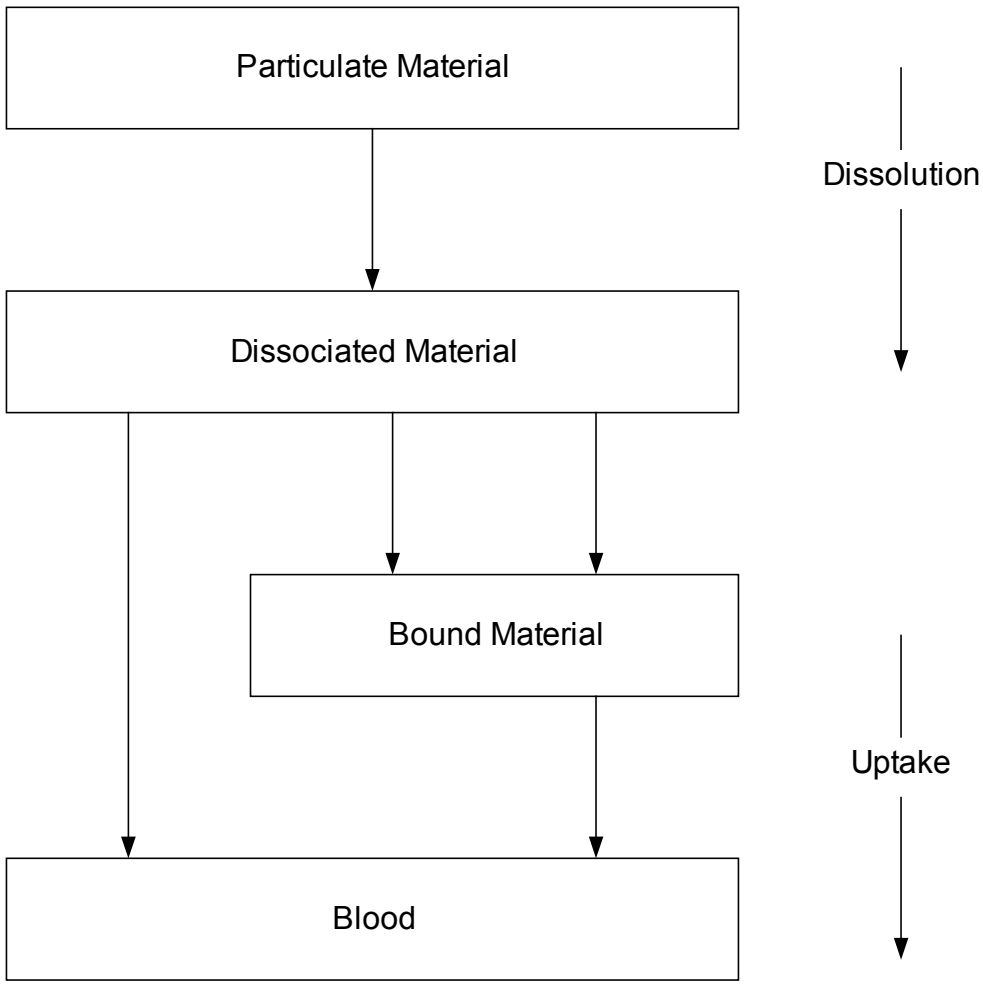
Ciliary action removes deposited particles from both the bronchi and bronchioles. Though it is generally thought that mucociliary action rapidly transports most particles deposited here toward the pharynx, a fraction of these particles is cleared more slowly. Evidence for this is found in human studies.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

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

In the alveolar-interstitial region, human lung clearance has been measured. The ICRP model uses 2 half-times to represent clearance: about 30% of the particles have a 30-day half-time, and the remaining 70% are assigned a half-time of several hundred days. Over time, AI particle transport falls, and some compounds have been found in lungs 10–50 years after exposure.

Absorption into Blood. The ICRP model assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages (ET_1), where no absorption occurs. It is essentially a 2-stage process, as shown in Figure 3-5. First, there is a dissociation

Figure 3-5. The Human Respiratory Tract Model: Absorption into Blood



Source: ICRP 1994b

(dissolution) of particles; then the dissolved molecules or ions diffuse across capillary walls and are taken up by the blood. Immediately following dissolution, rapid absorption is observed. For some elements, rapid absorption does not occur because of binding to respiratory-tract components. In the absence of specific data for specific compounds, the model uses the following default absorption rate values for those specific compounds that are classified as Types F (fast), M (medium), S (slow), and V (instantaneous):

- For Type F, there is rapid 100% absorption within 10 minutes of the material deposited in the BB, bb, and AI regions, and 50% of material deposited in ET_2. Thus, for nose breathing, there is rapid absorption of approximately 25% of the deposit in ET; for mouth breathing, the value is 50%.
- For Type M, about 70% of the deposit in AI reaches the blood eventually. There is rapid absorption of about 10% of the deposit in BB and bb, and 5% of material deposited in ET_2. Thus, there is rapid absorption of approximately 2.5% of the deposit in ET for nose breathing, and 5% for mouth breathing.
- For Type S, 0.1% is absorbed within 10 minutes and 99.9% is absorbed within 7,000 days, so there is little absorption from ET, BB, or bb, and about 10% of the deposit in AI reaches the blood eventually.
- For Type V, complete absorption (100%) is considered to occur instantaneously.

ICRP (1996a) classifies insoluble plutonium oxides as Type S and recommends assigning all other plutonium aerosols to Type M in the absence of specific information supporting an alternative classification.

ICRP (1994a) Plutonium Biokinetics Model

Description of the Model. ICRP (1990, 1994a) developed a compartmental model of the kinetics of ingested plutonium in humans that is applicable to infants, children, adolescents, and adults. The model is a modification and expansion of a similar model for plutonium (DOE/EPA 1984), described by Leggett (1985). The fraction of ingested plutonium that is absorbed (uptake to blood) is assumed to vary by chemical form and age (Table 3-8). Absorbed plutonium enters the blood plasma where it distributes to the skeleton, liver, and other tissues (Figure 3-6). Excretion pathways included in the model are plasma to urine and feces, including transfers to gastrointestinal tract from blood and liver. Transfer rate coefficients between compartments are age-specific and, depending on the specific coefficient, values can change at ages 3 months, 1, 5, 10, and 15 years, and adult (>15 years) (Table 3-8).

Table 3-8. Parameters of ICRP (1994a) Model of Plutonium Biokinetics in Humans[a]

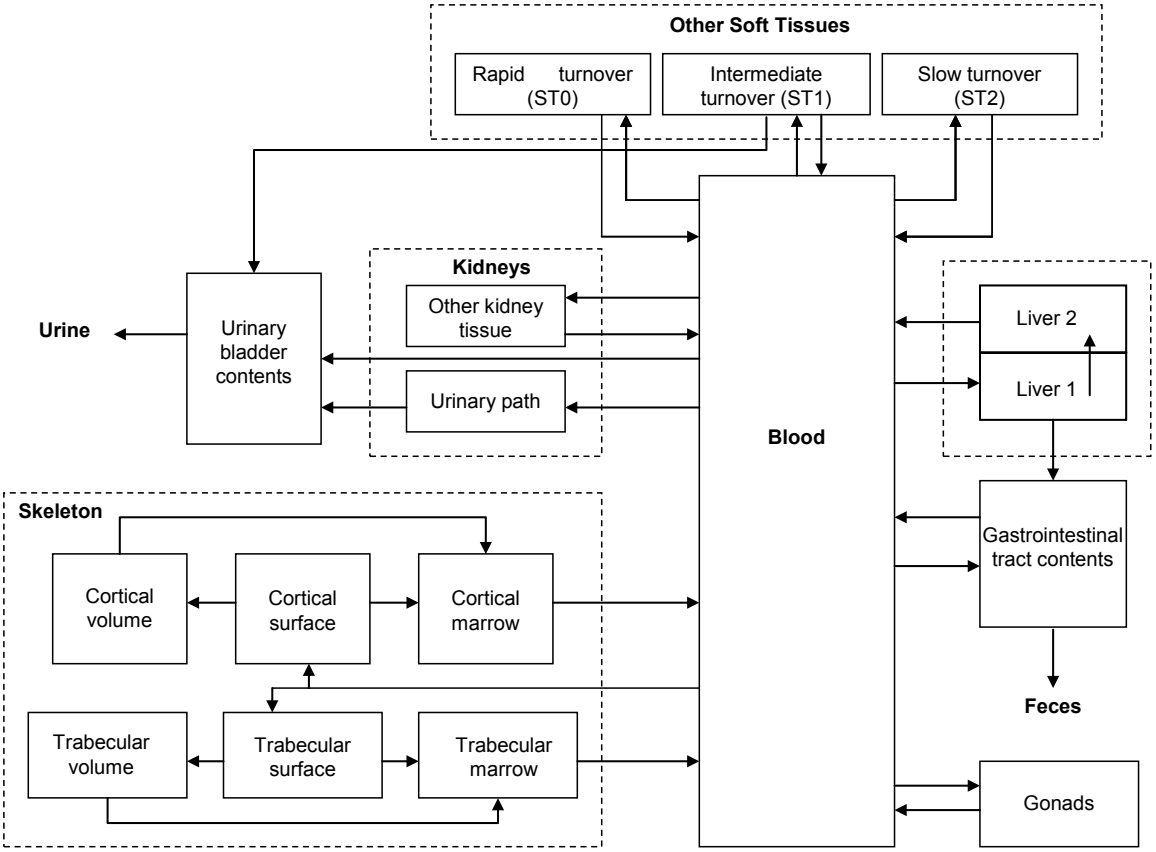
	Age					
Parameter[b]	3 months	1 year	5 years	10 years	15 years	Adult
Soft tissue (ST0) to blood	6.93×10^{-1}	6.93×10^{-1}	6.93×10^{-1}	6.93×10^{-1}	6.93×10^{-1}	6.930×10^{-1}
Soft tissue (ST1) to blood	4.75×10^{-4}	4.75×10^{-4}	4.75×10^{-4}	4.75×10^{-4}	4.75×10^{-4}	4.75×10^{-4}
Soft tissue (ST2) to blood	1.9×10^{-5}	1.9×10^{-5}	1.9×10^{-5}	1.9×10^{-5}	1.9×10^{-5}	1.9×10^{-5}
Cortical/trabecular bone marrow to blood	7.6×10^{-3}	7.6×10^{-3}	7.6×10^{-3}	7.6×10^{-3}	7.6×10^{-3}	7.6×10^{-3}
Other kidney tissue to blood	1.39×10^{-3}	1.39×10^{-3}	1.39×10^{-3}	1.39×10^{-3}	1.39×10^{-3}	1.39×10^{-3}
Liver (2) to blood	2.11×10^{-4}	2.11×10^{-4}	2.11×10^{-4}	2.11×10^{-4}	2.11×10^{-4}	2.11×10^{-4}
Gonads to blood	1.9×10^{-4}	1.9×10^{-4}	1.9×10^{-4}	1.9×10^{-4}	1.9×10^{-4}	1.9×10^{-4}
Blood to soft tissue (ST0)	2.773×10^{-1}	2.773×10^{-1}	2.773×10^{-1}	2.773×10^{-1}	2.773×10^{-1}	2.773×10^{-1}
Blood to soft tissue (ST1)	8.06×10^{-2}	8.06×10^{-2}	8.06×10^{-2}	8.06×10^{-2}	8.06×10^{-2}	8.06×10^{-2}
Blood to soft tissue (ST2)	1.29×10^{-2}	1.29×10^{-2}	1.29×10^{-2}	1.29×10^{-2}	1.29×10^{-2}	1.29×10^{-2}
Blood to trabecular surface	2.264×10^{-1}	2.264×10^{-1}	1.941×10^{-1}	1.941×10^{-1}	1.941×10^{-1}	1.941×10^{-1}
Blood to cortical surface	2.264×10^{-1}	2.264×10^{-1}	1.941×10^{-1}	1.941×10^{-1}	1.941×10^{-1}	1.294×10^{-1}
Trabecular surface to volume	8.22×10^{-3}	2.88×10^{-3}	1.81×10^{-3}	1.32×10^{-3}	9.59×10^{-4}	2.47×10^{-4}
Cortical surface to volume	8.22×10^{-3}	2.88×10^{-3}	1.53×10^{-3}	9.04×10^{-4}	5.21×10^{-4}	4.11×10^{-5}
Trabecular surface to marrow	8.22×10^{-3}	2.88×10^{-3}	1.81×10^{-3}	1.32×10^{-3}	9.59×10^{-4}	4.93×10^{-4}
Trabecular volume to marrow	8.22×10^{-3}	2.88×10^{-3}	1.81×10^{-3}	1.32×10^{-3}	9.59×10^{-4}	4.93×10^{-4}
Cortical surface to marrow	8.22×10^{-3}	2.88×10^{-3}	1.53×10^{-3}	9.04×10^{-4}	5.21×10^{-4}	8.21×10^{-5}
Cortical volume to marrow	8.22×10^{-3}	2.88×10^{-3}	1.53×10^{-3}	9.04×10^{-4}	5.21×10^{-4}	8.21×10^{-5}
Blood to other kidney tissue	3.23×10^{-3}	3.23×10^{-3}	3.23×10^{-3}	3.23×10^{-3}	3.23×10^{-3}	3.23×10^{-3}
Blood to liver (1)	6.47×10^{-2}	6.47×10^{-2}	1.294×10^{-1}	1.294×10^{-1}	1.294×10^{-1}	1.941×10^{-1}
Liver (1) to liver (2)	1.77×10^{-3}	1.77×10^{-3}	1.77×10^{-3}	1.77×10^{-3}	1.77×10^{-3}	1.77×10^{-3}
Blood to testes	1.3×10^{-5}	1.9×10^{-5}	2.2×10^{-5}	2.6×10^{-5}	2.1×10^{-4}	2.3×10^{-4}

Table 3-8. Parameters of ICRP (1994a) Model of Plutonium Biokinetics in Humans[a]

	Age					
Parameter[b]	3 months	1 year	5 years	10 years	15 years	Adult
Blood to ovaries	8.0×10^{-6}	1.0×10^{-5}	2.6×10^{-5}	4.5×10^{-5}	7.8×10^{-5}	7.1×10^{-5}
Liver (1) to small intestine	1.33×10^{-4}	1.33×10^{-4}	1.33×10^{-4}	1.33×10^{-4}	1.33×10^{-4}	1.330×10^{-4}
Blood to upper large intestine contents	1.29×10^{-2}	1.29×10^{-2}	1.29×10^{-2}	1.29×10^{-2}	1.29×10^{-2}	1.290×10^{-2}
Blood to kidney (urinary path)	6.47×10^{-3}	6.47×10^{-3}	6.47×10^{-3}	6.47×10^{-3}	6.47×10^{-3}	6.470×10^{-3}
Blood to urinary bladder contents	1.29×10^{-2}	1.29×10^{-2}	1.29×10^{-2}	1.29×10^{-2}	1.29×10^{-2}	1.290×10^{-2}
Soft tissue (ST1) to urinary bladder contents	4.75×10^{-4}	4.75×10^{-4}	4.75×10^{-4}	4.75×10^{-4}	4.75×10^{-4}	4.750×10^{-4}
Kidneys (urinary path) to bladder	1.386×10^{-2}	1.386×10^{-2}	1.386×10^{-2}	1.386×10^{-2}	1.386×10^{-2}	1.386×10^{-2}
Gastrointestinal tract to blood[c]	5.0×10^{-3}	5.0×10^{-4}	5.0×10^{-4}	5.0×10^{-4}	5.0×10^{-4}	5.0×10^{-4}

[a]See Figure 3-6 for schematic representation of model.
[b]Units are in $days^{-1}$, except for gastrointestinal tract to blood, which is unitless.
[c]Values shown for the absorption fraction are for general public exposures (e.g., diet). Recommended values for occupational exposures are as follows: oxides (excluding poly-disperse oxides), 1×10^{-5}; nitrates, 1×10^{-4}; other compounds or unknown mixtures, 1×10^{-4}.

Figure 3-6. Schematic Representation of the ICRP (1994a) Model of Plutonium Biokinetics in Humans*



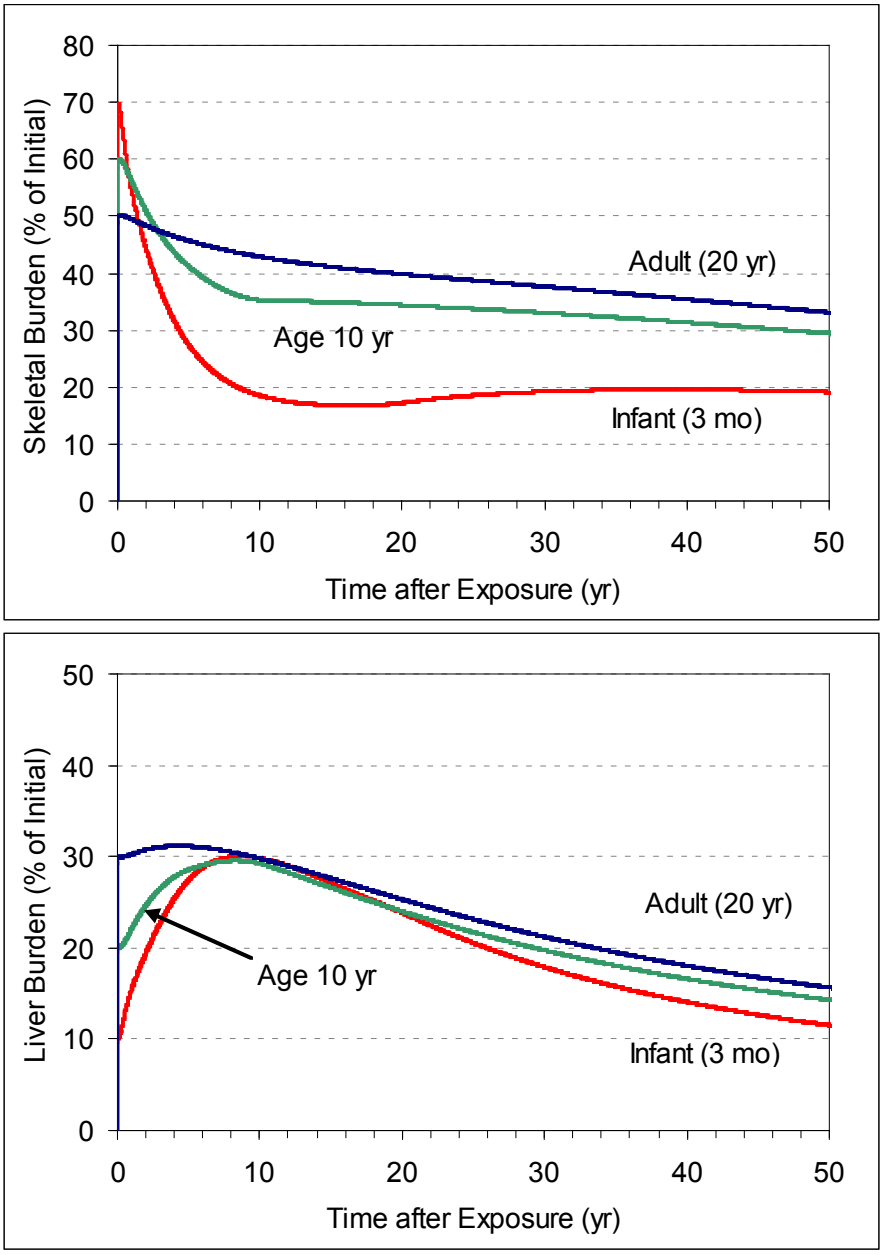
*See Table 3-8 for parameter values.

Bone is divided into trabecular and cortical components, with each further divided into bone surface, bone volume, and bone cavity (marrow compartment). Initial deposition of plutonium is assumed to occur from blood directly to bone surfaces, where it can be transferred to bone marrow or to bone volume. Elimination of plutonium in bone surface and bone volume is assumed to occur through bone marrow to blood. Transfers of plutonium within the cortical or trabecular bone compartments are modeled based on assumptions about rates of bone formation and resorption, which are assumed to be vary with age (ICRP 1990; Leggett 1985). Movement of plutonium to the marrow compartment is determined by the bone resorption rate, whereas movement from the bone surface to the bone volume is assumed to occur by burial of surface deposits with new bone and is determined by the bone formation rate. During growth, bone formation and resorption are assumed to occur at different sites within bone; therefore, the rate of removal of plutonium from the bone surface is approximated by the sum of the bone resorption rate (represented in the model by the movement of plutonium to the marrow compartment) and the rate of bone formation, which results in burial of surface deposits (represented by movement of plutonium from the bone surface to bone volume). In adults, the possibility of resorption and formation of bone occurring at the same site is assumed; therefore, only a portion (50%) of the bone formation rate results in burial of surface deposits and movement of plutonium from the bone surface to the bone volume. Rates of uptake of plutonium into bone surface are assumed to be relatively fast (half-life=3–6 days, adults) compared to rates for distribution within bone and exit from bone (half-life=10^3–10^4 days, adults; 10^2–10^3 days, children); this results in relatively rapid uptake and long retention of plutonium in bone. Rates of distribution within bone are assumed to be higher in children (by a factor of approximately 10), reflecting more rapid bone turn-over in children. Rates of uptake of plutonium into liver are assumed to be relatively fast (half-life=3–11 days) compared to elimination from liver ($t_{1/2}$=10^3 days), which results in relatively rapid uptake and long retention of plutonium in liver. Predicted kinetics of skeletal and liver plutonium burdens in adults and children, following a single dose of plutonium to blood (e.g., intravenous dose) are shown in Figure 3-7.

Validation of the Model. ICRP 1994a has been evaluated with data on plutonium excretion and postmortem tissue levels in plutonium workers (e.g., Carbaugh and La Bone 2003; Filipy and Kathren 1996; Fritsch 2007; Hodgson et al. 2003; James et al. 2003; Singh et al. 2003). Uncertainty analysis of model predictions has been reported (Suzuki et al. 2002).

Risk Assessment. The model has been used to establish the radiation dose (Sv) per unit of ingested or inhaled plutonium (Bq) for intake ages 3 months to 70 years (ICRP 1994a, 2001). The dose integration

Figure 3-7. ICRP (1994a) Model Simulation of Elimination of an Absorbed Plutonium Dose (e.g., Intravenous) from the Body in Infants, Children, and Adults



period is 50 years for acute intake as an adult (age 25 years) and from intake to age 70 years for acute intake at ages ≤15 years.

Target Tissues. The model is designed to calculate radiation dose coefficients (Sv/Bq) corresponding to specific inhalation or ingestion exposures to plutonium isotopes. Dose coefficients have been estimated for all major organs, including the bone surfaces, bone marrow, and liver, and other tissues (ICRP 1994a, 1996a).

Species Extrapolation. The model is based on both human and animal data. However, it is intended for applications to human dosimetry. Applications to other species would require consideration of species-specific adjustments in model parameters.

Interroute Extrapolation. The ICRP model is designed to simulate kinetics of ingested plutonium, injected plutonium, and if combined with a respiratory tract model (e.g., ICRP Human Respiratory Tract Model for Radiological Protection, ICRP 1994b), inhalation exposures to plutonium. The model can be applied to any other route of exposure for which the transfer rate to blood is available.

Luciani and Polig (2000) Plutonium Biokinetics Model

Description of the Model. Luciani and Polig (2000) developed a modification of the ICRP (1994a) model that provided a more physiological parameterization of urinary excretion pathways and modifications to the bone model. Modifications to the structure of the model were: (1) deletion of the transfer pathway from soft tissue ST1 to urinary bladder; (2) deletion of transfer pathways from cortical and trabecular bone surfaces to bone volume; and (3) addition of a transfer pathway from blood to bone volume (Figure 3-8). Specific changes made to rate coefficients are presented in Table 3-9.

Validation of the Model. The Luciani and Polig (2000) model was calibrated with data on long-term kinetics of plutonium in blood, urine, and feces following intravenous injection of Pu(IV) citrate into subjects suffering from chronic disorders (Langham et al. 1950, 1980; Moss and Gautier 1983; Rundo et al. 1976), and urinary excretion of plutonium in workers exposed to plutonium at the Mayak plant (Khokhryakov et al. 1994). Predicted urinary excretion of plutonium was compared to observations made on nine workers (USTUR 1993; Voelz et al. 1979, 1985). The Luciani and Polig (2000) model showed improved agreement between predictions and observations compared to the ICRP (1994a) model (Luciani

Figure 3-8. Schematic Representation of the Luciani and Polig (2000) Model of Plutonium Biokinetics in Humans

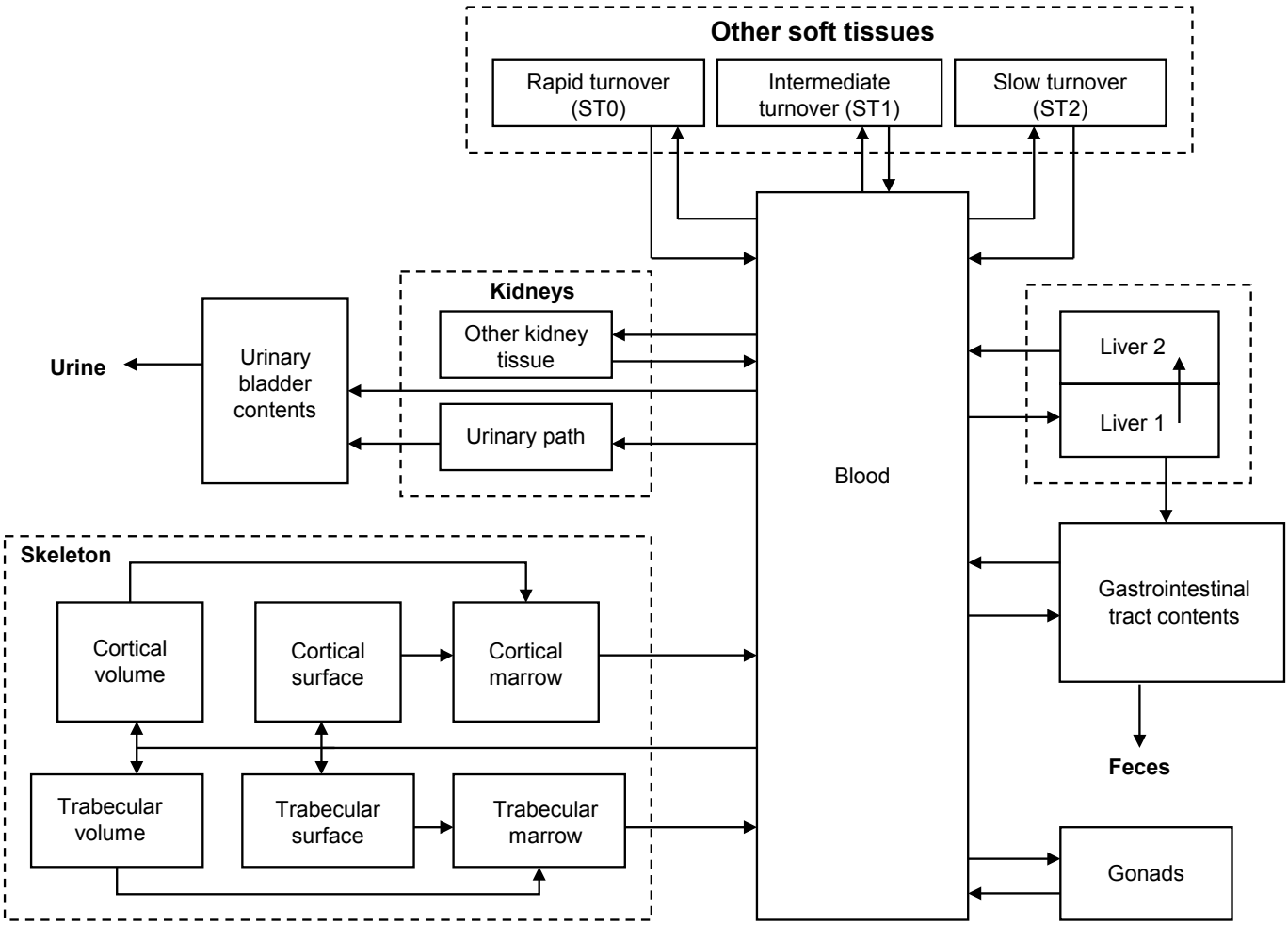


Table 3-9. Comparison of Parameters of ICRP (1994a) Model and Luciani and Polig (2000) Model of Plutonium Biokinetics in Humans[a]

	Adult parameter values	
Parameter[b]	ICRP (1994a)	Luciani and Polig (2000)
Soft tissue (ST0) to blood	6.93×10^{-1}	1.39×10^{-1} [d]
Soft tissue (ST1) to blood	4.75×10^{-4}	9.50×10^{-4} [d]
Soft tissue (ST2) to blood	1.9×10^{-5}	1.9×10^{-5}
Cortical/trabecular bone marrow to blood	7.6×10^{-3}	7.6×10^{-3}
Other kidney tissue to blood	1.39×10^{-3}	1.39×10^{-3}
Liver (2) to blood	2.11×10^{-4}	4.00×10^{-4} [d]
Gonads to blood	1.9×10^{-4}	1.9×10^{-4}
Blood to soft tissue (ST0)	2.773×10^{-1}	2.773×10^{-1}
Blood to soft tissue (ST1)	8.06×10^{-2}	8.06×10^{-2}
Blood to soft tissue (ST2)	1.29×10^{-2}	1.29×10^{-2}
Blood to trabecular surface	1.941×10^{-1}	2.26×10^{-1} [d]
Blood to cortical surface	1.294×10^{-1}	9.52×10^{-2} [d]
Trabecular surface to volume	2.47×10^{-4}	Deleted
Cortical surface to volume	4.11×10^{-5}	Deleted
Trabecular surface to marrow	4.93×10^{-4}	1.59×10^{-3} [d]
Trabecular volume to marrow	4.93×10^{-4}	1.59×10^{-4} [d]
Cortical surface to marrow	8.21×10^{-5}	1.56×10^{-4} [d]
Cortical volume to marrow	8.21×10^{-5}	8.22×10^{-5} [d]
Blood to other kidney tissue	3.23×10^{-3}	3.23×10^{-3}
Blood to liver (1)	1.941×10^{-1}	1.20×10^{-1} [d]
Liver (1) to liver (2)	1.77×10^{-3}	1.00×10^{-2} [d]
Blood to testes	2.3×10^{-4}	2.3×10^{-4}
Blood to ovaries	7.1×10^{-5}	7.1×10^{-5}
Liver (1) to small intestine	1.33×10^{-4}	4.00×10^{-4} [d]
Blood to upper large intestine contents	1.29×10^{-2}	8.0×10^{-3} [d]
Blood to kidney (urinary path)	6.47×10^{-3}	9.93×10^{-3} [d]
Blood to urinary bladder contents	1.29×10^{-2}	9.46×10^{-3} [d]
Soft tissue (ST1) to urinary bladder contents	4.75×10^{-4}	Deleted
Kidneys (urinary path) to bladder	1.386×10^{-2}	1.02×10^{-2} [d]
Gastrointestinal tract to blood[c]	5.0×10^{-4}	5.0×10^{-4}

[a]See Figure 3-8 for schematic representation of model.
[b]Units are in $days^{-1}$, except for gastrointestinal tract to blood, which is unitless.
[c]Values shown for the absorption fraction are for general public exposures (e.g., diet). Recommended values for occupational exposures are as follows: oxides (excluding poly-disperse oxides), 1×10^{-5}; nitrates, 1×10^{-4}; and other compounds or unknown mixtures, 1×10^{-4}.
[d]Modified in Luciani and Polig (2000).

and Polig 2000). Sensitivity and uncertainty analyses of model predictions have been reported (Luciani et al. 2001, 2003).

Risk Assessment. The model could be used to establish the radiation dose (Sv) per unit of ingested or inhaled plutonium (Bq) in adults if linked to radioactive decay and radiation dose models.

Target Tissues. The model is designed to calculate radiation dose coefficients (Sv/Bq) corresponding to specific inhalation or ingestion exposures to plutonium isotopes.

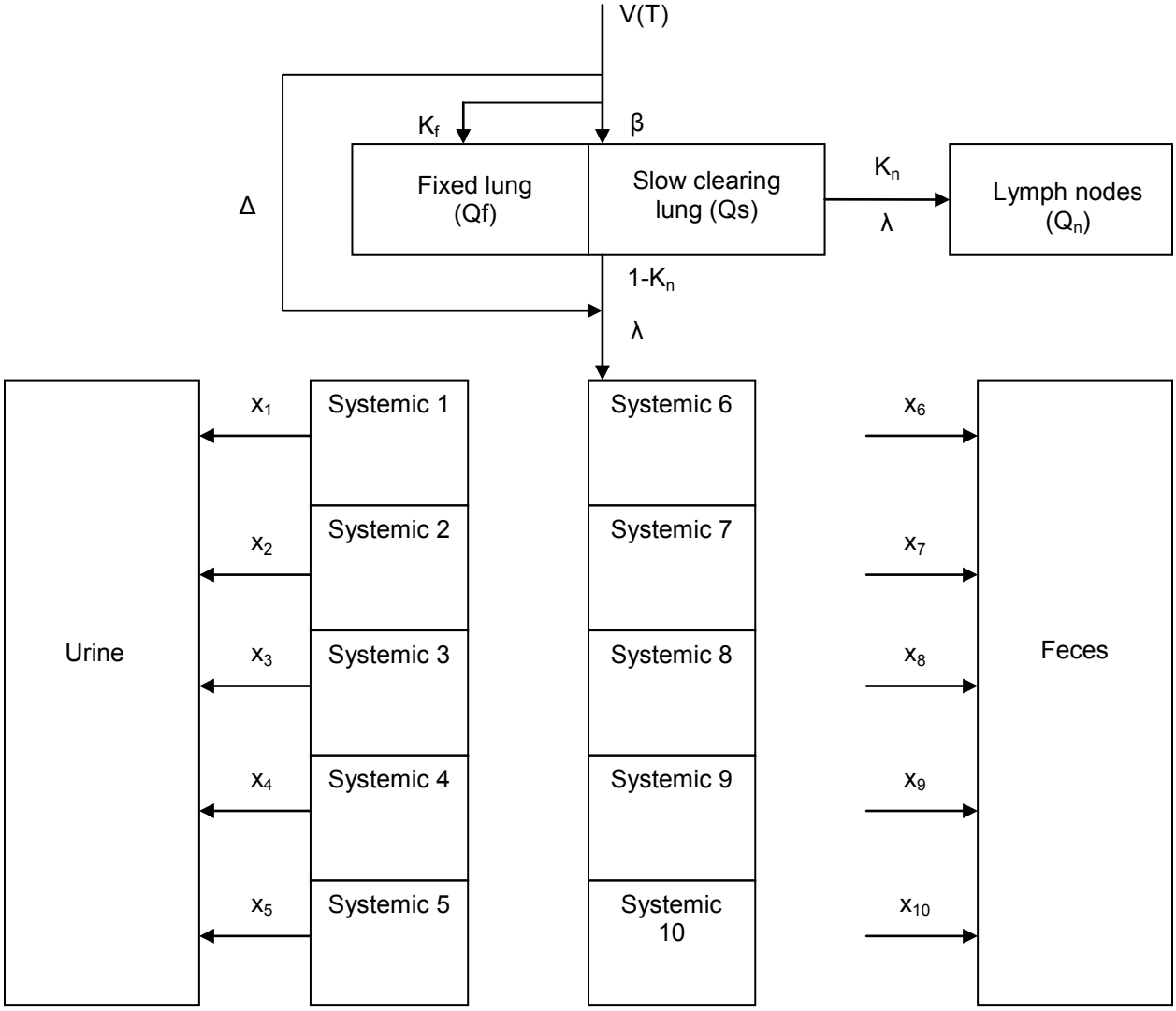
Species Extrapolation. The model is intended for applications to human dosimetry. Applications to other species would require consideration of species-specific adjustments in model parameters.

Interroute Extrapolation. The Luciani and Polig (2000) model is designed to simulate kinetics of absorbed plutonium, and includes gastrointestinal tract compartments for simulating absorption from ingestion. If combined with a respiratory tract model (e.g., ICRP 1994b), the model can be used to simulate inhalation exposures to plutonium. The model has been applied to injection exposures (Luciani and Polig 2000) and can be applied to any other route of exposure for which the transfer rate to blood is available.

First Branch of the First Institute of Biophysics (FIB-1) Biokinetic Plutonium Model

Description of the Model. Khokhryakov et al. (1994, 2000, 2002) developed a biokinetics model for predicting the accumulation of plutonium in the lungs (and corresponding radiation doses) of workers at the Mayak Production Association (Russian Federation), based on exposure information and biomonitoring of urinary plutonium. The model included a lung clearance model, which delivered plutonium into a multi-compartment elimination (urinary and fecal) model (Figure 3-9). In the lung clearance model shown in Figure 3-9, inhaled plutonium was distributed to three lung clearance pathways: rapid clearance, slow clearance (to systemic compartments and lymph nodes), or fixed (permanently retained in the lung). Plutonium compounds were assigned specific distributions to the three pathways according to estimates of "biological transportability" (S) as determined by dialysis through a semi-permeable membrane (Khokhryakov et al. 1998). Compounds in the low transportability class (S=0.3%; e.g., PuO_2) were assigned larger distribution fractions to fixed and slow clearance pathways, compared to higher transportability classes (e.g., S=3%, $Pu[NO_3]_4$). For PuO_2, lung retention

Figure 3-9. Schematic Representation of the First Institute of Biophysics (FIB) Model of Plutonium Biokinetics in Humans*



*See Table 3-10 for explanation of symbols and parameter values.

Source: Khokhryakov et al. 2002

half-times are assumed to be approximately 4.4 days (fast) and 2,000 days (slow; corresponding half-times for $Pu(NO_3)_4$ are 31 and 1,500 days, respectively.

Plutonium absorbed from the lung enters a systemic compartment composed of 10 sub-compartments from which plutonium is transferred to urine (5) or feces (5). The sub-compartments represent kinetically similar pools of plutonium in the body, rather than specific tissues (i.e., the model was intended to simulate lung retention and excretion, not plutonium burdens in other tissues), and are assigned unique excretion rate constants. Summing the outflow from all five compartments provides the estimated total excreted plutonium per day. Distribution fractions and transfer rates, and half-times for the various compartments are presented in Table 3-10. A recent configuration of the model (Khokhryakov et al. 2005) replaced the FIB-1 lung clearance model with the ICRP Human Respiratory Tract Model for Radiological Protection (ICRP 1994b).

Validation of the Model. The FIB-1 model has been evaluated with data on plutonium excretion and postmortem lung and total body burdens in 543 Mayak workers (Khokhryakov et al. 2002). An adaptation of the FIB-1 model, with the lung clearance model replaced by the ICRP Human Respiratory Tract Model for Radiological Protection (ICRP 1994b), has also been evaluated against the same data (Khokhryakov et al. 2005; Suslova et al. 2003). An uncertainty analysis of model predictions has been reported (Krahenbuhl et al. 2005).

Risk Assessment. The model has been used to establish the lung radiation dose (Sv) per unit of plutonium intake (Bq) in plutonium production workers (Khokhryakov et al. 2002, 2005).

Target Tissues. The model is designed to calculate radiation dose coefficients (Sv/Bq) to the lung corresponding to specific inhalation exposures to plutonium isotopes or from urine plutonium biomonitoring data (Khokhryakov et al. 2002, 2005).

Species Extrapolation. The model is based on both human and animal data. However, it is intended for applications to human dosimetry. Applications to other species would require consideration of species-specific adjustments in modal parameters.

Interroute Extrapolation. The FIB-1 model was constructed to simulate kinetics of inhaled plutonium. The systemic portion of the model is an empirical model (compartmental with no assignments of compartments to physiological entities) for which parameter values were derived from data on

Table 3-10. Parameters of the First Branch of the First Institute of Biophysics (FIB-1) Biokinetic Plutonium Model[a]

Parameter	Symbol	Unit	S=0.3%	S=1.0%	S=3.0%	
Fraction of inhaled deposited in lung	V(T)	percent	Particle size-dependent			
Fraction to fast lung clearance	Δ	percent	26.5±46.5	71.7±9.1	90.1±3.5	
Fraction to fixed lung compartment	K_f	percent	15.4±4.2	4.3±0.7	1.8±0.2	
Fraction to slow lung clearance compartment	β	percent	58.0±46.4	24.0±9.1	8.1±3.5	
Fraction to lymph nodes	K_n	percent	26.0±4.2	21.0±1.6	11.0±0.9	
Clearance rate from slow lung compartment	λ	$year^{-1}$	0.134±0.103	0.133±0.045	0.170±0.063	
				Urine		Feces
			a_i	x_i	a_i	x_i
Systemic compartment 1	a_1, x_1	day^{-1}	$4.1x10^{-3}$	$5.634x10^{-1}$	$6.0x10^{-3}$	$3.465x10^{-1}$
Systemic compartment 2	a_2, x_2	day^{-1}	$1.2x10^{-3}$	$1.26x10^{-1}$	$1.6x10^{-3}$	$1.05x10^{-1}$
Systemic compartment 3	a_3, x_3	day^{-1}	$1.3x10^{-4}$	$1.65x10^{-2}$	$1.2x10^{-4}$	$1.24x10^{-2}$
Systemic compartment 4	a_4, x_4	day^{-1}	$3.0x10^{-5}$	$2.31x10^{-3}$	$2.0x10^{-5}$	$1.8x10^{-3}$
Systemic compartment 5	a_5, x_5	day^{-1}	$1.3x10^{-5}$	$2.0x10^{-5}$	$5.2x10^{-6}$	$2.0x10^{-5}$

[a]See Figure 3-9 for schematic representation of model.

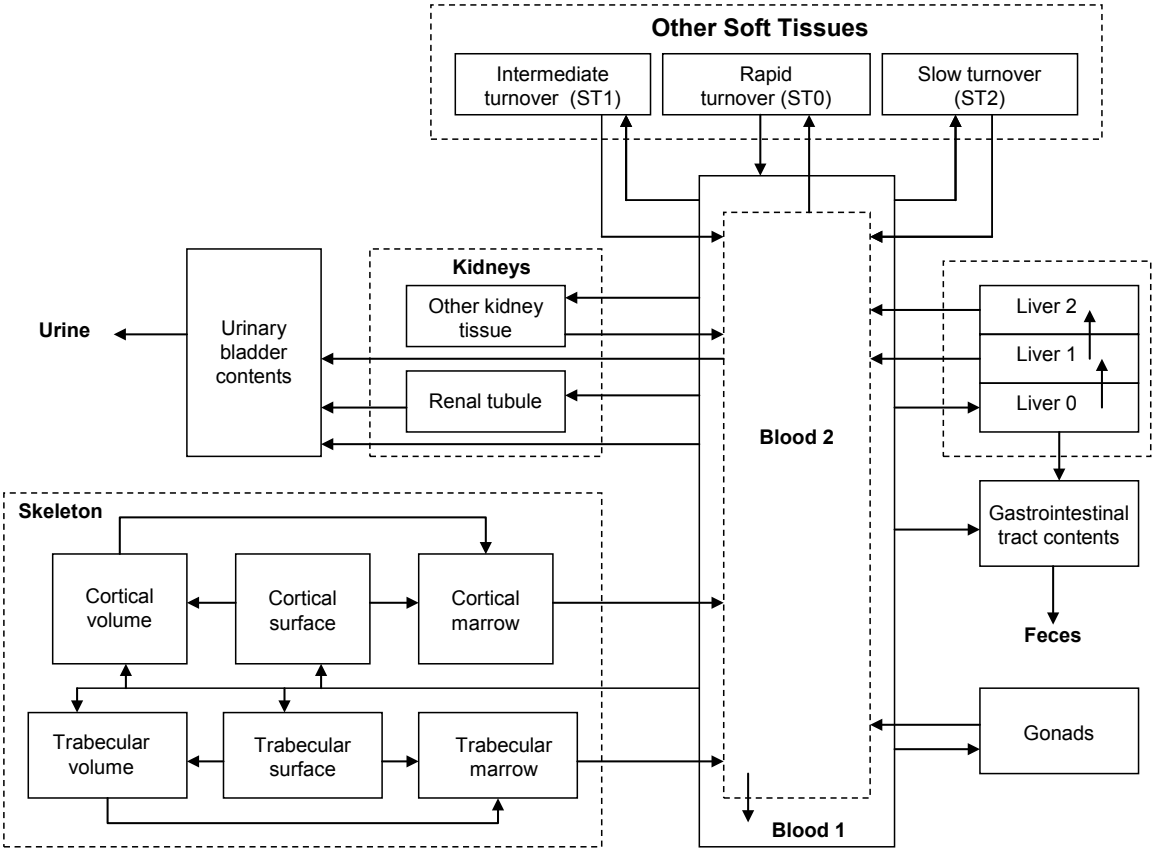
Source: Khokhryakov et al. 2002

plutonium excretion and postmortem lung and total body burdens in Mayak workers. The model cannot be directly extrapolated to predicting the kinetics of systemic plutonium following exposures by other routes (e.g., dermal, oral).

Leggett et al. (2005) Plutonium Biokinetics Model

Description of the Model. Leggett et al. (2005) developed a modification of the ICRP (1994a) model. A schematic diagram of the model and list of parameter values are presented in Figure 3-10 and Table 3-11, respectively. The major important features introduced into the Leggett et al. (2005) model are the simulations of blood and urinary excretion from blood, liver, and bone. The blood compartment in the Leggett et al. (2005) model is divided into two sub-compartments (blood 1, blood 2). Absorbed plutonium enters blood 1, from where it distributes to other tissues and is excreted into urine. Plutonium in tissues returns to blood 2 (recycled plutonium), from where it distributes to blood 1, the rapid soft tissue compartment (ST0), and is excreted in urine. The two blood compartments, with both contributing to urinary bladder contents, provides a simulation of a relatively fast pathway for urinary excretion of recycled plutonium (blood 2 to urine, $t_{1/2}$≈5 hours) and a slower excretion pathway for initially-absorbed plutonium (blood 1 to urine, $t_{1/2}$≈45 days). The liver is divided into three compartments (liver 0, 1, and 2). Liver 0 receives plutonium from blood 1 from where it can be secreted into the gastrointestinal tract (e.g., bile), or transferred to liver 1 and liver 2. The latter sub-compartments simulate faster and slower transfers of plutonium from liver to blood 2 (liver 1 to blood, $t_{1/2}$≈460 days; liver 2 to blood, $t_{1/2}$≈5,500 days). This configuration (i.e., fast and slower liver compartments) results in a gradual shift in the systemic plutonium distribution from liver to skeleton, with the liver burden being greater than skeletal burden, initially after absorption, and the liver contribution diminishing, relative to skeletal, over time. As in the ICRP (1994a) model, the skeleton is divided into trabecular and cortical components, with each further divided into surface bone, bone volume, and bone cavity (marrow) compartments. In the ICRP (1994a) model, initial deposition of plutonium is assumed to occur from blood directly to bone surfaces, where it can be transferred to bone marrow or to bone volume (i.e., burial). In the Leggett et al. (2005) model, plutonium in blood 1 is directly transferred to both bone surface and volume compartments. This configuration simulates faster and slower components of burial of plutonium in bone volume. The fast component is represented by direct transfer from blood 1 to bone volume ($t_{1/2}$≈50 days and 150 days for trabecular and cortical volume, respectively) and the slower component is represented by transfer from bone surface to volume ($t_{1/2}$≈ 15 and 93 years for trabecular and cortical, respectively).

Figure 3-10. Schematic Representation of the Leggett et al. (2005) Model of Plutonium Biokinetics in Humans*



*See Table 3-11 for parameter values.

Table 3-11. Parameters of Leggett et al. (2005) Model of Plutonium Biokinetics in Humans[a]

Parameter[b]	Adult value
Blood (1) to liver (0)	4.6200×10^{-1}
Blood (1) to cortical surface	8.7780×10^{-2}
Blood (1) to cortical volume	4.6200×10^{-3}
Blood (1) to trabecular surface	1.2474×10^{-1}
Blood (1) to trabecular volume	1.3860×10^{-2}
Blood (1) to urinary bladder contents	1.5400×10^{-2}
Blood (1) to renal tubules	7.7000×10^{-3}
Blood (1) to other kidney	3.8500×10^{-4}
Blood (1) to upper large intestine contents	1.1550×10^{-2}
Blood (1) to testes	2.6950×10^{-4}
Blood (1) to ovary	8.4700×10^{-5}
Blood (1) to soft tissue (1)	1.8511×10^{-2}
Blood (1) to soft tissue (2)	2.3100×10^{-2}
Soft tissue (0) to blood (1)	9.9000×10^{-2}
Blood (2) to urinary bladder contents	3.5000×10^{0}
Blood (2) to blood (1)	6.7550×10^{1}
Blood (2) to soft tissue (0)	2.8950×10^{1}
Renal tubules to urinary bladder contents	1.7329×10^{-2}
Other kidney to blood (2)	1.2660×10^{-4}
Soft tissue (1) to blood (2)	1.3860×10^{-3}
Soft tissue (2) to blood (2)	1.2660×10^{-4}
Liver (0) to small intestine contents	9.2420×10^{-4}
Liver (0) to liver (1)	4.5286×10^{-2}
Liver (1) to blood (2)	1.5200×10^{-3}
Liver (1) to liver (2)	3.8000×10^{-4}
Liver (2) to blood (2)	1.2660×10^{-4}
Tests to blood (2)	3.8000×10^{-4}
Ovaries to blood (2)	3.8000×10^{-4}
Cortical surface to cortical marrow	8.2100×10^{-5}
Cortical surface to cortical volume	2.0500×10^{-5}
Cortical volume to cortical marrow	8.2100×10^{-5}
Trabecular surface to trabecular marrow	4.9300×10^{-4}
Trabecular surface to trabecular volume	1.2300×10^{-4}
Trabecular volume to trabecular marrow	4.9300×10^{-4}

Table 3-11. Parameters of Leggett et al. (2005) Model of Plutonium Biokinetics in Humans[a]

Parameter[b]	Adult value
Cortical marrow to blood (2)	7.6000×10^{-3}
Trabecular marrow to blood (2)	7.6000×10^{-3}

[a]See Figure 3-10 for schematic representation of model.
[b]Units are d^{-1}.

Validation of the Model. The Leggett et al. (2005) model has been evaluated with data on plutonium excretion and postmortem tissue levels in plutonium workers at the Mayak production plant (e.g., Khokhryakov et al. 1994, 2000) and data from plutonium injection studies (Langham et al. 1950, 1980; Talbot et al. 1997). The model provides predictions of blood, liver, and fecal plutonium kinetics that more closely simulate observations made in injection studies compared to predictions from the ICRP (1994a) model (Leggett et al. 2005). The model also predicts urinary plutonium based on observed urinary excretion kinetics in Mayak production plant workers (Leggett et al. 2005).

Risk Assessment. The Leggett et al. (2005) model was developed to update and replace the ICRP (1994a) model that is currently being used to establish radiation doses (Sv) per unit of ingested or inhaled plutonium (Bq) (ICRP 1994a, 2001)

Target Tissues. The model was developed for calculating whole-body and tissue-specific radiation dose coefficients (Sv/Bq) corresponding to absorbed activities of plutonium isotopes. Target tissues represented in the model are shown in Figure 3-10.

Species Extrapolation. The model is intended for applications to human dosimetry. Applications to other species would require consideration of species-specific adjustments in modal parameters.

Interroute Extrapolation. The Leggett et al. (2005) model is designed to simulate kinetics of absorbed plutonium and, if combined with a gastrointestinal absorption or respiratory tract model (e.g., ICRP 1979, 1994a), could be used to simulate systemic kinetics of ingestion or inhalation exposures. The model can be applied to any other route of exposure for which the transfer rate to blood is available.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Several mechanisms appear to contribute to the absorption of inhaled plutonium: (1) physical transformation of plutonium particles deposited (or formed from hydrolysis reactions) in the lung, including fragmentation of particles, accelerated by alpha-radiation; (2) dissolution of particles; and (3) phagocytosis of particles by macrophages (Bair et al. 1973; Mewhinney and Diel 1983). The relative contributions of these mechanisms appear to depend on several factors, including: (1) particle size of the inhaled aerosol; (2) water solubility of the inhaled plutonium (e.g., PuO_2, $Pu[NO_3]_4$); (3) isotope specific

activity (e.g., ^{238}Pu, ^{239}Pu), which determines intensity of alpha-radiation of the particles; and (4) in the case of PuO_2, surface characteristics of the particles, affected by temperatures at which the PuO_2 was produced.

Mechanisms of absorption of plutonium from the gastrointestinal tract have not been elucidated. Studies conducted in animals have shown that gastrointestinal absorption of plutonium is increased in iron-deficiency, and is decreased in iron-deficient animals by the co-administration of Fe^{3+}, suggesting that mechanisms involved in iron absorption may contribute to plutonium absorption (Sullivan and Ruemmler 1988; Sullivan et al. 1986). Gastrointestinal absorption of plutonium compounds appears to be higher for more water-soluble compounds of plutonium; absorption of plutonium citrate tends to be greater than nitrate, which is greater than plutonium oxide (PuO_2) (Sullivan 1980a). This suggests that dissolution of plutonium in the gastrointestinal tract may contribute to absorption (possibly, in addition to endocytosis of particles). Gastrointestinal absorption is higher in neonatal animals compared to mature animals, which may reflect a more permeable gastrointestinal tract in neonates or physiological adjustments in neonates related to nutrient (e.g., iron) absorption that affect plutonium uptake (Sullivan 1980a, 1980b; Sullivan and Gorham 1983; Sullivan et al. 1985). Fasting tends to increase absorption, which suggests the possibility of binding interactions with food components in the gastrointestinal tract and/or competition for absorption with other nutrients (Bhattacharyya et al. 1986; USNRC 1992).

Results from these studies support the following general conclusions regarding factors that affect absorption: (1) in general, absorption of plutonium citrate tends to be greater than nitrate, which is greater than plutonium oxide (PuO_2) (Sullivan 1980a); (2) most estimates of absorption of plutonium citrate and nitrate in adult animals are <0.1% of the dose; (3) fasting tends to increase absorption (USNRC 1992); (4) absorption is 10–1,000 times greater in neonates compared to adults, depending on the animal species and chemical form of plutonium (Sullivan 1980a, 1980b; Sullivan and Gorham 1983; Sullivan et al. 1985); (5) iron deficiency increases absorption in juvenile rats and administration of ferric iron (Fe^{3+}) to iron-deficient rats decreases absorption (Sullivan and Ruemmler 1988); and (6) absorption of plutonium in surface dusts (e.g., bomb test sites) in guinea pigs was <0.001% of the dose (Harrison et al. 1994).

Distribution.

Distribution in Blood. Dissolved plutonium distributes in blood predominantly as Pu(IV) complexes with plasma proteins (Lehmann et al. 1983; Stevens et al. 1968; Stover et al. 1968a; Taylor 1973).

Although Pu(IV) forms complexes with a variety of plasma proteins, including albumin, γ-globulins, and low molecular weight proteins, the dominant complex is with transferrin. The dissociation constant of Pu(IV)-transferrin complex has not been measured; however, the complex appears to be less stable than Fe(III)-transferrin complex ($K_d \approx 10^{-22}$ M) (Aisen and Listowsky 1980). As a result, binding of Fe(III) to transferrin can influence the degree of binding of Pu(IV). Plutonium also forms complexes with nonprotein ligands, polycarboxylates (e.g., citrate, lactate). The stability constants for the mono- and di-citrate complexes are approximately 10^{15} and 10^{30} M, respectively (Taylor 1973).

Distribution within Soft Tissues. Plutonium, because it is strongly bound to proteins in blood, does not escape easily from the vasculature. However, at sites within the body where blood sinusoids are present (e.g., in the liver, red bone marrow), protein-plutonium complexes in plasma can leave the vasculature and distribute to sites within tissues. Plutonium can exist within tissues as an ion bound to binding sites on proteins, including those associated with iron metabolism (e.g., transferrin, haemosiderin, and ferritin) or as insoluble particulates. Particulates may derive from inhalation of particles of plutonium (e.g., PuO_2) or may form by aggregation of polymeric hydrolysis products of more soluble Pu(IV) compounds (e.g., plutonium citrate and plutonium nitrate) (Taylor 1973). In the lung, plutonium accumulates within alveolar macrophages and Type I alveolar epithelial cells (both of which phagocytize plutonium particles), and in lung-associated lymph nodes (Bair et al. 1973). Aggregation of macrophages can result in localized regions of high activity that can become encapsulated in fibrotic material, inhibiting the dissolution of the plutonium and the further migration of the macrophages from the lung. Plutonium is also found associated with hemosiderin (in bone marrow macrophages) and with ferritin in liver and other tissues (e.g., spleen, bone marrow) where ferritin is expressed (Gorden et al. 2003; Taylor 1973). The sequestration of plutonium into ferritin may contribute to the relatively long retention time of plutonium in liver. Following intravenous administration of ^{239}Pu-citrate or $^{239}Pu(NO_3)_4$ to rats, plutonium was found in hepatocytes and sinusoidal cells. Distribution of plutonium within liver was relatively homogeneous following injection of ^{239}Pu-citrate compared to a heterogeneous pattern of aggregation in liver following injection of $^{239}Pu(NO_3)_4$ (Fouillit et al. 2004). A similar pattern has been observed in dogs (Gearhart et al. 1980). These observations suggest distinct mechanisms of transfer of the two compounds into and/or within liver. The temporal changes in the distribution pattern of plutonium in liver and lung also occur. In liver, this may derive from regeneration of injured tissue. In the lung, plutonium deposits become focalized, over time, within macrophages. Within the lungs, after intakes of insoluble plutonium particles the number of contaminated macrophages decreases and the remaining macrophages become loaded with even larger amounts of plutonium. These often come together to form local hotspots that

sometimes form a fibroid capsule around them, which inhibits both the dissolution of the plutonium and the further migration of the macrophages.

Distribution within Bone. Plutonium in bone initially distributes to bone surfaces adjacent to blood sinusoids in bone marrow and can subsequently be redistributed within bone volume during bone growth and remodeling. Redistribution of plutonium from bone to bone marrow can also occur, at least in part, from macrophage phagocytosis of plutonium released from bone during bone resorption. Various studies of bone uptake of injected plutonium suggest the following general pattern of deposition of plutonium on bone surfaces (DOE 1989; Leggett 1985; Priest 1990; Rosenthal et al. 1972a, 1972b; Vaughan et al. 1973): (1) monomeric complexes of plutonium (e.g., monomeric plutonium citrate) deposit preferentially at bone surfaces, with relatively little initial distribution to marrow; whereas, highly polymeric plutonium deposits preferentially in marrow; (2) initial deposition is greater on trabecular compared to cortical bone surfaces; (3) initial deposition occurs preferentially on endosteal surfaces compared to periosteal surfaces; (4) deposition is greater on surfaces where active resorption is occurring compared to surfaces undergoing mineralization; and (5) deposition is greater on surfaces of the axial skeleton (i.e., skull, hyoid bone, sternum, ribs, and vertebrae) then on the appendicular skeleton (i.e., limbs). Mechanisms of plutonium deposition at bone surfaces are not completely understood. Plutonium (IV) can form complexes with bone glycoproteins, collagen, and bone mineral (Vaughan et al. 1973).

The deposition pattern in bone is age-dependent. A comparison of bone distribution of plutonium in juvenile (3 months) beagles, compared to young adult (17–20 months) and mature (60 months) beagles that received a single injection of plutonium citrate showed the following patterns (Bruenger et al. 1991a): (1) deposition (per cent of dose) was higher in juveniles; (2) a larger fraction of the skeletal deposition occurred in limb bones of juveniles; and (3) plutonium in bone volume (as opposed to bone surface) was more pronounced in juveniles. These observations are consistent with the concept that plutonium preferentially deposits in regions adjacent to red marrow, which has a wider distribution in juveniles than in adults, and is more prominent in trabecular bone than in cortical bone, and in bones of the axial skeleton. High bone turn-over in juveniles contributes to more rapid distribution of plutonium from bone surface to bone volume as a result of burial of surface deposits, uncovering buried deposits, and recycling of the plutonium between marrow, bone, and blood (Bruenger et al. 1991a; Leggett 1985; Priest 1990; Vaughan et al. 1973).

Metabolism. Plutonium metabolism in physiological systems consists, primarily, of hydrolytic reactions and formation of complexes with protein and nonprotein ligands.

Excretion. Absorbed plutonium is excreted in urine and feces. Following inhalation exposure to plutonium aerosols, plutonium particulates are transported from the respiratory tract to the gastrointestinal tract. Because the fractional absorption of plutonium in the gastrointestinal tract is approximately $1x10^{-3}$–$1x10^{-4}$, nearly all of this transported plutonium is excreted in feces. This mechanism explains the fecal excretion that has been observed in humans and animals during the first few days following exposure. Mechanisms for fecal excretion that persists for months to years following exposure are not as well understood. Plutonium injected intravenously is excreted in feces in humans (Langham 1959; Talbot et al. 1993, 1997), nonhuman primates (USNRC 1985), dogs (Bair et al. 1974; Ballou et al. 1972; Guilmette and Muggenburg 1993; Stover et al. 1959), and rodents (Carritt et al. 1947). Direct evidence for biliary secretion of injected plutonium comes from studies conducted in rats (Ballou et al. 1972; Bhattacharyya et al. 1978).

Mechanisms of urinary excretion have not been elucidated and may involve excretion of plutonium from plasma, or secretion of plutonium into urine from renal tissue. In plasma, plutonium exists predominantly bound to proteins; <5% appears to be in the form of low-molecular weight complexes. The dominant protein complex is with transferrin (molecular weight=88 kDa), which can account for 90% of plasma plutonium following intravenous administration of either Pu-citrate complex or $Pu(NO_3)_4$ (Lehmann et al. 1983; Stevens et al. 1968; Stover et al. 1968a; Taylor 1973). Renal clearance (plasma-to-urine) of transferrin in humans is approximately $1\text{-}3x10^{-4}$ L/day (Pesce and First 1979); this corresponds to a plasma half-time of approximately 20–40 years (assuming a plasma volume in the adult human of 3 L). Therefore, excretion of circulating Pu-transferrin complex is unlikely to account for blood-to-urine clearances reported in adults (e.g., corresponding half-times 7–30 days) (Etherington et al. 2003; Leggett 1985). Other possible mechanisms that contribute to urinary excretion are blood-to-urine clearance of low molecular weight plutonium complexes, or secretion of plutonium from tissue into urine.

3.5.2 Mechanisms of Toxicity

Toxicity of plutonium derives from the biological effects of radiation emitted during the radiological decay of plutonium isotopes. The isotopes ^{238}Pu and ^{239}Pu decay by emitting a high-energy alpha particle. A very small amount of the energy in the form of gamma rays is also released during the decay of plutonium isotopes. However, gamma radiation from ^{238}Pu and ^{239}Pu decay is of such small magnitude and energy that the dominant mechanisms of toxicity are associated with alpha radiation. Molecular damage results from the direct ionization of atoms that are encountered by alpha (and gamma) radiation

and by interactions of resulting free radicals (e.g., $H^{\bullet}$, $OH^{\bullet}$) with nearby macromolecules (e.g., lipids, nucleic acids, proteins). Tissue damage results when the molecular damage is sufficiently extensive and/or repair of the damage is not sufficiently rapid.

Alpha radiation emitted by plutonium isotopes cannot penetrate the outer layers of the skin. However, once plutonium is internalized, the extremely short-range alpha radiation produces a very localized radiation dose. As a result, toxicity of plutonium coincides with the distribution of plutonium in the body. As discussed in Section 3.4, Toxicokinetics, the distribution of plutonium depends on many factors, including route of exposure, chemical form and physical characteristics of the plutonium compound (and its complexes), and isotope specific activity (i.e., Bq/g). The patterns of toxicity observed in dogs exposed to various compounds of plutonium reflect, primarily, the distribution of plutonium that follows exposure to each compound. Lung cancers and other effects of $^{239}PuO_2$ on the lung (e.g., pneumonitis) were the dominant effects observed in dogs following inhalation of $^{239}PuO_2$, which is cleared relatively slowly from the lung (and from thoracic lymph nodes). As a result, following inhalation exposures to $^{239}PuO_2$, the highest radiation doses (i.e., effective dose equivalents) occur in the lung. In contrast, inhaled $^{238}PuO_2$ is more rapidly cleared from the lung and, once absorbed, distributes primarily to skeletal tissues (bone surfaces and marrow) and liver, resulting in relatively high radiation doses to bone and liver, as well as to lung. This is consistent with observations of bone, liver, and lung toxicity in dogs following inhalation exposures to $^{238}PuO_2$.

3.5.3 Animal-to-Human Extrapolations

Mechanisms of toxicity and toxicokinetics of plutonium, described in Sections 3.5.1 and 3.5.2, are directly applicable to humans. Numerous studies of the distribution of plutonium in humans (i.e., autopsy studies of individuals occupationally exposed to plutonium) have shown that the general pattern of distribution of plutonium in humans is consistent with that observed in various animal models, with the highest portion of the body burden in lung (following inhalation exposures), skeletal tissues, and liver. Epidemiologic studies of health outcomes among workers in industries that produce and/or process plutonium have provided evidence for increased risk of lung, liver, and bone cancers in association with exposures to plutonium. These observations are consistent with the pattern of health effects observed in animals.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans or animals after exposure to plutonium. No *in vitro* studies were located regarding endocrine disruption of plutonium.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

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

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

tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

Numerous epidemiological studies of ionizing radiation exposures have found higher cancer risks associated with exposures of infants and children infancy and childhood, compared to adults (Agency for Toxic Substances and Disease Registry 1999). Although there is no direct evidence for increased susceptibility of children to toxicity from plutonium, several kinds of observations made in animals suggest that immature animals may be more vulnerable to plutonium as a result of higher deposition of absorbed plutonium on bone surfaces and higher turn-over of bone. Studies conducted in immature beagles (inhalation exposures to $^{239}PuO_2$ at age 2.6–3.6 months) showed that, in comparison to similar exposures of adult beagles, a larger fraction of the initially deposited lung burden was transferred to the skeleton (DOE 1988d, 1989). This observation is consistent with the results from injection studies. A comparison of bone distribution of plutonium in juvenile beagles (3 months of age), compared to young adult (17–20-month-old) and mature (60-month-old) beagles that received a single injection of plutonium citrate showed that skeletal deposition (percent of dose) was higher in juveniles, occurred more extensively in growing limb bones, and within bone, a larger portion of the bone burden was associated within bone volume (Bruenger et al. 1991a). As discussed in Section 3.5, Mechanisms of Toxicity, these observations are consistent with the concept that plutonium preferentially deposits in regions adjacent to red marrow, which has a wider distribution in juveniles than in adults, and is more prominent in trabecular bone than in cortical bone, and in bones of the axial skeleton. High bone turn-over in juveniles may also contribute to more rapid distribution of plutonium from bone surface to bone volume as a result of burial of surface deposits, uncovering buried deposits, and recycling of the plutonium between marrow, bone, and blood (Bruenger et al. 1991a; Leggett 1985; Vaughan et al. 1973). These observations suggest the possibility that children may have a higher susceptibility to bone marrow toxicity and related outcomes (e.g., leukemia) and skeletal toxicity of plutonium than adults, although this has not been verified either experimentally, or in epidemiological studies. One observation that may be pertinent is

that dogs, examined 5 years after an inhalation exposure to $^{239}PuO_2$ at age 2.6–3.6 months, showed a lower incidence of radiation pneumonitis than dogs exposed as adults. This would be consistent with a greater transfer of plutonium from the lung to the skeleton. Lung tissue growth in the younger dogs may have resulted in some lung tissue with little or no plutonium.

Gastrointestinal absorption of ingested plutonium is higher in neonatal animals compared to mature animals, which may reflect a more permeable gastrointestinal tract in neonates or physiological adjustments in neonates related to nutrient (e.g., iron) absorption that affect plutonium uptake. Absorption has been shown to be 10–1,000 times greater in neonates compared to adults, depending on animal species and chemical form of plutonium (Sullivan 1980a, 1980b; Sullivan and Gorham 1983; Sullivan et al. 1985). Iron deficiency increases absorption in juvenile rats (Sullivan and Ruemmler 1988). However, available animal data have not demonstrated that increased plutonium uptake by neonatal and juveniles results in increased susceptibility to the toxic effects of internalized plutonium.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by plutonium are discussed in Section 3.9.2.

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

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Plutonium

Plutonium is a radioactive element. Plutonium within the body can be inferred from radioassays of urine, feces, or tissue samples by gross alpha analysis, alpha spectroscopy, gamma-ray spectroscopy, mass spectrometry, and liquid scintillation techniques (Alvarez and Navarro 1996; Dacheux and Aupiais 1997; DOE 1990b, 1997; Guilmette 1986).

3.8.2 Biomarkers Used to Characterize Effects Caused by Plutonium

Limited information is available regarding biomarkers of effect of plutonium exposure and observed effects are not specific to radiation from plutonium or any other radionuclide. The presence of chromosome aberrations has been reported in humans and laboratory animals following the internalization of plutonium (see Section 3.3 for a discussion of plutonium-induced genotoxic effects). Relatively early adverse health effects in animals following the internalization of inhaled plutonium include radiation pneumonitis and lymphopenia; late-occurring effects may include bone, lung, and liver tumors (see Section 3.2.1 for detailed discussion of plutonium-induced health effects following inhalation exposure).

3.9 INTERACTIONS WITH OTHER CHEMICALS

The toxicokinetics of plutonium appear to be influenced by exposure to cigarette smoke. Cigarette smoke, when administered to mice following inhalation exposure to $^{239}PuO_2$, appeared to inhibit the clearance of plutonium (Talbot et al. 1987). At 49 days postexposure, animals exposed to plutonium and cigarette smoke retained approximately 20% more plutonium than those animals exposed to plutonium alone. In another study, rats were given single pernasal exposures to $^{239}PuO_2$ with or without chronic exposure to cigarette smoke (Finch et al. 1998). Rats receiving both plutonium and cigarette smoke exposure exhibited retarded ^{239}Pu clearance from the lung. The above toxicokinetic interactions may contribute to interactions relevant to the estimation of lung cancer risks associated with plutonium exposures in human populations. Both additive and multiplicative interaction models have been used to model interactions between smoking and lung cancer risk in studies of plutonium workers (Jacob et al. 2005; Kreisheimer et al. (2003).

Increased lung retention of ^{239}Pu (as the hydroxide colloid containing a relatively high concentration of gadolinium) and decreased fecal excretion of plutonium were noted in rats administered ^{239}Pu (as the hydroxide colloid) containing a relatively high concentration of gadolinium compared to rats receiving ^{239}Pu in the absence of gadolinium (Sato et al. 2001).

Exposure to inhaled $^{239}PuO_2$ followed by intratracheal instillation of benzo(a)pyrene resulted in a higher incidence of lung tumors and a decrease in median survival time compared to animals exposed to $^{239}PuO_2$ alone (Métivier et al. 1984). As the dose of benzo(a)pyrene increased, survival time decreased. Exposure of rats to a single intra-abdominal injection of a mixture of $^{239}PuO_2$ and benzo(a)pyrene resulted in an additive effect in the induction of abdominal sarcomas, compared to animals given benzo(a)pyrene or plutonium only (AEC 1973b).

A decrease in median survival time was observed in rats injected intravenously with ^{239}Pu, immediately followed by exposure to x-rays (Ballou et al. 1962), as compared to those animals exposed to plutonium alone. As exposure to x-rays increased, survival time decreased. However, when exposure to x-ray was delayed (as much as 14 days) following exposure of the rats to ^{239}Pu, the number of deaths occurring before 40 days was reduced.

Exposure of rats to $^{239}PuO_2$ and asbestos by intraperitoneal injection resulted in a higher incidence of abdominal tumors compared to animals exposed to $^{239}PuO_2$ alone (AEC 1973b). However, this additive

effect of asbestos and plutonium was not observed in the induction of pulmonary sarcomas when asbestos was administered to rats in combination with $^{239}PuO_2$ via intratracheal instillation (Sanders 1975b). In the same study, asbestos did not influence the translocation of plutonium in rats. However, asbestos increased the pulmonary retention of plutonium compared to plutonium-only exposure (Sanders 1975b).

An increased incidence of metaplasia was observed in rats experiencing a single inhalation exposure to $^{239}PuO_2$ followed by administration of 1 or 10 mg vitamin C/mL of drinking water for 1 year postexposure, compared to rats exposed to plutonium only (Sanders and Mahaffey 1983). However, the incidence of squamous cell carcinomas in animals exposed to plutonium and vitamin C decreased with increasing dose of vitamin C. The authors stated that vitamin C may interfere with the progression of squamous cell metaplasia to squamous cell carcinoma.

Studies in laboratory animals have also demonstrated the influence of metals on the toxicokinetics of plutonium. Pretreatment of rats with subcutaneous injection of cadmium or copper followed by intravenous injection of ^{238}Pu or ^{239}Pu resulted in changes in the distribution patterns of plutonium, but not in total retention of either isotope. Plutonium retention of both isotopes, following pretreatment with either metal, was increased in the spleen and the kidneys, as compared to animals treated with plutonium only (Volf 1980). Liver retention of plutonium appeared to be increased by copper pretreatment and decreased by cadmium pretreatment; these differences may reflect different properties of the respective metal-binding proteins or different mechanisms of action (Volf 1980).

Inhalation exposure of rats to beryllium oxide, followed by $^{239}PuO_2$, resulted in increased retention of plutonium in the lungs and subsequently-increased translocation of plutonium to thoracic lymph nodes (Sanders et al. 1978). Although lung retention of plutonium was increased and beryllium and plutonium are both considered to be lung carcinogens, combined exposures of rats to beryllium and ^{239}Pu did not significantly increase the incidence of lung tumors, compared to plutonium-only exposure (Sanders et al. 1978).

Administration of alcohol prior to exposure to plutonium appears to have an effect on the toxicokinetics of plutonium. Rats were treated orally with 12.5 or 25% ethanol (in 25% sucrose) for 1 or 6 weeks, followed by an intravenous injection of polymeric ^{239}Pu and sacrifice 1 or 41 days postexposure (DOE 1978e). In animals given ethanol for 6 weeks, retention of plutonium in the liver was increased at 1 day postexposure, but returned to normal 41 days postexposure, compared to plutonium-only exposure. At 1-day postexposure, lung retention of plutonium was increased in animals given ethanol for 1 week, while

lung retention of plutonium was decreased in animals given ethanol for 6 weeks. These differences were still apparent at 41 days postinjection (DOE 1978e).

Animal studies have been conducted to study the relative hazards of "diffuse" versus "localized" irradiation of the lung (Anderson et al. 1979; Muggenburg et al. 2008) in an effort to determine if there is a "hot particle" or "hot spot" effect. The theory hypothesized that larger particles with higher activity and less uniform distribution might be more likely to cause cancer than smaller, more uniformly dispersed particles. In perhaps the most direct and relevant study of this theory using plutonium, Muggenburg et al. (2008) provide direct evidence against the “hot particle” theory. The authors exposed beagle dogs by inhalation to three uniform sizes of $^{239}PuO_2$ particles (0.75, 1.5, and 3.0 μm AMAD, representing particle activities spanning more than 2 orders of magnitude from 0.048 to 7.7 mBq) as part of a composite lifespan study. They found that smaller and more uniformly distributed particles have the same or greater potential to produce neoplasms than less uniformly distributed particles. In the Anderson et al. (1979) studies, hamsters were exposed by instillation of $^{238}PuO_2$ or $^{239}PuO_2$ contained in zirconium dioxide spheres. Both installation and the use of the ^{238}Pu isotope represent confounders to assessing the “hot particle” theory. Instillation is a less relevant route than inhalation since it more coarsely distributes material in a less defined manner to a smaller portion of the lung. Also, the specific activity of the ^{238}Pu particles is several hundred times greater that of its ^{239}Pu counterpart, and the intense radiation that it emits causes particles to fragment. Following "localized" exposure, the incidence of lung tumors was significantly increased (3/102) only at the highest exposure level ($3.5x10^6$ pCi [$1.3x10^5$ Bq] ^{238}Pu/kg body weight). However, following "diffuse" exposure, a significant increase in the incidence of lung tumors was observed at exposures of $8.4x10^5$ pCi ($3.1x10^4$ Bq) ^{238}Pu/kg body weight and $9.4x10^5$ pCi ($3.5x10^4$ Bq) ^{239}Pu/kg body weight. The authors concluded that for a given lung burden of plutonium, the most hazardous distribution was "diffuse."

Animal studies have shown the effects of chelation therapy on the removal of previously incorporated actinide elements, such as plutonium. Single intravenous injection of polymeric ^{239}Pu (plus ^{237}Pu as a tracer) into young adult beagle dogs, followed by weekly exposure to diethylenetriamine-pentaacetate (DTPA) as calcium salt (Ca-DTPA) or daily exposure of DTPA as zinc salt (Zn-DTPA), resulted in 14.6 or 10.4% ^{237}Pu excretion, respectively, vs. 7.1% plutonium excretion at 24 hours postexposure in those animals exposed to plutonium alone (Lloyd et al. 1978c). After 28 days, cumulative excretion (corrected for radioactive decay) reached 38.2% for Ca-DTPA, 49.4% for Zn-DTPA, and 12.1% for those animals treated with plutonium alone. The study indicated that daily exposure of beagle dogs to Zn-DTPA is more effective in increasing the excretion of incorporated plutonium than weekly exposure to Ca-DTPA. As

speculated by the authors, the enhanced plutonium excretion may have occurred as a result of calcium replacement in Ca-DTPA or zinc replacement in Zn-DTPA by plutonium at the cellular level.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Studies designed to assess unusual susceptibility of human populations to the effects of plutonium exposure were not located. Epidemiological studies typically involve healthy workers occupationally exposed to low levels of plutonium; these studies have not identified unusually susceptible populations. However, present knowledge regarding the behavior of plutonium in humans and animals provides some insight into populations that might exhibit increased susceptibility to the effects of plutonium exposure.

Children may be particularly susceptible to the adverse effects of plutonium. Cells are replicating much more rapidly in growing children than in adults. Rapidly regenerating cells are more radiosensitive than slowly regenerating cells (see Appendix D). Therefore, children may be more susceptible to the radiation effects of plutonium than adults.

Persons with chronic obstructive lung diseases may be more susceptible to the toxic effects of inhaled plutonium. Based on results from studies in rats with pulmonary emphysema, plutonium deposition would be decreased in a person with pulmonary emphysema, but retention would be increased (Lundgren et al. 1981). Therefore, a greater radiation dose would be delivered to the lungs of a person with emphysema or other chronic obstructive lung diseases.

Persons who are anemic due to an iron deficiency may be more susceptible to the toxic effects of plutonium. Studies by DOE (1977a) demonstrated that gastrointestinal absorption of plutonium was 4-fold higher in iron-deficient mice than in mice with normal iron levels. Therefore, persons who are iron deficient may absorb more plutonium (Sullivan and Ruemmler 1988).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Radiation poisoning. Ellenhorn's medical toxicology. Diagnosis and treatment of human poisoning. Baltimore, MD: Williams & Wilkins, 1682-1723.

REAC/TS. 2010a. Package insert-instructions for use: Pantetate calcium trisodium injection. Radiation Emergency Assistance Center/Training Site. Oak Ridge Institute for Science and Education. U.S. Department of Energy. http://orise.orau.gov/files/reacts/Calcium-DTPA-package-insert.pdf. May 22, 2010.

REAC/TS. 2010b. Package insert-instructions for use: Pantetate zinc trisodium injection. Radiation Emergency Assistance Center/Training Site. Oak Ridge Institute for Science and Education. U.S. Department of Energy. http://orise.orau.gov/files/reacts/Zinc-DTPA-package-insert.pdf. May 22, 2010.

Viccellio P, Bania T, Brent J, et al., eds. 1998. Ionizing radiation. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers, 991-996.

Wang RY, Chiang WK. 1998. Radiation poisoning. In: Haddad LM, Shannon MW, Winchester JF, eds. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: W.B. Sanders Company, 413-425.

Compounds used to reduce absorption and body burden are used for heavy metals in general. However, treatment procedures have been adapted and used for the management of plutonium exposures in the workplace. Treatments using chelators are well accepted. REAC/TS has tested and possesses the investigational new drug license for the use of calcium and zinc diethylaminetriaminepentaacetic acid (Ca-DTPA and ZN-DTPA) in the United States. These substances were tested on adults and their safety and effectiveness was established for the adult population. This was extrapolated to the pediatric population based on comparability of pathophysiologic mechanisms (REAC/TS 2010a, 2010b). Pulmonary lavage is a unique treatment for reducing the lung burden from inhaled insoluble plutonium compounds. It has been used only occasionally and is useful only in cases involving relatively high lung burdens of insoluble plutonium compounds.

3.11.1 Reducing Peak Absorption Following Exposure

Topical applications of DTPA solution have been used to remove plutonium from skin and wounds after accidental dermal exposure (Khokhryakov et al. 2003). In extracellular fluid, the chelating agent, DTPA (a polycarboxylate compound), forms stable water-soluble complexes, which can be excreted in the urine (Durbin 1973; Taylor 1973). Both Ca-DTPA and Zn-DTPA complexes are used to decrease the risk of calcium and zinc depletion. Based on animal experiments, it appears that administered DTPA aerosols would form stable complexes with soluble forms of inhaled plutonium in the lung, thus reducing the amount of plutonium available for systemic deposition following absorption (Gervelas et al. 2007; Ménétrier et al. 2005; Sérandour et al. 2007; Stradling et al. 2000b). Bronchopulmonary lavage has been recommended in cases where inhalation of insoluble plutonium compounds such as $^{239}PuO_2$ may result in doses to the lung in excess of 5 mSv within a few weeks (CEC/DOE 1992; Wood et al. 2000).

Postexposure treatments that are effective in reducing toxic effects of radionuclides such as plutonium typically concentrate on decorporation (removal of plutonium from the body following absorption) and are discussed in Section 3.11.2.

3.11.2 Reducing Body Burden

Numerous animal studies have been performed to assess the effectiveness of various methods for decorporation of absorbed plutonium and other radionuclides. Recent summaries of results from animal studies and published guidance for decorporation of radionuclides such as plutonium include CEC/DOE (1992); Gorden et al. (2003); Ménétrier et al. (2005); Stradling et al. (2000a, 2000b); and Wood et al. (2000).

DTPA has been used as a chelating agent to accelerate the urinary excretion of plutonium in humans who were accidentally exposed to plutonium. In one case of accidental exposure to plutonium nitrate, absorption into the blood from a skin wound reached 4.3% of the amount deposited on the skin; as a result of prompt and repeated intravenous injections of DTPA, most of the absorbed plutonium was excreted in the urine (Khokhryakov et al. 2003). Recent recommendations suggest using the Ca-DTPA complex for initial treatment and the Zn-DTPA complex for subsequent administrations (Ménétrier et al. 2005), although Zn-DTPA has not been universally authorized for use. Prolonged use of Ca-DTPA results in the depletion of essential metals (particularly zinc), whereas gram quantities of Zn-DTPA can be administered indefinitely without such depletion. With the exception of the liver, DTPA appears to form complexes primarily with plutonium in soft tissues other than the liver, which exchanges more

rapidly with plutonium in plasma than in bone. Therefore, DTPA may be less effective in reducing bone plutonium levels (Durbin 1973).

Several recent investigations have focused on methods to enhance DPTA-based decorporation of plutonium in laboratory animals. Encapsulation of DTPA in conventional and stealth liposomes resulted in increased accumulation of DTPA in liver, bone, and spleen of rats administered a single intravenous dose of ^{238}Pu (as the citrate) and, presumably, increased decorporation of plutonium from these tissues and increased urinary excretion (Phan et al. 2004, 2006b). Previous reports had demonstrated that DTPA liposomes were more efficient than free DTPA at reducing plutonium deposited in bone and liver of mice (Rahman et al. 1973; Rosenthal et al. 1975). Pulmonary administration of a dry powder formulation of DTPA to rats that had been exposed (nose only) to aerosols of relatively insoluble $^{239}PuO_2$ resulted in a 3-fold increase in plutonium urinary excretion in the absence of enhanced dissolution of $^{239}PuO_2$ in the lungs (Gervelas et al. 2007; Sérandour et al. 2007). Lifetime oral administration (via drinking water) of ZnDTPA to rats that had received single intravenous injection of ^{239}Pu (as the citrate) reduced the incidence of osteosarcomas (Volf et al. 1999).

Other agents have been recently tested for efficacy in decorporation of internalized plutonium. Oral or intravenous administration of octadentate spermine-based siderophore analogues, 3,4,3-LIHOPO and 4,4,4-LIHOPO, appears to be much more effective than DTPA for decorporation of internalized plutonium in laboratory animals (Durbin et al. 2003; Ramounet-Le Gall et al. 2003). Orally-administered amphipathic triethylenetetraminepentaacetic acids (TT) appear to be useful in removal of plutonium and other actinide elements from the body, particularly when longer-term decorporation is indicated (Miller et al. 2006).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No information was located regarding reduction of the toxic effects of plutonium through interfering with mechanisms of action.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of plutonium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the

initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of plutonium.

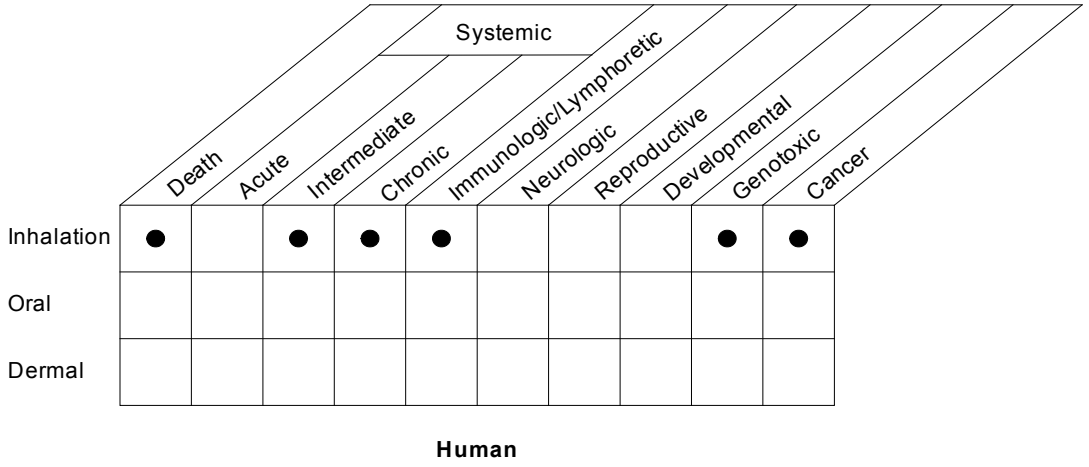
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

3.12.1 Existing Information on Health Effects of Plutonium

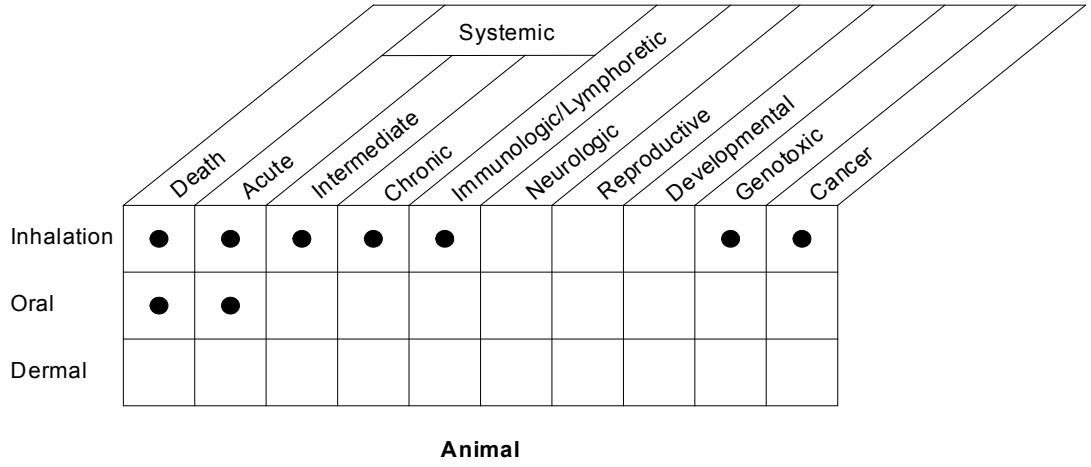
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to plutonium are summarized in Figure 3-11 for radioactive plutonium. The purpose of this figure is to illustrate the existing information concerning the health effects of plutonium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-11 graphically describes whether a particular health effect end point has been studied for a specific route and duration of exposure. Information on health effects in humans is very limited largely because exposed populations are small. Epidemiological studies of people who have been occupationally exposed by inhalation to plutonium have evaluated end points such as mortality, cancer, and systemic effects following chronic-duration exposure. No information on health effects in humans after acute- or intermediate-duration exposure to plutonium was located. Information on health effects from animal studies is more extensive than that which has been reported in epidemiological studies. These studies in animals provide information on health effects following both acute- and intermediate-duration inhalation exposure and limited information on acute oral exposure.

Figure 3-11. Existing Information on Health Effects of Plutonium



Human



Animal

● Existing Studies

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The possibility of brief exposure of humans to plutonium exists at hazardous waste sites or at accidental spill sites. However, no data are available for humans exposed acutely via inhalation or oral routes. Information on the toxicity of plutonium in laboratory animals following single high-dose inhalation exposure is extensive and indicates that the lung is the main target organ for inhaled plutonium. Laboratory animals exposed by this route have developed pneumonitis, fibrosis, metaplasia, and cancer. Acute exposure of laboratory animals to lower doses of plutonium would be useful to identify possible inhalation toxicity in humans. Limited information on adverse effects in laboratory animals following acute oral exposure indicates that the gastrointestinal tract is the main target organ. However, kinetic studies indicate that plutonium absorbed from the gastrointestinal tract is distributed to the skeleton and other tissues; therefore, other organs may also be affected. Because there are no data on humans, and animal data are insufficient, additional information is needed on adverse effects following acute exposure by the oral route. No data are available on adverse effects following acute dermal exposure in humans or animals. Limited information from kinetics studies in humans and animals indicates that there is little absorption of plutonium through intact skin. However, plutonium deposited in wounds is absorbed and distributes to numerous organs, including regional lymph nodes and the liver. Since industrial accidents resulting in plutonium-contaminated wounds are known to occur, additional information on adverse effects following this type of exposure would be helpful. One outstanding problem with all of the existing acute exposure tests in laboratory animals is that the doses tested are extremely high. Further single-dose studies for all exposure routes using a number of lower exposure concentrations would be useful in determining any dose-response relationship for adverse health effects.

Intermediate-Duration Exposure. All of the major studies of cancer and other health end points in animals have involved lifetime follow up of animals acutely exposed to plutonium aerosols. The relatively long retention time of plutonium in the body produces a chronic radiation dosing of tissues that retain plutonium. These studies have provided the bases for absorbed radiation dose-response relationships for inhaled plutonium compounds (e.g., $^{238}PuO_2$, $^{238}PuO_2$, and $^{238}Pu[NO_3]_4$). Toxicokinetic studies, and models derived from these studies, allow predictions of the tissue distribution of plutonium that would be expected with repeated exposures. These can be used to predict dose-response relationships for repeated dosing scenarios. The feasibility of conducting studies of intermediate- or chronic-duration exposures to plutonium compounds should be weighed against current uncertainties in predicting the

outcomes from existing knowledge. Furthermore, repeated exposure does not alter risk; the total dose of alpha radiation is important, not the temporal pattern of exposure.

Few studies of the health effects of plutonium administered to animals by the oral route have been reported. A single study in rats found profound effects on the gastrointestinal epithelium, consistent with radiation-induced injury. Given the relatively small fractional absorption of ingested plutonium (<0.1% of administered dose), it is very likely that repeated (or single) oral dosing studies that produce systemic toxicity will produce lethal effects on the gastrointestinal tract. Thus, the feasibility of conducting studies of intermediate- or chronic-duration oral exposures to plutonium compounds should be weighed against current uncertainties in predicting the outcomes from existing knowledge.

Chronic-Duration Exposure and Cancer. Epidemiological studies of occupational cohorts with long-term exposure to plutonium include those established from employees at U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). Studies of Mayak cohorts provide evidence for an association between cancer mortality and exposure to plutonium. Plutonium dose-response relationships for lung cancer mortality have been corroborated in four Mayak studies (Gilbert et al. 2004; Jacob et al. 2005; Kreisheimer et al. 2003; Sokolnikov et al. 2008). Studies of U.K. and U.S. facilities have examined cohorts of workers who had substantially lower estimated plutonium exposures and corresponding internal radiation doses than the Mayak cohorts. Collectively, findings from these studies are not as consistent as the Mayak studies; although significantly higher incidence of cancer mortality in certain groups of plutonium workers has been found in some studies, higher cancer incidence and/or risks for tissues that received the highest plutonium radiation doses (i.e., lung, liver, bone) have not been found, making causal connections of these outcomes to plutonium exposure more uncertain (Brown et al. 2004; Carpenter et al. 1998; Gilbert et al. 1989b; McGeoghegan et al. 2003; Omar et al. 1999; Wing et al. 2004). Uncertainties in exposures received by each of these populations are a major contributor to the overall uncertainty in estimates of radiation doses and dose-response relationships. For the Mayak cohort, an extensive collaborative effort between U.S. and Russian scientists has led to many improvements in both external and internal doses. The improved doses (Leggett et al. 2005) have not been used in published analyses, but are likely to be used future analyses (Leggett et al. 2005; Vasilenko et al. 2007). Continued follow up of these cohorts, using improved exposure estimates, would extend our understanding of dose-response relationships.

All of the major studies of cancer and other health effects in animals have involved lifetime follow up of animals acutely exposed to plutonium aerosols. The relatively long retention time of plutonium in the body produces a chronic radiation dosing of tissues that retain plutonium. These studies have provided the bases for absorbed radiation dose-response relationships for inhaled plutonium compounds (e.g., $^{238}PuO_2$, $^{239}PuO_2$, and $^{239}Pu[NO_3]_4$). Toxicokinetic studies, and models derived from these studies, allow predictions of the tissue distribution of plutonium that would be expected with repeated exposures. These can be used to predict dose-response relationships for repeated dosing scenarios. The feasibility of conducting studies of chronic-duration exposures to plutonium compounds should be weighed against current uncertainties in predicting the outcomes from existing knowledge.

Few studies of the health effects of plutonium administered to animals by the oral route have been reported. A single study in rats found profound effects on the gastrointestinal epithelium, consistent with radiation-induced injury. Given the relatively small fractional absorption of ingested plutonium (<0.1% of administered dose), it is very likely that repeated (or single) oral dosing studies that produce systemic toxicity will produce lethal effects on the gastrointestinal tract. Thus, the feasibility of conducting studies of chronic-duration oral exposure to plutonium compounds should be weighed against current uncertainties in predicting the outcomes from existing knowledge.

Genotoxicity. Although epidemiological studies do not provide conclusive evidence that plutonium produces genetic damage in humans, results of some studies provide suggestive evidence of dose-related increases in chromosomal aberrations in plutonium workers with measurable internalized plutonium. *In vitro* tests using human lymphocytes irradiated with plutonium demonstrated increases in sister chromatid exchange. Laboratory animals have exhibited increases in chromosomal aberrations in blood lymphocytes following exposure to plutonium by inhalation. Other effects in plutonium-exposed animals include dominant lethality and reciprocal chromosomal translocation. *In vitro* tests using mammalian cells confirm the *in vivo* results. The evidence is clear that plutonium is genotoxic. However, more extensive study of occupationally exposed individuals would be useful, and would hopefully clarify the equivocal reports of previous studies. Results of *in vitro* assessment of the potential for plutonium-induced hprt mutations would also be useful.

Reproductive Toxicity. No data are available regarding the reproductive toxicity of plutonium after inhalation, oral, or dermal exposure in either humans or animals. In laboratory animals given a single injection of a high dose of plutonium, significantly increased incidences of fetal death were reported and attributed to dominant lethality. Kinetic studies following single injection of plutonium indicate that

plutonium is distributed to the testes or ovaries of laboratory animals (Green et al. 1976, 1977) and is retained there for an indefinite period of time (>575 days) (Green et al. 1977; Taylor 1977). However, Brooks et al. (1979) noted the lack of significantly increased frequency of chromosomal aberrations in spermatogonia of rodents following intravenous injection of ^{239}Pu (as the citrate) at levels high enough to induce marked life shortening and increased cancer incidence. Therefore, studies designed to assess the reproductive toxicity of internalized plutonium do not appear necessary at this time.

Developmental Toxicity. No data are available regarding the developmental toxicity of plutonium after inhalation, oral, or dermal exposure in either humans or animals. However, results of kinetics studies in which animals were given a single injection of plutonium demonstrated that plutonium crosses the placenta and is retained in the fetus (DOE 1978c; Green et al. 1977). These results indicate a potential for adverse health effects in fetuses exposed to plutonium via their mothers; animal studies could be designed to investigate the developmental toxicity of internalized plutonium.

Immunotoxicity. No data are available regarding the immunotoxicity of plutonium after inhalation, oral, or dermal exposure in humans. In dogs exposed to plutonium via inhalation for a single day, damage to lymph nodes was observed in conjunction with radiation pneumonitis (Gillett et al. 1988). Once plutonium particles have been deposited in the lung, macrophages play a role in the clearing process. In this clearing process, macrophages phagocytize plutonium particles and ultimately deposit them in the lymph nodes. This mechanism may lead to secondary damage to the lymph nodes and thus to the immune system. In dogs given a single subcutaneous injection of plutonium, damage to lymph nodes draining the injection site, as well as lymphopenia, were observed (Dagle et al. 1984). The studies in dogs, together with knowledge of the clearing process in the lung, indicate that studies designed to evaluate the direct toxic effects of plutonium on the immune system would be useful.

Neurotoxicity. No studies have been performed to determine the neurotoxicity of plutonium. However, cells and tissues of the nervous system may be less radiosensitive than faster regenerating cells of the gastrointestinal tract or pulmonary epithelium. Consequently, neuronal impairment would not be expected. For this reason, assessment of plutonium neurotoxicity is not considered necessary at this time.

Epidemiological and Human Dosimetry Studies. Epidemiological studies of occupational cohorts with long-term exposure to plutonium include those established from employees at U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). Studies of Mayak cohorts provide

evidence for an association between cancer mortality and exposure to plutonium. Plutonium dose-response relationships for lung cancer mortality have been corroborated in four Mayak studies (Gilbert et al. 2004; Jacob et al. 2005; Kreisheimer et al. 2003; Sokolnikov et al. 2008). Studies of U.K. and U.S. facilities have examined cohorts of workers who had substantially lower estimated plutonium exposures and corresponding internal radiation doses than the Mayak cohorts. Collectively, findings from these studies are not as consistent as the Mayak studies, although significantly higher incidence of cancer mortality in certain groups of plutonium workers has been found in some studies, higher cancer incidence and/or risks for tissues that received the highest plutonium radiation doses (i.e., lung, liver, bone) have not been found, making causal connections of these outcomes to plutonium exposure more uncertain (Brown et al. 2004; Carpenter et al. 1998; McGeoghegan et al. 2003; Omar et al. 1999; Wing et al. 2004). Uncertainties in exposures received by each of these populations are a major contributor to the overall uncertainty in estimates of radiation doses and dose-response relationships. For the Mayak cohort, an extensive collaborative effort between U.S. and Russian scientists has led to many improvements in both external and internal doses. The improved doses (Leggett et al. 2005) have not been used in published analyses, but are likely to be used future analyses (Leggett et al. 2005; Vasilenko et al. 2007). Continued follow up of these cohorts, using improved exposure estimates, would extend our understanding of dose-response relationships. Examination of these cohorts for end points other than cancer may extend our understanding of dose-response relationships for effects that have been consistently observed in animals (e.g., lymphopenia and neutropenia and potential secondary consequences of these effects on the immune system). Continued epidemiological studies should receive high priority.

Biomarkers of Exposure and Effect.

Exposure. Biomarkers of exposure to plutonium are well established. Plutonium-specific radioactivity from internalized plutonium can be detected by external radiation detection devices. Plutonium can also be detected in the blood, urine, feces, and tissue samples from individuals who have internalized plutonium deposits. Estimates of the extent of exposure can be made using PBBK models. Additional studies designed to assess biomarkers of exposure to plutonium are not necessary.

Effect. Biomarkers of effect resulting from plutonium-released radiation are not specific to plutonium. Radiological effects in animals exposed to plutonium have been well documented. Additional studies of biomarkers of effect for plutonium are not necessary.

Absorption, Distribution, Metabolism, and Excretion. For laboratory animals, detailed quantitative information is available regarding the absorption, distribution, and excretion of plutonium compounds following acute exposure by inhalation or injection. There is no information on the toxicokinetics of plutonium following chronic exposure to low levels, and studies in this area would be more applicable to human exposure situations than single exposure studies. Information concerning the toxicokinetics of plutonium in adult animals following oral exposure is available. However, previous animal studies have indicated that very little plutonium is absorbed following oral exposure. Therefore, studies of kinetics following oral exposure are not needed at this time. Additional studies of age-related differences in the toxicokinetics of plutonium would be useful. Little is known regarding the absorption, distribution, and excretion of plutonium compounds following dermal exposure. However, it appears that the skin is an effective barrier against most plutonium compounds.

Comparative Toxicokinetics. Numerous studies of the distribution of plutonium in humans (i.e., autopsy studies of individuals occupationally exposed to plutonium) have shown that the general pattern of distribution of plutonium in humans is consistent with that observed in various animal models, with the highest portion of the body burden in lung (following inhalation exposures), skeletal tissues, and liver. Epidemiologic studies of health outcomes among workers in industries that produce and/or process plutonium have provided evidence for increased risk of lung, liver, and bone cancers in association with exposures to plutonium. These observations are consistent with the pattern of health effects observed in animals, particularly dogs. Additional comparative toxicokinetics studies do not appear necessary at this time.

Methods for Reducing Toxic Effects. Current strategies for reducing toxic effects of plutonium are to hasten the elimination of plutonium from the body by administering complexing/chelating agents. A major challenge in applying this strategy is that Pu(IV) in the body forms insoluble precipitates within tissues which are unavailable for interaction with dissolved substances. Most agents that have been tested perform relatively poorly at mobilizing plutonium from bone, which harbors a large fraction of the body burden. Continued research to develop more effective agents that have low toxicity would potentially lead to more successful therapies for reducing toxic effects of plutonium. This research should receive high priority.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Studies conducted in animals have shown that exposures to plutonium that occur in young animals result in greater distribution of plutonium to skeletal tissues and that neonates absorb a substantially larger fraction of an ingested dose of plutonium than adults. These observations suggest that infants and children may have a higher, or altered, susceptibility to plutonium toxicity. Studies on toxicokinetics and health effects for exposures that occur during postnatal development would improve our understanding of potential vulnerabilities of children to plutonium.

In adults, approximately 50% of the plutonium body burden resides in bone. The potential effects of increased mobilization of bone mineral during pregnancy, to support the development of the fetal skeleton, on maternal-fetal transfer of plutonium has not been examined. Studies of plutonium levels in offspring of mothers who carry a bone burden of plutonium would improve our understanding of potential pre- and postnatal exposures the might emanate from maternal-fetal transfer.

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

3.12.3 Ongoing Studies

Dr. Charles Watson, from Washington State University, and several active or retired Pacific Northwest National Laboratory scientists are finishing a comprehensive report on the biological effects of inhaled $^{239}PuO_2$ in beagle dogs; the completed report will be submitted to Radiation Research.

The following ongoing studies were identified in the Federal Research In Progress database (FEDRIP 2007).

Dr. Richard Day, from the University of Pittsburgh, Pittsburgh, Pennsylvania, is continuing longitudinal follow-up health effects assessment of radiation exposures in a cohort of workers from the Mayak facilities in Russia. Dr. Martha Linet, from the Division of Cancer Epidemiology and Genetics, National Cancer Institute, is studying populations exposed to occupational radiation, which includes a cohort of 26,000 Mayak nuclear facility workers (in the former Soviet Union) exposed to particularly high doses of external radiation and alpha radiation from internalized plutonium. Dr. Ray Lloyd, from the University of Utah, Salt Lake City, Utah, is testing recently-developed plutonium biokinetic models to human data from Russian nuclear workers to extend current biokinetic, dosimetric, and risk models to the human.

4. CHEMICAL, PHYSICAL, AND RADIOLOGICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of plutonium and selected plutonium compounds is located in Table 4-1.

4.2 PHYSICAL, CHEMICAL, AND RADIOLOGICAL PROPERTIES

Information regarding the physical and chemical properties of plutonium and selected plutonium compounds is located in Table 4-2. Information regarding the radiological properties of selected plutonium isotopes is located in Table 4-3. The decay schemes for ^{239}Pu and ^{241}Pu are summarized in Figures 4-1 and 4-2, respectively.

Plutonium is a member of the actinide series and is a human-made element (atomic number 94). Actinides are the 15 elements starting with actinium, atomic number 89, and extending to lawrencium, atomic number 103. All of the isotopes of the actinide elements are radioactive. Plutonium was the first human-made element to be synthesized in weighable amounts. ^{238}Pu was discovered in 1940 by Seaborg and co-workers; it was synthesized by the bombardment of uranium with deuterons (^{2}H). Isotopes with mass numbers 228–247 have been identified for plutonium; all are radioactive. The most important isotope is ^{239}Pu, which has a half-life that is sufficiently long (24,100 years) to permit its preparation in large amounts, making it possible to perform chemical studies. Metallic plutonium exists in six allotropic modifications under ordinary pressure; a seventh phase exists under high pressure. Five oxidation states, Pu(III), Pu(IV), Pu(V), Pu(VI), and Pu(VII), are known to exist in compounds and solution (Clark et al. 2006). Plutonium(III) and plutonium(IV) are considered to be the reduced forms of plutonium, while plutonium(V) and plutonium(VI) are the oxidized forms (DOE 1987a). While the atomic mass of plutonium depends on the isotope, 244 is frequently listed as the mass of plutonium on periodic tables. ^{244}Pu is the isotope with the longest half-life.

Table 4-1. Chemical Identity of Plutonium and Selected Plutonium Compounds

Characteristic	Information[a]		
Chemical name	Plutonium	Plutonium(IV) dioxide	Plutonium nitride
Synonym(s)	No data	Plutonium dioxide	No data
Registered trade name(s)	No data	No data	No data
Chemical formula	Pu	PuO_2	PuN
Identification numbers:			
CAS registry	7440-07-5[b]	12059-95-9	12033-54-4
NIOSH RTECS	No data	No data	No data
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
EINECS	231-117-7	235-037-3	No data
HSDB	6465	No data	No data
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Plutonium and Selected Plutonium Compounds

Characteristic	Information[a]			
Chemical name	Plutonium nitrate	Plutonium(VI) fluoride	Plutonium(IV) Oxalate[c]	Plutonium(IV) fluoride
Synonym(s)	Nitric acid, plutonium(4+) salt	Plutonium hexafluoride	No data	Plutonium tetrafluoride
Registered trade name(s)	No data	No data	No data	No data
Chemical formula	$Pu(NO_3)_4$	PuF_6	$Pu(C_4O_8)_2$	PuF_4
Identification numbers:				
CAS registry	13823-27-3	13693-06-6	14448-76-1[c] 13278-81-4[d]	13709-56-3
NIOSH RTECS	No data	No data	No data	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data	No data
EINECS	238-979-3[e]	No data	No data	No data
HSDB	No data	No data	No data	No data
NCI	No data	No data	No data	No data

[a]All information obtained from ChemIDplus 2009, Lide 2008, and HSDB 2009 except where noted
[b]This is the generic CAS Registry Number for plutonium (unspecified form). Each isotope has an individual CAS Registry Number (Table 4-3)
[c]ChemBioFinder 2009
[d]Clark et al. 2006
[e]This EINCES number refers to plutonium nitrate (CAS Registry No. 14913-29-2) with a chemical formula of $Pu(NO_3)_x$. (ChemIDplus 2009)

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

Table 4-2. Physical and Chemical Properties of Plutonium and Selected Plutonium Compounds

Property	Information[a]		
Chemical name	Plutonium	Plutonium dioxide	Plutonium nitride
Molecular weight[b]	244	276	258
Physical description	Silver, white metal Six allotropic modifications under ordinary pressure[c]	Yellow-brown cubic crystals	Gray cubic crystals
Melting point	640 °C	2,390 °C	2,550 °C
Boiling point	3,228 °C	No data	No data
Density	19.7 g/cm^3	11.5 g/cm^3	14.4 g/cm^3
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	No data	No data	No data
Organic solvents	No data	No data	No data
Other	Soluble in hydrochloric acid; insoluble in nitric acid, concentrated hydrogen sulfide	No data	No data
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Plutonium and Selected Plutonium Compounds

Property	Information[a]			
Chemical name	Plutonium nitrate	Plutonium hexafluoride	Plutonium oxalate	Plutonium tetrafluoride
Molecular weight[b]	No data	358	No data	320
Physical description	No data	Red-brown orthorhombic crystals	Green-yellow solid[d]	Red-brown monoclinic crystals
Melting point	No data	51.6 °C	No data	1,037 °C
Boiling point	No data	No data	No data	No data
Density	No data	5.08 g/cm^3	No data	7.1 g/cm^3
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	No data	No data	No data	No data
Organic solvents	No data	No data	No data	No data
Other	No data	No data	No data	No data
Partition coefficients:				No data
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

[a]All information obtained from HSDB 2009 and Lide 2008, except where noted
[b]Molecular weights will be dependent on the isotope of plutonium
[c]α-phase, simple monoclinic; β-phase, body-centered monoclinic; γ-phase, face-centered orthorhombic; δ phase, face-centered cubic; δ'' phase, body-centered tetragonal; $\varepsilon\varepsilon$ phase, body-centered cubic (Clark et al. 2006)
[d]$Pu(C_2O_4)_2 \cdot 6H_2O$ (CAS No. 26588-74-9) (Clark et al. 2006)

Table 4-3. Radiological Properties of Plutonium Isotopes

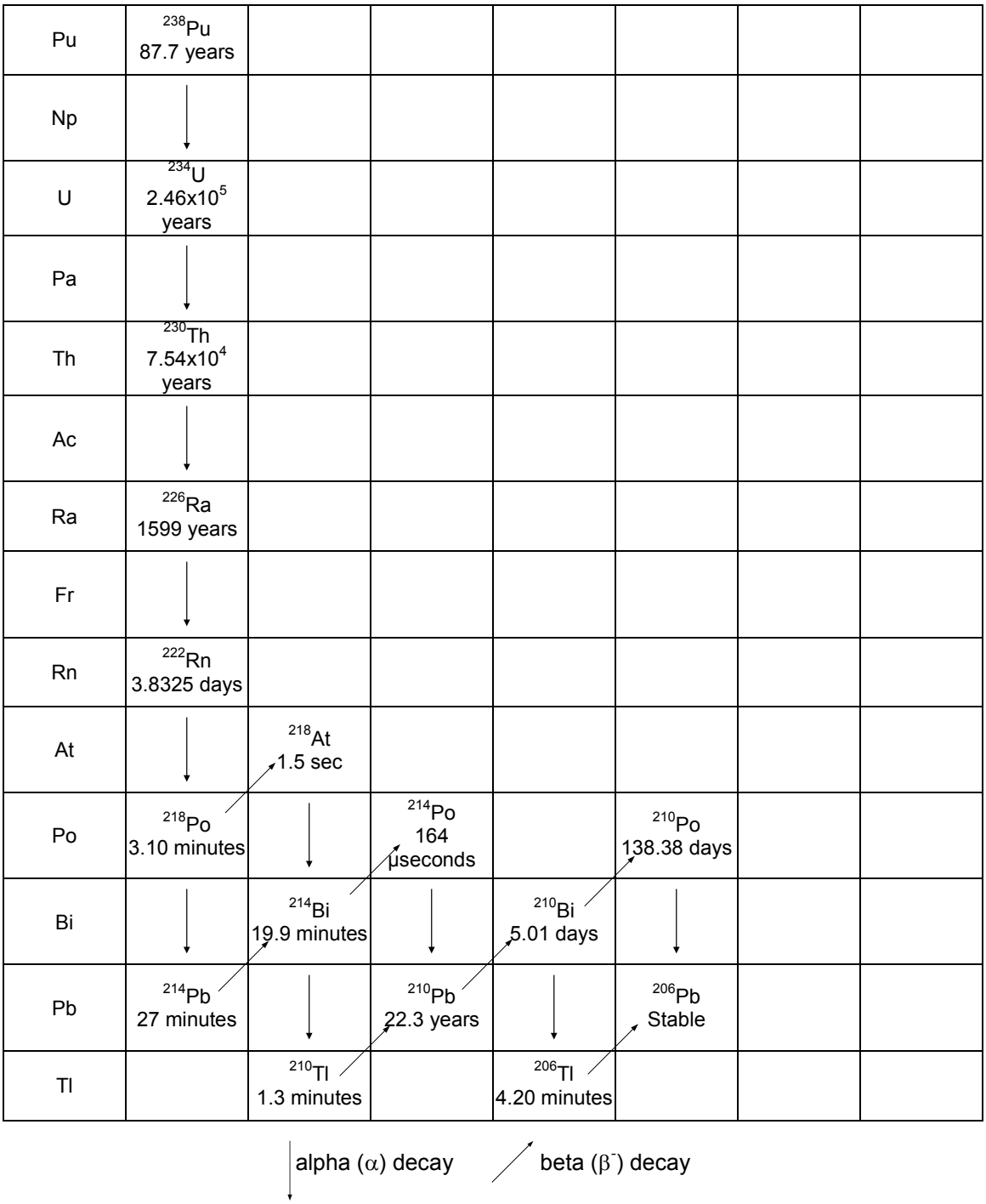
Isotope	CAS Registry No.	Half-life	Decay mode(s)/ Energy (MeV)	Decay product(s)	Specific activity (Ci/g)
^{236}Pu	15411-92-4	2.87 years 1.5×10^{9} years	α/5.867 MeV SF/1.9×10^{-7} MeV	^{232}U	540
^{237}Pu	15411-93-5	45.7 days	EC/0.220(99.9%) α/ 5.747 (0.003%)	^{233}U	12,100[a]
^{238}Pu	13981-16-3	87.7 years 4.75×10^{10} years	α/5.593 SF/ 1.8×10^{-7}	^{234}U	17
^{239}Pu	15117-48-3[b] 19257-39-7[c]	2.410×10^{4} years 8×10^{15} years	α/5.244 SF/3×10^{-10}	^{235}U	0.063
^{240}Pu	14119-33-6	6.56×10^{3} years 1.14×10^{11} years	α/5.255 SF/5.7×10^{-6}	^{236}U	0.23
^{241}Pu	14119-32-5	14.3 years <6×10^{16} years	β^-/0.0208 (99+%) α/5.139 (0.002%) SF/>2.4×10^{-14}	^{241}Am ^{237}U	100
^{242}Pu	13982-10-0	3.75×10^{5} years 6.77×10^{10} years	α/4.983 SF/5.5×10^{-4}	^{238}U	0.0040
^{243}Pu	15706-37-3	4.956 hours	β^-/0.582	^{243}Am	2.6×10^{6}[c]
^{244}Pu	14119-34-7	8.00×10^{7} years 6.6×10^{10} years	α/4.665 (99.9%) SF/0.12	^{240}U	1.8×10^{-5}

[a]Calculated values
[b]Another CAS Registry number listed for ^{239}Pu is 97918-67-7
[c]CAS Registry Number for $^{239}Pu^{4+}$ ion

α = alpha particle emission; β^- = negative beta emission; SF = spontaneous fission

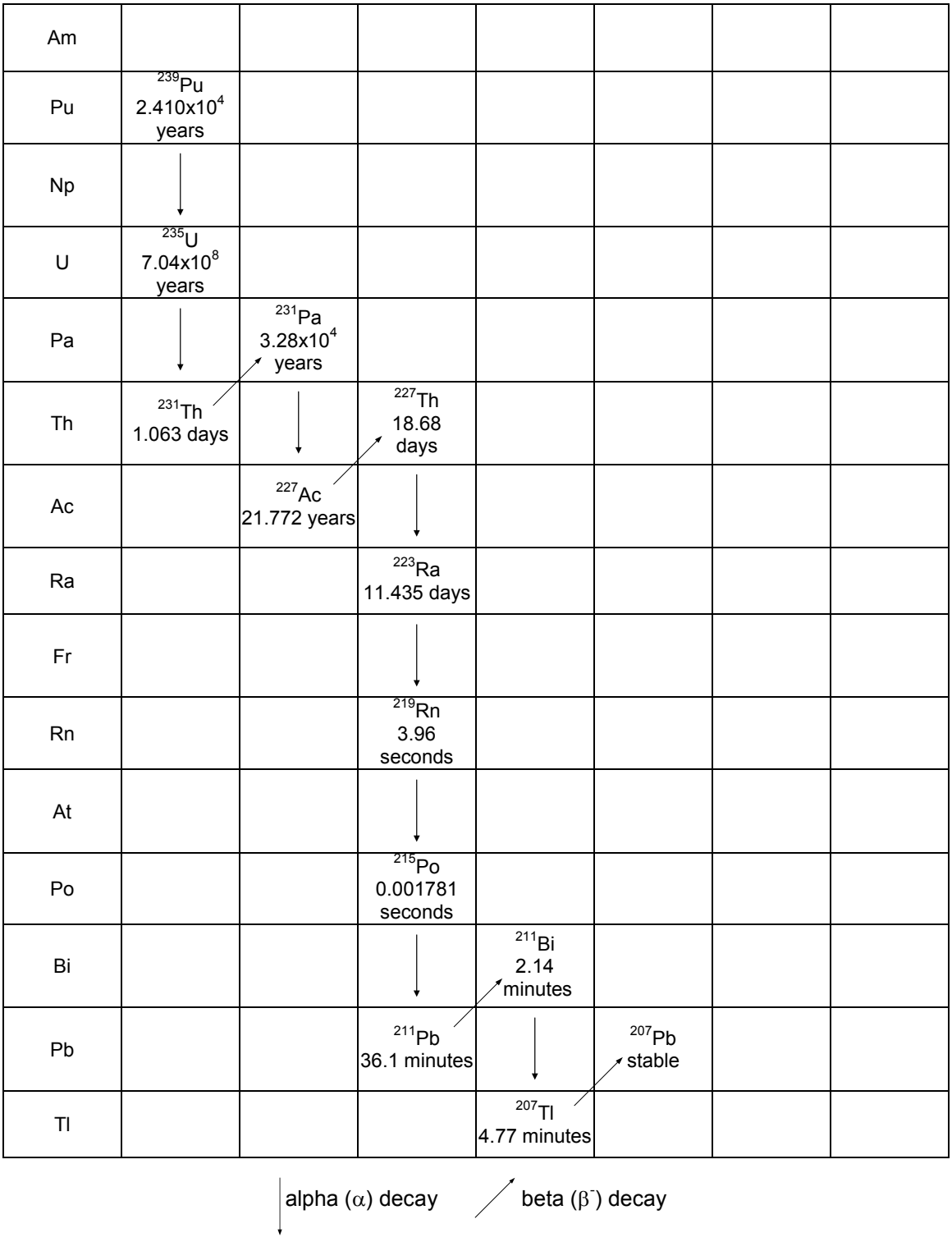
Sources: Baum et al. 2002; ChemIDplus 2009; Clark et al. 2006; DOE 2005a; Lide 2008

Figure 4-1. ^{238}Pu Decay Series



Sources: Baum et al. 2002; Lide 2005

Figure 4-2. ^{239}Pu Decay Series



Sources: Baum et al. 2002; Lide 2005

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

5.1 PRODUCTION

No information is available in the TRI database on facilities that manufacture or process plutonium because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 1998).

Plutonium was the first human-made element to be synthesized in weighable amounts. ^{238}Pu was discovered in 1940 by Seaborg and co-workers; it was synthesized by the bombardment of uranium with deutrons (^{2}H). Isotopes with mass numbers 228–247 have been identified; all are radioactive (Clark et al. 2006). Trace amounts of plutonium are found worldwide, mostly due to fall-out from atmospheric nuclear testing, which ended in 1980 and released several isotopes of plutonium, including ^{238}Pu, ^{239}Pu, ^{240}Pu, and ^{241}Pu (Clark et al. 2006; DOE 2005a; Eisenbud and Gesell 1997). Plutonium is not considered a naturally occurring element; however, trace amounts of ^{239}Pu are found in naturally occurring uranium ores, but the amounts are in such small amounts that extraction is not practical (Clark et al. 2006; EPA 2006b; Lide 2008). Small amounts of ^{244}Pu exist in nature from remnants of primordial stellar nucleosynthesis (Clark et al. 2006). Small amounts of plutonium were produced in natural reactors, such as the Oklo natural reactor in Gabon, which existed about 2 billion years ago (DOE 2005a). The most common form of plutonium found in the environment is ^{239}Pu, followed by ^{240}Pu (DOE 1999a).

Large quantities of plutonium were first produced during the 1940's as part of the Manhattan Project in order to produce the atomic bomb. Production continued throughout the years of the Cold War (DOE 2005a). The United States built and operated 14 plutonium-production reactors at the Hanford and Savannah River Sites starting in 1944 and ending in 1988 with the shutdown of the last reactor. A total of approximately 100 metric tons of plutonium was produced during this time (DOE 1996b). Currently, ^{238,239,240,241,242}Pu are commercially available from Oak Ridge National Laboratory for laboratory research (DOE 2007a).

Plutonium is a byproduct of nuclear energy generation. Most plutonium isotopes are produced in uranium-fueled reactors through neutron capture by ^{238}U (Clark et al. 2006; Koch 2005). Approximately 1,855 metric tons of plutonium were estimated to exist worldwide at the end of 2003. Most of the plutonium (1,370 metric tons) was found in irradiated fuel from nuclear power plants. A plutonium

production rate of 70–75 metric tons/year was estimated for reactors worldwide at the end of 2003 (Albright and Kramer 2004; Clark et al. 2006).

Plutonium from spent nuclear fuel is recovered by the PUREX (Plutonium, Uranium, Reduction, Extraction) liquid-liquid extraction process (Clark et al. 2006; Koch 2005). This process is the main method to separate plutonium and uranium from used reactor fuel and neutron-irradiated actinide material (Clark et al. 2006). The basis of the PUREX process involves the selective extraction of U(VI) and Pu(IV) from a nitric acid solution of dissolved irradiated fuel into an aliphatic hydrocarbon solvent that contains tri(*n*-butyl)phosphate. Most of the fission products are left in the acid solution (Clark et al. 2006). Other processes (e.g., the bismuth phosphate process at the Hanford site) have been used to separate and purify plutonium from irradiated fuels; however, many of these are now of only historical interest (Clark et al. 2006).

Modern plutonium metal production involves recovery and recycling of residues and scrap (Clark et al. 2006). Plutonium metal is produced by pyrochemical processes in either centrifugal or stationary bombs. The major pyrochemical processes used by large facilities are bomb reduction of plutonium tetrafluoride, direct oxide reduction (DOR), molten salt extraction (MSE), anode casting, electrorefining (ER), and pyroredox. In DOR, plutonium dioxide is reduced with calcium metal to produce plutonium metal and calcium oxide. The MSE process reduces the amount of ^{241}Am, which is a decay product of ^{241}Pu, in plutonium metal. It also separates the more reactive elements (e.g., rare earth (lanthanide), alkali, and alkaline-earth metals) from the plutonium metal. In the ER process, liquid plutonium oxidizes from the anode ingot, which is cast from the plutonium metal derived from the MSE process, into a molten-salt electrolyte. The Pu(III) ions are transported through the salt to the cathode where they are reduced to the metal. The pyroredox process recovers plutonium metal from impure scrap material and from spent anode heels from the ER process (Clark et al. 2006).

5.2 IMPORT/EXPORT

There is no information on the import or export of plutonium. The import and export of plutonium in the United States is governed by the U.S. Nuclear Regulatory Commission (USNRC 2009b).

5.3 USE

^{239}Pu was first used in fission weapons beginning in 1945 (DOE 2005a). In a reactor of a nuclear power plant, the fissioning of ^{235}U produce two or three neutrons, which can be absorbed by ^{238}U to produce

^{239}Pu. The ^{239}Pu formed can also absorb neutrons and undergo fission, which provides about one-third of the total energy produced in a typical commercial nuclear power plant (DOE 2005a). ^{238}Pu is used as a heat source in nuclear batteries to produce electricity in devices such as unmanned spacecraft, and interplanetary probes (DOE 2005a; Koch 2005). Plutonium is a carefully regulated material under government control. Small quantities are used in research laboratories (Clark et al. 2006) and quantities of plutonium oxides are used in MOX (mixed oxide plutonium and uranium) fuels as an alternative to low enriched uranium fuel used in light water nuclear power reactors (Makhijani 1997). ^{236}Pu and ^{242}Pu are used as tracers in plutonium determinations in environmental and biological samples (Brouns 1980; DOE 1997; Kressin et al. 1975).

5.4 DISPOSAL

Plutonium isotopes are classified as hazardous substances under Section 102(a) of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), commonly known as Superfund. Under CERCLA, spills or discharges into the environment of plutonium isotopes of more than 0.01 Ci (370 MBq) (^{238}Pu, ^{239}Pu, ^{240}Pu, ^{242}Pu, and ^{244}Pu), 1 Ci (3.7×10^4 MBq) (^{241}Pu), or 1,000 Ci (3.7×10^7 MBq) (^{237}Pu and ^{243}Pu) must be reported immediately to the National Response Center (EPA 2007c). The final reportable quantities for all radionuclides apply to chemical compounds containing the radionuclides and elemental forms regardless of the diameter of pieces of solid material (EPA 2007c).

During 1944–1988, most nuclear fuel rods and targets irradiated in the reactors at the 14 plutonium-production reactors at the Hanford and Savannah River Sites were reprocessed to extract the plutonium. When the Department of Energy stopped reprocessing spent-fuel elements in April 1992, approximately 2,700 metric tons of spent fuel were accumulated in 30 storage ponds. About 99% of this spent fuel is stored at the Hanford Site in Washington, the Savannah River Site in South Carolina, the Idaho National Engineering Laboratory, and West Valley in New York. Approximately 30,000 metric tons of spent fuel from commercial nuclear power plants are stored at more than 100 nuclear reactor sites around the United States (DOE 1996b). Most spent nuclear fuel is stored in specially designed pools at individual reactor sites around the country in 33 states (USNRC 2009a, 2009c).

The disposal of radioactive waste is regulated by the rules of the USNRC and EPA. Spent fuel, which contains approximately 0.88% ^{239,240,241,242}Pu combined, is considered high-level waste (HLW) (Murray 2005; Murray and Fentiman 2006). Currently, the preferred method for HLW disposal is deep underground burial in a mined cavity; however, no facilities in the United States have been authorized for

the disposal of HLW. An alternative to burial of spent fuel is to store it for future use as fuel for nuclear reactors. The uranium and plutonium could be extracted from spent fuel to be used as fuel in nuclear power plants.

Transuranic wastes (TRUs) contain significant amounts of plutonium or other transuranic elements. As of 2006, the Waste Isolation Pilot Plant (WIPP) near Carlsbad, New Mexico was the only operating geological disposal facility in the world; TRU has been disposed of in the WIPP since 1999 (Murray and Fentiman 2006).

In 2002, Yucca Mountain was approved by the Congress and the President as the site for the nation's first permanent spent nuclear fuel and high-level radioactive waste geologic repository (DOE 2007b). Most of the waste that may be disposed at Yucca Mountain will be spent nuclear fuel and high-level radioactive waste. About 90% of this waste is from commercial nuclear power plants and the rest comes from defense programs. Currently, this waste is stored at facilities in 43 states. By Department of Energy (DOE) projections, the earliest the proposed repository at Yucca Mountain could open and begin accepting waste is 2017; however, various steps must first be met before this can occur (EPA 2009). Spent fuels must be stored in water pools or in dry storage casks at nuclear plant sites until a repository is completed (Murray 2005).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Plutonium has been identified in at least 16 of the 1,689 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for plutonium is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, all are located within the United States.

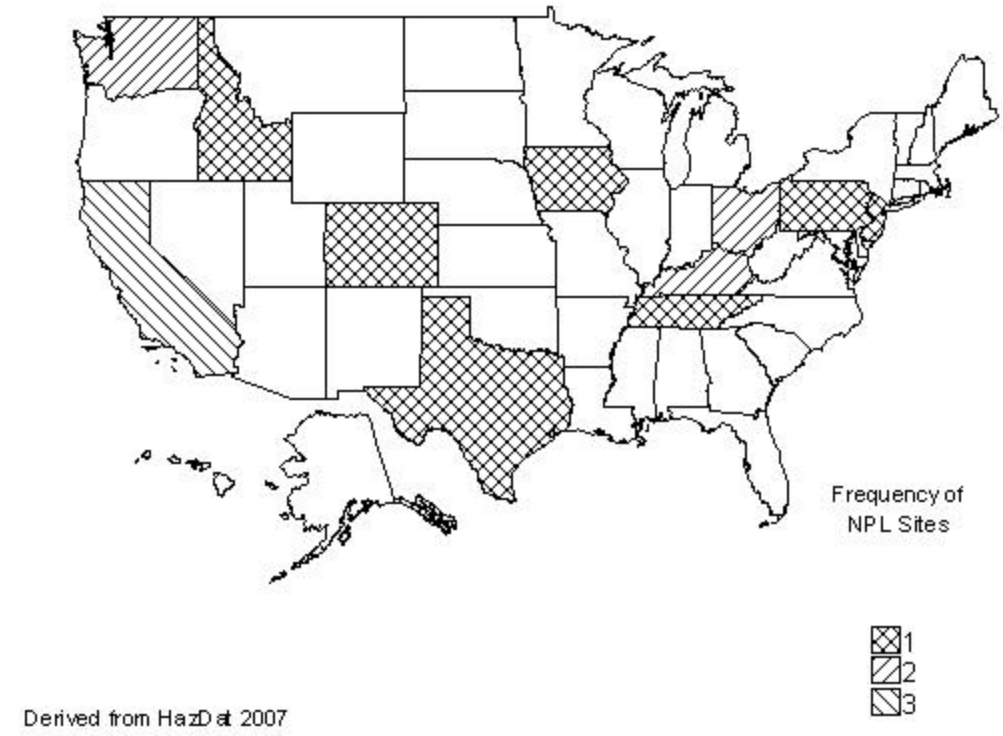
Trace amounts of plutonium are found worldwide, mostly due to fallout from atmospheric nuclear testing, which ended in 1980, and released several isotopes of plutonium, including ^{238}Pu, ^{239}Pu, ^{240}Pu, and ^{241}Pu (Clark et al. 2006; DOE 2005a; Eisenbud and Gesell 1997). Plutonium is not naturally occurring; however, trace amounts of ^{239}Pu are found in naturally occurring uranium ores, but the amounts are in such small amounts that extraction is not practical (Clark et al. 2006; Lide 2005). Small amounts of ^{244}Pu exist in nature from remnants of primordial stellar nucleosynthesis (Clark et al. 2006). Small amounts of plutonium were produced in natural reactors, such as the Oklo natural reactor in the African nation of Gabon, which existed about 2 billion years ago (DOE 2005a). The most common form of plutonium found in the environment is ^{239}Pu, followed by ^{240}Pu (DOE 1999a).

Large quantities of plutonium were first produced during the 1940s as part of the Manhattan Project in order to produce the atomic bomb. Production continued throughout the years of the Cold War (DOE 2005a). The United States built and operated 14 plutonium-production reactors at the Hanford, Washington and Savannah River, South Carolina sites starting in 1944 and ending in 1988 with the shutdown of the last reactor. A total of approximately 100 metric tons of plutonium was produced during this time (DOE 1996b).

The principal plutonium isotopes used in military and nonmilitary applications are ^{238}Pu and ^{239}Pu. These two isotopes are used because of their ease of production and their relatively long half-lives. ^{238}Pu is used as a heat source in nuclear batteries to produce electricity in devices such as unmanned spacecraft, and interplanetary probes (DOE 2005a; Koch 2005). ^{239}Pu and ^{240}Pu are produced in nuclear power plants as a product of nuclear fission as well as in production facilities for use in nuclear weapons.

Possible sources of plutonium to the environment include: past atmospheric weapons testing, accidents involving weapons transport, accidents involving failed space launches of satellites, operating nuclear reactors and radioisotope generators, fuel processing and reprocessing activities, and fuel transport

Figure 6-1. Frequency of NPL Sites with Plutonium and Selected Isotopes Contamination



(NEA/OECD 1981). Plutonium is a byproduct of nuclear energy generation. It is produced in uranium-fueled reactors through neutron capture by uranium-238 (^{238}U) (Clark et al. 2006; Koch 2005). Approximately 1,855 metric tons of plutonium were estimated to exist worldwide at the end of 2003, with 1,370 metric tons found within used fuel from nuclear power plants. A plutonium production rate of 70–75 metric tons/year was estimated for reactors worldwide at the end of 2003 (Albright and Kramer 2004; Clark et al. 2006).

The main sources of plutonium in the environment are releases from research facilities, past atmospheric nuclear weapons testing, waste disposal, nuclear weapons production facilities, and accidents (DOE 1999a). Atmospheric testing of nuclear weapons, which ended in 1980, is the source of most of the plutonium in the environment worldwide, which released approximately 10,000 kg of plutonium (DOE 2005a). Nuclear reactor accidents (e.g., the Chernobyl reactor in 1986) and other accidents involving non-U.S. nuclear-powered submarines or nuclear weapons have also released plutonium into the environment. The total amount of plutonium released during these accidents is small on a global scale as compared to the amount of plutonium released during atmospheric nuclear weapons testing. Plutonium released to the atmosphere reaches the earth's surface through wet and dry deposition to the soil and surface water. Once in these media, plutonium can sorb to soil and sediment particles or bioaccumulate in terrestrial and aquatic food chains.

6.2 RELEASES TO THE ENVIRONMENT

Concentrations of plutonium are generally expressed in terms of activity, either in the curie (Ci) or the SI unit, the becquerel (Bq), where 1 Ci=3.7x10^{10} Bq=0.037 TBq or 1 Bq=2.7x10^{-11} Ci=27 pCi. Activities may be converted into mass units using the specific activities for each plutonium isotope. Specific activities for various plutonium isotopes are provided in Table 4-3. Throughout this chapter, the units used to express concentration or intake of plutonium are generally the same units reported by the authors, which are followed by converted units in parenthesis. However, in some cases, the units originally reported by the authors may be converted (e.g., from Bq to mBq or from nCi to pCi) for ease of comparison of concentrations within a section. Common metric prefixes are provided in Table 6-1.

Possible sources of plutonium to the environment include: atmospheric weapons testing, accidents involving weapons transport, operating nuclear reactors and radioisotope generators, fuel processing and reprocessing activities, and fuel transport (NEA/OECD 1981). However, plutonium or plutonium

Table 6-1. Common Metric Prefixes

Factor	Prefix	Symbol	Factor	Prefix	Symbol
10^{-18}	atto	a	10^{2}	hecto	h
10^{-15}	femto	f	10^{3}	kilo	k
10^{-12}	pico	p	10^{6}	mega	M
10^{-9}	nano	n	10^{9}	giga	G
10^{-6}	micro	μ	10^{12}	tera	T
10^{-3}	milli	m	10^{15}	peta	P
10^{-2}	centi	c	10^{18}	exa	E

compounds are listed on the Superfund Amendments and Reauthorization Act (SARA) Section 313 toxic chemical list and, therefore, are not included in the Toxics Release Inventory (TRI).

6.2.1 Air

The main sources of plutonium in the environment are releases from research facilities, nuclear weapons testing, waste disposal, nuclear weapons production facilities, and accidents (DOE 1999a). Areas contaminated with plutonium, such as the Nevada Test Site or other national facilities, could release plutonium if the contaminated soils are re-suspended during windy or fire conditions (e.g., Cerro Grande fire in New Mexico), surface cleanup, construction, vehicular travel, or other disturbances to the contaminated soil (DOE 2005b).

Atmospheric testing of nuclear weapons, which ended in 1980, is the source of most of the plutonium in the environment worldwide, which released approximately 10,000 kg of plutonium (DOE 2005a). Approximately 320 kCi (1.2×10^4 TBq) of ^{239,240}Pu and 9 kCi (300 TBq) of ^{238}Pu have been released to the atmosphere by nuclear tests and distributed worldwide (Eisenbud and Gesell 1997). Concentrations of transuranics introduced into the environment through underground test venting, accidents involving U.S. nuclear weapons, and releases during weapon production operations have been negligible in comparison with those released during atmospheric testing of nuclear explosives in the 1960s (DOE 1980g).

In April, 1964, a Transit Navigational Satellite was launched in California with a payload that included a Satellite for a Nuclear Auxiliary Power Generator (SNAP-9A) containing 17 kCi (630 TBq) of ^{238}Pu. The rocket system failed and the satellite reentered the atmosphere in the Southern Hemisphere and burned over the Indian Ocean at an altitude of about 50 km (Harley 1980). The destruction of the SNAP-9A resulted in the largest single release of ^{238}Pu to the atmosphere, primarily in the form of very small oxide particles (Harley 1980). An estimated 37 TBq (1 kCi) of ^{239,240}Pu was released during the Chernobyl accident, April 26, 1986 (Clark et al. 2006). The only area around Chernobyl after the April 1986 accident with plutonium levels exceeding 4 kBq/m^2 was located within the 30-km zone. ^{239,240}Pu deposition densities ranged from 0.07 to 0.7 kBq/m^2 in the Gomel-Mogilev-Bryansk area, 200 km north-northeast of the reactor, and from 0.07 to 0.3 kBq m^2 in the Kaluga-Tula-Orel area, 500 km northeast of the reactor. At Korosten, located about 115 km southwest of the Chernobyl power plant, the ^{239,240}Pu deposition density due to the Chernobyl accident was about 0.06 kBq/m^2, 4–8 times lower than the ^{239,240}Pu deposition density from global fallout (UNSCEAR 2000b). Garger et al. (2006) reported that the

total flow of activity through the gaps of the shelter of the Chernobyl reactor measured during 1996–1999 was 8.64×10^9 Bq/year (0.234 Ci/year); 0.4% of this was due to ^{239,240}Pu.

Research facilities and plants have also released plutonium to the atmosphere. For example, the Department of Energy (DOE) Mound Plant in Miamisburg, Ohio, released about 30 Ci (1×10^{12} Bq) to the atmosphere from the beginning of its operation through 1976 (NEA/OECD 1981). The vast majority of these releases occurred in the 1960s. By 1972, total ^{238}Pu air releases were about 0.1% of the quantity released in 1967, and they have been much lower than that in the years since 1972 (Agency for Toxic Substances and Disease Registry 1998). A commercially operated reprocessing plant in West Valley, New York, has reportedly released 5×10^{-3} Ci (2×10^{-8} Bq) of plutonium to the atmosphere over the course of 6 years (NEA/OECD 1981). The Savannah River Site, which produced plutonium and tritium as well as other nuclear materials, released 1.4×10^{11} Bq (3.8 Ci) of plutonium to air during the period of 1954–1989 (Carlton et al. 1996). An estimated total air emissions from the Nevada Test Site (NTS) of 0.29 Ci (1.1×10^{10} Bq) ^{239,240}Pu was reported for calendar year 2004 (DOE 2005b). Air samplers in two areas of the NTS showed that ^{239,240}Pu is routinely detected due to blowing contaminated soil; however, concentrations are only slightly above minimum detectable concentrations. Air sampling in the past has shown that ^{238}Pu is not detected in air at the NTS (DOE 2005b).

Small amounts of various long-lived radionuclides, including ^{238}Pu, ^{239,240}Pu, and ^{241}Pu, are still released to the environment through state and federally permitted release points at the Hanford Site. Generally, the radionuclide emissions in these releases are near concentrations that are indistinguishable from background radionuclide concentrations that occur naturally or are from fallout (DOE 2005c). From 1994 to 2004, releases of ^{239,240}Pu to air from the Hanford Site ranged from 6×10^{-4} Ci (2×10^7 Bq) in 1998 to 1×10^{-4} Ci (4×10^6 Bq) during 2002–2004. During 2004, releases of ^{238}Pu to air ranged from 1.1×10^{-8} to 2.7×10^{-6} Ci (407–1.0×10^5 Bq) in three areas at the Hanford Site. Releases of ^{241}Pu to air were 1.5×10^{-4} and 5.3×10^{-4} Ci (5.6×10^6 and 2.0×10^7 Bq) at two areas, and not detected at two other areas. Releases of ^{239,240}Pu, which included gross alpha data, ranged from 1.4×10^{-7} to 6.7×10^{-5} Ci (5.2×10^3–2.5×10^6 Bq) at five areas at the Hanford Site during 2004 (DOE 2005c).

Plutonium has been identified in 9 air sample collected from 1,689 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007).

6.2.2 Water

Fallout from atmospheric weapons testing, accidents involving nuclear weapons, planned as well as accidental reactor effluent releases, and disposal of radioactive wastes are all means by which plutonium can be introduced into water systems (Harley 1980; NEA/OECD 1981). In a typical 1,000 megawatt electric (MWe) light water reactor in a nuclear power plant, about 200 kg of plutonium [equivalent to 1.3×10^4 Ci (4.8×10^{14} Bq), one curie of ^{239}Pu=16 g] are generated per year of operation (DOE 1980g; NEA/OECD 1981). Contaminated cooling water containing plutonium from nuclear production facilities may have been discharged into oceans or rivers. If release occurs from waste containers, buried radioactive wastes may migrate or seep into groundwater (NEA/OECD 1981). As an example of plant emissions, the Mound Plant in Miamisburg, Ohio, discharged a total of about 0.5 Ci (2×10^{10} Bq) ^{238}Pu into a river near the site from the beginning of its operation through 1976 (NEA/OECD 1981). The Savannah River Site, South Carolina, which produced plutonium and tritium as well as other nuclear materials from 1954 to 1988, released 2.3×10^{10} Bq (0.62 Ci) of plutonium to site streams and ponds during the period of 1954–1989 (Carlton et al. 1996). From 1954 to 1988, the plutonium and uranium extraction (PUREX) process was used in the F-area of the Savannah River Site to recover ^{239}Pu, as well as other radionuclides, from irradiated ^{238}U. During this time, the total reported release of ^{239}Pu to the seepage basin at the F-area was 2.09×10^{11} Bq (5.65 Ci) (Dai et al. 2002).

Liquid effluent containing various radionuclides is discharged from some of the facilities at the Hanford Site. During 2004, 5.5×10^{-6} Ci (2.0×10^5 Bq) of ^{239,240}Pu were released to the Columbia River from the 100 areas at the Hanford Site (DOE 2005c).

In January, 1968, while attempting to make an emergency landing, a U.S. military aircraft with four nuclear weapons on board crashed in Thule, Greenland. The impact resulted in detonation of the high explosives in all four nuclear weapons aboard. The oxidized plutonium was dispersed by both the explosion and the fire involving the fuel in the jet (Harley 1980). Amounts of plutonium released to the air in this accident have been estimated at 24 Ci (8.9×10^{11} Bq) of insoluble plutonium (NEA/OECD 1981). The maximum concentration of plutonium in ocean sediments was found 1 km from the point of impact. The sediment-bound plutonium was found to migrate both downward in the sediment column and horizontally from the point of impact. The concentrations decreased with distance from the point of impact.

Sediments can act as both a repository for and a source of waterborne plutonium. Atmospheric fallout reaching surface water can settle in the sediments. The plutonium in the ocean sediments at Bikini Atoll, for example, was found to be resuspended and released to the bottom waters (DOE 1980b). In a freshwater waste pond at the Hanford reactor, plutonium was found to be bound to the sediments and was not available for uptake by plants or animals in the pond (DOE 1980f). The difference between the observations in the two ecosystems may be due to the dynamic nature of the ocean water near Bikini Atoll versus the relatively static nature of a waste water pond.

On May 4, 2000, a prescribed burn grew out of control in Cerro Grande, New Mexico near the Los Alamos National Laboratory (LANL), which burned about 7,400 acres of forest on the LANL site (DOE 2004). The burned landscapes resulted in increased storm runoff and transport of various contaminants, which included plutonium and other radionuclides by runoff and erosion in the canyons traversing LANL. Compared with amounts measured in the 5 years before the fire, the yearly average amount of radioactivity carried by storm runoff flows beyond LANL downstream boundary in the two to three years following the fire increased about 55 times for ^{239,240}Pu. The increases were due mostly to erosion of LANL contaminated sediments. Annually, the estimated postfire transport of ^{239,240}Pu downstream ranged from 2 millicuries (mCi) in the first year after the fire to 28 mCi in year 1 and a total of about 64 mCi of ^{239,240}Pu was transported downstream in storm runoff through the 4-year period from 2000 through 2003 (DOE 2004).

Plutonium has been identified in 6 groundwater and 7 surface water samples collected from 1,689 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2007).

6.2.3 Soil

Plutonium has been detected in extremely small amounts as a naturally occurring constituent of some minerals and ores. Uranium and thorium ores in Canadian pitchblende, Belgium Congo pitchblende, Colorado pitchblende, Brazilian monazite, and North Carolina monazite have been found to contain ^{244}Pu at a weight ratio of up to 9.1×10^{-12} kg plutonium/kg ore (Leonard 1980).

Soils may become contaminated from fallout associated with nuclear weapons tests, such as those conducted at the Trinity Site in southern New Mexico, the Pacific Proving Ground at the Enewetak Atoll, and the Nevada Test Site or with accidental, nonnuclear detonation of nuclear weapons, such as occurred at Palomares, Spain. Research facilities, such as the Los Alamos National Laboratory, Los Alamos, New

Mexico, may release treated radioactive wastes under controlled conditions. Production facilities, such as the Hanford and Savannah River Plants, and experimental reactor stations, for example, the Idaho National Engineering Laboratory, Idaho Falls, Idaho, also released treated plutonium-bearing radioactive wastes under controlled conditions to soils (Hanson 1975).

Atmospheric weapons testing fallout has been a global source of transuranics, including plutonium, in soils (Agency for Toxic Substances and Disease Registry 1999; Harley 1980; NEA/OECD 1981). The Centers for Disease Control and Prevention (CDC) has estimated that the total deposition of plutonium from weapons tests at the Nevada Test Site was 1.8×10^{4} Ci (6.7×10^{14} Bq) (CDC 2005).

During 2004, only facilities in the 200 Areas of the Hanford Site discharged radioactive liquid effluents to the ground at a State-Approved Land Disposal Site. Releases of ^{238}Pu and ^{239,240}Pu were 6.9×10^{-6} and 7.5×10^{-6} Ci (2.5×10^{5} and 2.8×10^{5} Bq), respectively (DOE 2005c).

Several of the major nuclear facilities in the United States use plutonium and some of these have released plutonium to the environment. These releases have taken place at remote sites and generally have not been measurable outside the plant property. Approximately 2 Ci (7×10^{10} Bq) of plutonium have been disposed in the Los Alamos National Laboratory canyon waste disposal sites (Harley 1980). The Savannah River Plant, Aiken, South Carolina, has released a total of 5 Ci (2×10^{11} Bq) of plutonium to local soil (Harley 1980). Leakage of stored waste released between 10–100 Ci (3.7×10^{11}–3.7×10^{12} Bq) of plutonium to the soil over a period of several years at the Rocky Flats facility, Golden, Colorado (DOE 1980g). A break in a waste transfer line caused the release of about 300 Ci (1×10^{13} Bq) of ^{238}Pu at the Mound Plant, Miamisburg, Ohio, in 1969 (DOE 1980g).

A fire on May 11, 1969, occurred at the plutonium processing facility at Rocky Flats, which caused concerns about possible contamination of the surrounding areas (Agency for Toxic Substances and Disease Registry 2005). Studies showed that while trace amounts of plutonium were present in soil, the distribution was not consistent with the wind direction at the time of the fire. It was determined that the major source of plutonium contamination was leakage from drums of machine oil containing plutonium that were being stored in an outdoor area (Eisenbud and Gesell 1997).

Another source of soil contamination at Rocky Flats was the leakage of plutonium-contaminated oil. Plutonium was present as the dioxide when it was released. The dioxide was then adsorbed to the soil. Fugitive dust emissions caused plutonium-contaminated soil to be distributed away from the spill. Most

of the plutonium remained on the surface, although some was released and migrated downward through the soil column (Little and Whicker 1978).

A U.S. military aircraft carrying four nuclear bombs collided with a tanker aircraft during refueling in Palomares, Spain, in January, 1966. The bombs broke free of the airplane and the high explosive in two of the weapons detonated when the bombs hit the ground. Initial surveys showed plutonium concentrations of $3x10^{-5}$ Ci/m^2 ($1x10^6$ Bq/m^2), in the form of a finely powdered dioxide, were spread over 2 hectares (20,000 m^2) (Harley 1980). A large amount of the contaminated soil was brought back to the Savannah River facility in the United States for decontamination and the soil with low-level contamination was plowed to a depth of 30 cm (Harley 1980).

Plutonium has been identified in 6 soil and 9 sediment samples collected from 1,689 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2007).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Plutonium enters the environment primarily through releases to the atmosphere or direct discharge to ponds, streams, or oceans. Emissions to the atmosphere will result in plutonium fallout. In the case of weapons testing, approximately one-fifth of the plutonium released falls on the test site (Harley 1980). The rest is carried in the atmosphere, adsorbed to particulate matter and is transported back to earth via dry or wet deposition. Once plutonium is deposited either on the land or surface water, sorption to soils or sediments is the primary environmental fate of plutonium. A small fraction of plutonium reaching the soil will become solubilized either through chemical or biological processes, depending upon its chemical form. In soluble form, plutonium can either migrate in groundwater or surface water or be available for uptake into plants; colloidal forms of plutonium are not as available for uptake as soluble forms.

Atmospheric releases of plutonium occurred as a result of former atmospheric nuclear weapons testing or routine or nonroutine nuclear reactor operations and fuel reprocessing. The rate at which plutonium is removed from the atmosphere depends on the chemical and physical properties of the particles, as well as the meteorological conditions. The larger the particles, the faster fallout will occur. The particle size expected to be released from either of the above mentioned sources ranges from 0.3 to 1.1 μm. At the highest altitudes, aerosols in the atmosphere descend by gravity; at lower levels, they are transported with the general air movement (UNSCEAR 2000a). In the lower stratosphere, the mean residence time of

aerosols range from 3–12 and 8–24 months in the polar and equatorial regions, respectively. Removal half-times from the upper atmosphere to the next lower region range from 6 to 9 months and removal half-times from the high atmosphere were found to be 24 months (UNSCEAR 2000a). The global fallout rate of ^{238}Pu, predominantly from the SNAP-9 accident, as determined by Harley (1980), was 0.002 pCi/m^2/day (7.4×10^{-5} Bq/m^2/day) based on plutonium levels measured in surface soils. The global deposition rate of ^{239,240}Pu was equal to 0.03 pCi/m^2/day (1×10^3 Bq/m^2/day) (Corey et al. 1982).

Plutonium deposited on soil surfaces may be resuspended in the atmosphere especially in areas that have low soil moisture levels, such as the Nevada Test Site. In drier areas, the levels of ambient airborne dust are expected to be higher than in areas with normal rainfall (Harley 1980). The highest concentrations of plutonium are likely to be found in the fine silt-clay particle size range. Particles of this size tend to be transported the farthest distance by wind and water (WHO 1983).

The transport and partitioning of plutonium in soils depends on the form of the compound. The solubility of plutonium depends on the properties of the soil, the presence of organic and inorganic complexing agents, the form of plutonium that enters the soil environment, and the presence of soil microorganisms (Bell and Bates 1988; DOE 1980c; Kabata-Pendias and Pendias 1984; WHO 1983). Plutonium fallout from the atmosphere, for example, tends to be deposited primarily as the insoluble dioxide (DOE 1987b; Harley 1980). The majority of plutonium remains within the top few centimeters of the soil surface as the dioxide form (WHO 1983). Microorganisms can change the oxidation state of plutonium, thereby either increasing or decreasing its solubility.

The types of organic and inorganic materials disposed of in waste streams can also affect the mobility of plutonium. For example, in some waste streams, such as the Hanford location, the chelating agent ethylenediaminetetraacetate (EDTA) was used during the production and processing of plutonium and was widely present in the mixed wastes at the site (Smith and Amonette 2006). EDTA forms complexes with plutonium, which will increase its mobility in soils and also possesses the ability to adsorb onto soil itself, thus reducing the number of available surface sites at which plutonium can adsorb to.

Plutonium will migrate in soils as the hydrolyzed ion or as a complex, formed with organic or inorganic acids. Mewhinney et al. (1987) found that particles subjected to wetting and drying, such as those found on the soil surface, released more plutonium than soils continually immersed in a solvent, such as that found in lakes. This phenomenon is attributed to the formation of a soluble dioxide layer on the particle's surface during the drying phase. Soil organisms have also been found to enhance the solubility of

plutonium (DOE 1987b). Once plutonium enters the soluble phase, it then becomes available for uptake by plants. The plutonium(IV) oxidation state is found in plants due to the ability of the environment to hydrolyze it (DOE 1987c; Garland et al. 1981). Cataldo et al. (1987) postulate that reduction of the higher oxidation states, such as plutonium(VI), occurs prior to absorption/transport across the root membrane.

In aqueous solution, plutonium typically exists in one of four common oxidation states and the environmental fate of plutonium in surface waters is dependent upon both the oxidation state and the nature of the suspended solids and sediments contained in the water column. Under reducing conditions, plutonium(III) and plutonium(IV) are the most stable oxidation states, with plutonium(III) dominating at pH values <8.5 and plutonium(IV) dominating at pH values >8.5 (Smith and Amonette 2006). Under oxidizing conditions, plutonium(IV), plutonium(V), and plutonium (VI) oxidation states tend to form at pH values >4. The plutonium(V) and plutonium(VI) oxidation states typically form more soluble complexes and possess greater mobility than the plutonium(III) and plutonium(IV) complexes. Humic materials (naturally occurring organic acids) were found to reduce plutonium(V) to plutonium(IV) in seawater. This was followed by adsorption of plutonium(IV) onto iron dioxides and deposition into the sediments (DOE 1987h).

The partitioning of plutonium from surface water to sediments in freshwater and marine environments depends on the equilibrium between plutonium(IV) and plutonium(V), and the interaction between plutonium(IV) in solution and plutonium sorbed onto sediment particle surfaces (NCRP 1984). Sorption onto marine clays was found to be largely irreversible (Higgo and Rees 1986). Higgo and Rees (1986) also found that the initial sorption of plutonium onto clays was effective in removing most of the plutonium species that would be able to sorb onto the clay. When sorption to carbonate marine sediments was investigated, it was found that some desorption from the surface would also occur. This behavior was due to the presence of plutonium carbonate complexes on the sediment surfaces which were sorbed less strongly than plutonium dioxide complexes (Higgo and Rees 1986). In fact, the formation of plutonium complexes with organic carbon causes plutonium to remain in solution as a complex (NCRP 1984). Plutonium can become adsorbed onto colloids, small (micrometer) particles that are often found in groundwater. Adsorption to colloidal particles can enhance the mobility of plutonium in groundwater (DOE 1999a).

Carroll et al. (1999) reported distribution coefficients (K_d) ranging from $3x10^4$ to $8x10^4$ for plutonium in bottom sediments from the Kara Sea. The International Atomic Energy Agency (IAEA)-recommended K_d value for sediments is $1x10^5$ for plutonium (Carroll et al. 1999; IAEA 2004).

Plutonium can be taken up from various environmental media into plants and animals. The primary factor that governs whether plutonium in soil can be taken up by plants roots is the presence of soluble forms of plutonium in adjacent subsurface soils. The highest concentrations of plutonium in plants are generally found in the roots where plutonium is present as a surface-absorbed plutonium complex, a stabilized complex, or a soluble plutonium complex (Garland et al. 1981). Concentration ratios (concentration of plutonium per gram of dry plant tissue divided by concentration in the soil) of $1x10^{-6}$–$2.5x10^{-4}$ were calculated based on radioisotope experiments in soybean plants grown in controlled environments. The stems and leaves were found to possess lower overall concentrations of plutonium than the roots, but higher concentrations of soluble plutonium (Cataldo et al. 1987).

In studies on orange trees, Pinder et al. (1987) found that ^{238}Pu was deposited on the leaf or soil surface, remained there, and that no measurable quantities were transferred to the fruits. Grain crops grown near the Savannah River Plant, Aiken, South Carolina, were found to contain higher concentrations of plutonium the closer to the facility they were grown. During harvesting, plutonium from soils or straw was resuspended and mixed with the crop. Plutonium in vegetable crops grown at Oak Ridge National Laboratory, Oak Ridge, Tennessee, contained higher plutonium concentrations in the foliage biomass than in the fruit. Peeling of potatoes and beets removed 99% of the residual plutonium (DOE 1980d).

The Mayak Production Association (PA), which processed weapons-grade plutonium from 1949 to 1952, discharged radioactive wastes into the Techa River, which belongs to the Kara Sea basin of the Arctic Ocean. Akleyev et al. (2000) reported plutonium accumulation coefficients ranged widely from $2x10^{-4}$ to 0.8 for vegetation samples the area of the Techa River. The authors noted that plutonium accumulation is highly species-dependent.

Plutonium uptake by grazing herbivores was predominantly located within the animal's pelt and gastrointestinal tract (DOE 1980i). Rodents studied near the Los Alamos and Trinity sites in New Mexico support this claim. DOE (1980i) found no evidence of bioconcentration through the food chain from soil to plants to rodents. They concluded that soil was the source of plutonium in rodents. In contrast, a study by Sullivan et al. (1980) showed that rodents absorbed more ^{238}Pu when it was incorporated into alfalfa (by growing it in soil containing plutonium) than when it was administered in the

inorganic form (Sullivan et al. 1980). This study suggests that plutonium bound to organic compounds may have increased availability.

Plutonium was found to bioaccumulate in aquatic organisms, primarily at the lower end of the food chain. The bioconcentration factors (i.e., the amount of the chemical found in the organism divided by the concentration in the surrounding water over the same time period) were 1,000 for mollusks and algae, 100 for crustacea, and 10 for fish (WHO 1983). Plutonium is concentrated in the bones of fish rather than in muscle tissues, as seen by whole fish to muscle tissue ratios of 40:1 (NCRP 1984). Swift (1992) reported that whole-body concentration factors for juvenile lobsters did not exceed 250 over an exposure period of 49 days in seawater containing ^{237}Pu. ^{237}Pu was found to accumulate mostly in the gills and exoskeleton.

6.3.2 Transformation and Degradation

Plutonium isotopes are transformed by radioactive decay to either uranium or americium based on the isotope, but as an element, plutonium cannot degrade. The most common isotopes of plutonium are ^{238}Pu, ^{239}Pu, ^{240}Pu, and ^{241}Pu with respective half-lives of 87.7, 2.410×10^4, 6.56×10^3, and 14.4 years (Lide 2005). The half-lives for ^{239}Pu and ^{240}Pu are very long, and only a small amount of transformation would occur over a human lifetime. ^{241}Pu has a much shorter half-life and would undergo transformation over a human lifetime. ^{241}Pu decays into ^{241}Am, which has a half-life of 432.7 years and is also an alpha particle emitter (Baum et al. 2002). Information on the radioactive transformation of various plutonium isotopes can be found in Table 4-3.

6.3.2.1 Air

Plutonium does not undergo transformation processes in the air beyond those related to radioactive decay. Radioactive decay in air is not significant for those plutonium isotopes with long half-lives compared with residence times in the atmosphere. For plutonium injected into the atmosphere from a weapon detonation, the residence half-time of particulate debris in the troposphere of approximately 30 days (Bennett 1979; Nero 1979).

6.3.2.2 Water

The solution chemistry of plutonium is complex due to the ease with which it can undergo oxidation-reduction reactions and its extreme oxophilicity (tendency to bind oxygen) of plutonium cations (Clark et

al. 2006). Oxidation states (III)–(VII) can be prepared and stabilized in solution under appropriate conditions. The lower oxidation states (III and IV) are more stable under acid conditions; the higher oxidation states (VI and VII) are more stable under alkaline conditions. Pu(IV) is the most stable and most studied oxidation state, followed by (III) and (VI). Pu(V) and Pu(VI) cations are strong Lewis acids and hydrolyze in solution to form trans dioxo cations, PuO_2^+ and PuO_2^{2+}, which are commonly referred to as plutonyl ions. The reduction potentials that couple the four most common oxidation states of plutonium (III, IV, V, VI) in acidic solution are very close in magnitude and are close to 1 volt vs. the standard hydrogen electrode. In addition the kinetics oxidation-reduction reactions between these oxidation states are such that multiple oxidation states of plutonium can exist in aqueous solution under appropriate conditions (Clark et al. 2006; EPA 2006b).

The important chemical transformation process in surface water is the oxidation or reduction of plutonium. In waters with low suspended solids, plutonium is generally found in oxidized forms, dissolved in the water. In waters with high suspended solids, plutonium is generally reduced and sorbed onto either suspended solids or sediments (DOE 1987a, 1987h; Higgo and Rees 1986).

Plutonium behaves differently than many other inorganic elements in that it can exist simultaneously in four oxidation states over a range of pH values. Under acidic conditions, the nature of the complexing ligands present in solution will influence the oxidation state of plutonium. The presence of fulvic acid (a naturally occurring organic acid) facilitates the reduction of plutonium(IV) to plutonium(III), especially below pH 3.1. The reduction of the higher oxidation states appears to be even less dependent on pH, especially below pH 6 (IAEA 1976d).

6.3.2.3 Sediment and Soil

Plutonium found in soils may undergo the same oxidation/reduction reactions described for surface waters in places where soil contacts water. In addition to oxidation/reduction reactions, plutonium can react with other ions in soil to form complexes. These complexes may then be absorbed by roots and move within plants; however, the relative uptake by plants is low. In plants, the complex can be degraded but the elemental plutonium will remain.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to plutonium depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of

plutonium in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on plutonium levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring plutonium in a variety of environmental media are detailed in Chapter 7.

Monitoring studies typically report combined ^{239,240}Pu concentrations because ^{239}Pu and ^{240}Pu are not readily distinguishable by alpha spectroscopy (Eisenbud and Gesell 1997).

6.4.1 Air

Atmosphere nuclear weapons testing, which ended in 1980, is the major source of plutonium contamination. Since this time, essentially all fallout ^{239}Pu has been removed from the atmosphere, allowing for measurement of baseline measurement of plutonium in air.

Air concentrations of ^{239}Pu at the Pacific Northwest National Laboratory near Richland, Washington averaged 1.3×10^{-7} Bq/m^3 (3.5×10^{-6} pCi/m^3). During 2004, a network of 85 continuously operating air samplers were used to monitor radioactive material in air near the Hanford Site (DOE 2005c). In 2004, ^{238}Pu was detected in 4 of 40 site-wide composite air samples, with average and maximum concentrations of 5×10^{-7} and 1.3×10^{-5} pCi/m^3 (2×10^{-8} and 4.8×10^{-7} Bq/m^3), respectively. From 1999 to 2003, ^{238}Pu was detected in 10 site-wide air samples, with a maximum concentration of 5.3×10^{-6} pCi/m^3 (2.0×10^{-7} Bq/m^3). Only 7 of the 40 site-wide air samples had detectable amounts of ^{239,240}Pu in 2004 with an average concentration of 1.5×10^{-6} pCi/m^3 (5.6×10^{-8} Bq/m^3). One of the 28 perimeter samples had a detectable amount of ^{239,240}Pu at a concentration of 2.5×10^{-6} pCi/m^3 (9.3×10^{-8} Bq/m^3). In 2004, none of the nearby or distant communities site air samples contained detectable amounts of ^{238}Pu or ^{239,240}Pu. From 1999 to 2003, ^{238}Pu was found in one air sample each from perimeter site and nearby communities sites; ^{239,240}Pu was detected in seven, four, and one of the perimeter, nearby, and distant communities air samples, respectively (DOE 2005c).

Concentrations measured at the Argonne National Laboratory-East near Chicago, Illinois ranged from 6×10^{-8} to 1.4×10^{-7} Bq/m^3 (1.6×10^{-6}–3.8×10^{-6} pCi/m^3) (DOE 1999a).

^{239,240}Pu concentrations in airborne particulate matter collected during 2005 from five locations at the site boundary of the Rocky Flats Environmental Technology Site (RFETS), Colorado, a former nuclear

weapons plant, were all <$1x10^{-5}$ pCi/m^3 (<$4x10^{-7}$ Bq/m^3) (DOE 2005d, 2005e, 2005f, 2006a). ^{239,240}Pu concentrations in airborne particulate matter collected during the first and second quarters of 2005 at RFETS from an industrial area were $8.3x10^{-5}$ and $1.2x10^{-4}$ pCi/m^3 ($3.1 x10^{-6}$ and $4.4 x10^{-6}$ Bq/m^3), respectively.

Aerosol particulate samples were collected at three sites (On Site, Near Field, and Cactus Field) near the Waste Isolation Pilot Plant (WIPP), a deep underground nuclear waste-storage facility near Carlsbad, New Mexico (Arimoto et al. 2005). The On Site sampling location was 0.1 km downwind of the WIPP exhaust shaft. The Near Field station was 1 km downwind of WIPP. The Cactus Field station was 19 km upwind of the WIPP, and served as a reference background site. Concentrations of ^{241}Pu were below the minimum detection limit ($1.2x10^{-6}$ Bq/m^3 [$3.2x10^{-5}$ pCi/m^3]) for all 204 samples collected. ^{238}Pu was detected above the minimum detection limit ($3.9x10^{-9}$ Bq/m^3 [$1.1x10^{-7}$ pCi/m^3]) in 6 of the 204 samples. ^{239,240}Pu was detected above the minimum detection limit ($2.6x10^{-9}$ Bq/m^3 [$7x10^{-8}$ pCi/m^3]) in 203 of the 204 samples. Mean concentrations of ^{239,240}Pu in the 10 μm particulate matter fraction were $1.1x10^{-8}$ and $8.1x10^{-9}$ Bq/m^3 ($3.0x10^{-7}$ and $2.2x10^{-7}$ pCi/m^3) at the Cactus Flats and Near Field stations, respectively. Mean concentrations of ^{239,240}Pu in the total suspended particulate were $1.8x10^{-8}$, $1.3x10^{-8}$, and $1.4x10^{-8}$ Bq/m^3 ($4.9x10^{-7}$, $3.5x10^{-7}$, and $3.8x10^{-7}$ pCi/m^3) at the Cactus Flats, Near Field, and On Site stations, respectively (Arimoto et al. 2005).

Lehto et al. (2006) determined radionuclide concentrations from air sampler filters collected in the town of Kurchatov and the city of Astana in Kazakhstan. Kurchatov is near the former Semipalatinsk nuclear test site, which is highly contaminated from nuclear explosions carried out from 1949 to 1989. Astana is about 500 km west of Kurchatov. Median concentration of $1x10^{-7}$ and $3.4x10^{-8}$ Bq/m^3 ($2.7x10^{-6}$ and $9.2x10^{-7}$ pCi/m^3) for ^{239,240}Pu and ^{238}Pu, respectively, were reported in weekly air samples (25,000 m^3 volume) collected during 2000–2001 in Kuchatov. Median concentrations of $2.9x10^{-8}$ and $9x10^{-9}$ Bq/m^3 ($7.8x10^{-7}$ and $2.4x10^{-7}$ pCi/m^3) for ^{239,240}Pu and ^{238}Pu, respectively, were reported in air samples collected during a 3-month period in 2001 in Astana; ^{238}Pu activity was below the detection limit in half of the filters (Lehto et al. 2006).

Hölgye (2008) reported ^{239,240}Pu and ^{238}Pu concentrations in air collected from 1997 to 2006 in Prague, Czechoslovakia of 0.53–5.06 and <0.16–1.10 nBq/m^3($1.4x10^{-8}$–$1.7x10^{-7}$ and <$4.3x10^{-9}$–$3.0x10^{-8}$ pCi/m^3), respectively. ^{239,240}Pu concentrations in Prague post-Chernobyl air samples taken in April 29–May 5, 1986 were 10–28Bq/m^3 ($2.7x10^{-4}$–$7.6x10^{-4}$ pCi/m^3).

6.4.2 Water

Hirose and Aoyama (2003) used the HAM database, a comprehensive data set of various anthropogenic radionuclides, to calculate background levels of ^{239,240}Pu concentrations surface waters of the Pacific Ocean. In this study, the authors divided the Pacific Ocean basin into 12 "boxes", which take into account the analyses of latitudinal and longitudinal distributions of anthropogenic radionuclides. Based on their analysis, ^{239,240}Pu concentrations ranged from $6x10^{-7}$ to $2.7x10^{-6}$ Bq/L ($2x10^{-5}$–$7.3x10^{-5}$ pCi/L) within the 12 "boxes".

Seawater samples collected in 1999 in various regions of the southern Baltic Sea were analyzed for plutonium (Struminska and Skwarzec 2004). The highest concentrations of plutonium were generally found in the dissolved fractions of seawater, and ranged from $1.5x10^{-6}$ to $1.45x10^{-4}$ Bq/L ($4.1x10^{-5}$–$3.92x10^{-3}$ pCi/L) for ^{238}Pu in samples from Gdansk Bay seaport and ^{239,240}Pu in samples from Pomeranian Bay, respectively. The lowest plutonium concentrations were found in the colloidal fractions. ^{238}Pu and ^{239,240}Pu concentrations in the colloidal fractions were generally ≤$1x10^{-6}$ Bq/L ($2.7x10^{-5}$ pCi/L) (Struminska and Skwarzec 2004). Hirose and Aoyama (2002) reported that the ^{239,240}Pu particulate concentrations in surface waters of the western North Pacific Ocean ranged from $3x10^{-8}$ to $3x10^{-7}$ Bq/L ($8x10^{-7}$–$8x10^{-6}$ pCi/L) during 1987–1997. Ahier and Tracy (1995) reported ^{239,240}Pu water concentrations in Lake Michigan, Huron, Erie, and Ontario of $4.4x10^{-7}$, $4.8x10^{-7}$, $1.8x10^{-7}$, and $1.7x10^{-7}$ Bq/L ($1.1x10^{-5}$, $1.3x10^{-5}$, $4.8x10^{-6}$, and $4.6x10^{-6}$ pCi/L), respectively.

Hirose et al. (2007) reported ^{239,240}Pu concentrations in surface waters collected during 2003–2004 from the South Pacific Ocean mid-latitude region (32.5°S) ranging from 0.5 to 4.1 mBq/m^3 (0.01–1.1 pCi/m^3). Yamada and Zheng (2008) reported ^{239,240}Pu surface water concentrations in samples taken in the vicinity of the nuclear fuel reprocessing plant at Rokkasho, Japan of 7.6 and 7.8 mBq/m^3 (0.20 and 0.21 pCi/m^3) on sampling dates September, 1991 and June 1993, respectively. ^{239,240}Pu concentrations in surface water collected at sites along the Japan Sea coast sampled in June, 2003 were 4.9 and 5.9 mBq/m^3 (0.13 and 0.16 pCi/m^3) at Sado Island and at Ajigasawa, respectively. Yamada et al. (2007) reported ^{239,240}Pu concentrations of 13.4, 20.7, 37.2, 26.8, 39.6, 20.6, and 19.2 mBq/m^3 (0.362, 0.559, 1.01, 0.724, 1.07, 0.557, and 0.519 pCi/m^3) at depths of 0, 150, 250, 600, 900, 1,200, and 1,490 m, respectively, in samples from Sagami Bay, Japan, western Northwest Pacific Ocean collected on March 23, 1992.

During 2004, water samples from the Columbia River were collected at Priest Rapids Dam, the most upstream dam from the Hanford Site, and from Richland, Washington, on the Hanford Site. Average

^{239,240}Pu concentrations in water samples collected at the Priest Rapids Dam were $9.5x10^{-6}$ and $2.7x10^{-5}$ pCi/L ($3.5x10^{-7}$ and $1x10^{-6}$ Bq/L) in the particulate and dissolved fractions, respectively, in samples collected in 2004, and were $3.2x10^{-5}$ and $2.4x10^{-5}$ pCi/L ($1.2x10^{-6}$ and $8.9x10^{-7}$ Bq/L) in the particulate and dissolved fractions, respectively, collected in 1999–2003 (DOE 2005c, 2005g). Average ^{239,240}Pu concentrations in river water samples collected at Richland, Washington were $1.5x10^{-5}$ and $3.0x10^{-5}$ pCi/L ($5.6x10^{-8}$ and $1.1x10^{-6}$ Bq/L) in the particulate and dissolved fractions, respectively, in samples collected in 2004, and were $2.5x10^{-5}$ and $3.0x10^{-5}$ pCi ($9.3x10^{-7}$ and $1.1x10^{-6}$ Bq/L)in the particulate and dissolved fractions, respectively, collected in 1999–2003 (DOE 2005c, 2005g). Dai et al. (2005) reported ^{239}Pu concentrations ranging from $<3x10^{-4}$ to $9.71x10^{-2}$ pCi/kg ($<1x10^{-5}$–$3.6x10^{-3}$ Bq/kg) in unfiltered water collected from the Hanford Site 100K-Area groundwater monitoring wells.

The Mayak nuclear fuel reprocessing plant in Russia PA, discharged radioactive wastes into the Techa River, which belongs to the Kara Sea basin of the Arctic Ocean. ^{239,240}Pu concentrations in water samples from the Techa River showed a decrease from approximately $3x10^3$ Bq/L down to 2 Bq/L, over a distance of 150 km starting from Dam 11, which is 30 km from the site of radioactive waste disposal (Akleyev et al. 2000). Børretzen et al. (2005) reported concentrations of 0.31 and 0.088 mBq/kg ($8.4x10^{-3}$ and $2.4x10^{-3}$ pCi/kg) for ^{239}Pu and ^{240}Pu, respectively, in water samples collected on June 26, 1994 from Reservoir 11 at Mayak, which received radioactive wastes,. Levels in samples from the Asanov Swamp, downstream from the Mayak PA, were 0.12 and 0.13 mBq/kg ($3.2x10^{-3}$ and $3.5x10^{-3}$ pCi/kg) for ^{239}Pu and ^{240}Pu, respectively.

Skipperud et al. (2009) reported average ^{239,240}Pu concentrations of 40.6, 29.0, and 6.4 Bq/m^3 (1,100, 780, and 170 pCi/m^3), respectively, in water samples collected in 1996 from the Ob Estuary, Yenisey Estuary (both of which have weapons-grade plutonium sources in their catchment areas), and Kara Sea, Russia. Surface water samples upstream and downstream from the Savannah River Site are analyzed quarterly or on a bi-annual basis for ^{238}Pu and ^{239}Pu (Agency for Toxic Substances and Disease Registry 2007). From 1993 to 2004, there were no detectable levels of ^{238}Pu or ^{239}Pu upstream or downstream from the facility (Agency for Toxic Substances and Disease Registry 2007).

Groundwater samples were collected in May 1998 from four of the F-area wells at the Savannah River Site (Dai et al. 2002). Well 1 is upgradient from the F-area seepage basins, and wells 2–4 define a transect along the contamination plume. ^{239}Pu concentrations were lowest in well 1, at approximately $1x10^6$ and $1x10^5$ atoms/kg (approximately $2x10^{-5}$ and $2x10^{-6}$ pCi/kg [$7x10^{-7}$ and $7x10^{-8}$ Bq/kg]) in unfiltered and filtered fractions, respectively. ^{239}Pu concentrations were highest in well 2, which is

closest to the seepage basins, and were approximately $1x10^8$ and $1.5x10^8$ atoms/kg (approximately $2x10^{-3}$ and $3.7x10^{-3}$ pCi/kg [$7.4x10^{-5}$ and $1.4x10^{-4}$ Bq/kg]) in the unfiltered and filtered fractions, respectively (Dai et al. 2002).

^{238}Pu concentrations ranging from <0.01 to 0.078 pCi/L (<$3.7x10^{-4}$–$2.9x10^{-3}$ Bq/L) and from <0.01 to 0.059 pCi/L (<$3.7x10^{-4}$–$2.2x10^{-3}$ Bq/L) were reported in unfiltered and filtered (0.05 μm filtrate) groundwater, respectively, sampled near the disposal well at the Idaho Chemical Processing Plant, Idaho National Engineering Laboratory (Cleveland and Rees 1982). Mururoa and Fangataufa Atolls were used from 1975 to 1996 for underground testing of nuclear weapons (Mulsow et al. 1999). Of the nine sites at Mururoa sampled for underground water, only the site at Ceto, had a measurable concentration of ^{239,240}Pu at $2x10^{-5}$ Bq/L ($5x10^{-4}$ pCi/L). The remaining eight sites at Mururoa and the two sites at Fangataufa had ^{239,240}Pu concentrations ranging from <$5x10^{-5}$ to <$4x10^{-6}$ Bq/L (<$1x10^{-3}$–<$1x10^{-4}$ pCi/L). ^{238}Pu concentrations at both of these sites ranged from <$2x10^{-6}$ to <$5x10^{-5}$ Bq/L ($5x10^{-5}$–<$1x10^{-3}$ pCi/L) (Mulsow et al. 1999).

Gordeev et al. (2007) reported ^{239,240}Pu concentrations in groundwater samples obtained in 2005 from the Sary-Uzen nuclear excavation explosion site of the Semipalatinsk test area, Russia, ranging from $4x10^{-3}$ to $6.0x10^{-2}$ Bq/L (0.1–1.6 pCi/L). Concentrations of ^{239,240}Pu in water samples from the Tobol-Irtysh area of the Techa-Iset-Tobol-Irtysh-Ob river system, through which Mayak PA radioactive wastes are transported, were studied using samples collected from September 11 to 28, 2004 (Nikitin et al. 2007). ^{239,240}Pu concentrations ranged from 4.1 mBq/m^3 (0.11 pCi/m^3) at the left-bank confluence of the Iset-Tobol Rivers to 7.5 mBq/m^3 (0.20 pCi/m^3) at the left bank confluence of the Tobol-Irtysh Rivers; a value of 13.0 mBq/m^3 (0.35 pCi/m^3) was reported at midstream samples of the Ob River (Nikitin et al. 2007).

6.4.3 Sediment and Soil

Average plutonium concentrations in surface soil from fallout range from about 0.01 to 0.1 pCi/g ($4x10^{-4}$–$4x10^{-3}$ Bq/g) (DOE 2005a). Essentially all of the plutonium found in the surface of the Earth's crust is a product of human activity occurring over the past 60 years (Ketterer and Szechenyi 2008).

The Rocky Flats Plant in Colorado processed weapons-grade plutonium from 1952 to 1989 (Ibrahim et al. 1997). Contamination from plutonium production is composed mostly of ^{239,240}Pu and a small amount (~3%) of ^{238}Pu. Other releases of plutonium to this site, now called the RFETS, include global fallout, low-level releases during normal plant operations, accidental releases during fires between 1957 and

1969, and leakage of drums of plutonium contaminated cutting oil to soil onsite. Resuspension of contaminated soils during remediation activities resulted in most of the releases of plutonium at the RFETS. Soil samples collected at the RFETS during 1992–1994 were reported to range from 1.1 Bq/kg (30 pCi/kg) offsite to 57 Bq/kg (1,500 pCi/kg) onsite. Isotopic ratios of ^{240}Pu:^{239}Pu increased from 0.055 onsite to 0.123 at 19 km east of the RFETS boundary. An isotopic ratio of 0.06 is associated with contamination from activities at the RFETS, whereas the world mean isotopic ratio due to fallout was estimated at 0.176 (Ibrahim et al. 1997). ATSDR examined surface-soil contamination from an industrial portion of RFETS known as the "903 Pad Area", because multiple site reports indicate that off-site surface-soil contamination largely originated from this location (Agency for Toxic Substances and Disease Registry 2005). Surface soils in the 903 Pad Area were originally contaminated when industrial oils containing trace amounts of plutonium leaked from steel drums stored at the site between 1958 and 1968. Although DOE contractors remediated many of the highest priority waste sites to levels meant to be protective of workers and rural residents near the site, soil sampling activities in this area found ^{239,240}Pu levels as high as 457,000 pCi/kg (16,909 Bq/kg), which is nearly 10 times greater than the action level of 50,000 pCi/kg (Agency for Toxic Substances and Disease Registry 2005). The highest off-site concentration of ^{239,240}Pu observed during a remedial investigation was 6,500 pCi/kg (240 Bq/kg). A separate sampling study conducted in the 1990s at 42 locations adjacent to RFETS measured ^{239,240}Pu concentrations in soil ranging from 0.22 to 14.80 Bq/kg (5.9–400 pCi/kg) (Litaor 1999).

In 1960 at the McGuire Air Force Base in New Jersey, a missile caught fire at the Boeing Michigan Aeronautical Research Center and the warhead partially burned and melted, releasing weapons-grade plutonium (WGP) to the local environment (Lee and Clark 2005). The WGP at this site consisted of mostly ^{239,240}Pu, with a small amount of ^{241}Pu and a negligible amount of ^{241}Am (Amercium-241) at the time of its manufacture. Soil samples (0–2 inches) were collected from this site in June 2000 and analyzed for various plutonium isotopes. Concentrations were 0.42–6.34 Bq/g (11–171 pCi/g) for ^{239,240}Pu, 0.010–0.110 Bq/g (0.3–3.0 pCi/g) for ^{238}Pu, and 0.33–8.17 Bq/g (8.9–220 pCi/g) for ^{241}Pu in soil samples with various particle size fractions. The soil fraction with the smallest particle size (75–147 μm) contained the highest concentrations of plutonium, which were about 4 orders of magnitude higher than fallout levels. Based on the activity ratios of ^{241}Pu/^{239,240}Pu and ^{241}Am/^{239,240}Pu in the samples, the origin of the plutonium isotopes was identified as WGP (Lee and Clark 2005).

Soil samples were collected in 2004 on and around the Hanford Site (DOE 2005c). Average ^{239,240}Pu concentrations in surface soil collected on the 100-N Area, near facilities and operations in the 200 and 600 areas, and near facilities and operations in the 300 and 400 Areas were 0.004, 0.35, and 0.03 pCi/g ($1x10^{-4}$, $1.3x10^{-2}$, and $1x10^{-3}$ Bq/g) dry weight, respectively. With the exception of the concentration from the 200 and 600 Areas, the soil concentrations in 2004 were similar to levels determined from 1999 to 2003. Average ^{239,240}Pu concentrations in surface soil collected near Hanford Site facilities and operations in the 200 and 600 Areas from 1999 to 2003 were reported as 0.08, 0.29, 0.10, 0.12, and 0.09 pCi/g ($3x10^{-3}$, $1.1x10^{-2}$, $4x10^{-3}$, $4x10^{-3}$, and $3x10^{-3}$ Bq/g) dry weight, respectively. An average ^{239,240}Pu concentration of 0.0033 pCi/g ($1.2x10^{-4}$ Bq/g) dry weight was reported in surface soil collected from a distant community in 2004 (DOE 2005c). Radionuclides, including ^{239,240}Pu, were detected in river sediment adjacent to and downstream from the Hanford Site during 2004. Maximum ^{239,240}Pu concentrations in Columbia River sediment collected from four sites near the Hanford Site ranged from $7.8x10^{-4}$ to 0.011 pCi/g ($2.9x10^{-5}$–$4.1x10^{-4}$ Bq/g) dry weight (DOE 2005c, 2005g). Median ^{239,240}Pu concentrations from two of these sites, where more than one sample was collected, were 0.0084 and 0.0078 pCi/g ($3.1x10^{-4}$ and $2.9x10^{-4}$ Bq/g) dry weight. Median ^{239,240}Pu concentrations in sediment collected from 1999 to 2003 from six sites in the Columbia River near the Hanford Site ranged from 0.0016 to 0.0098 pCi/g ($5.9x10^{-5}$–$3.6x10^{-4}$ Bq/g) (DOE 2005c).

Concentrations of ^{239,240}Pu ranged from 0.006 to 0.80 pCi/g ($2x10^{-4}$–$3x10^{-2}$ Bq/g) dry weight in soil collected from communities surrounding the Nevada Test Site in southern Nevada and southern Utah during the summer 1996 and spring 1997. The activity ratios of radiocesium to plutonium in the soil samples suggest that the Nevada Test Site had a significant contribution to plutonium levels in this area as compared to global fallout (Cizdziel et al. 1998).

A study on radionuclide levels in west Cumbrian soils contaminated by low-level discharges from Sellafield reported ^{238}Pu levels detected at a range of 200–18,000 pCi/kg (8–670 Bq/kg) and ^{239,240}Pu levels detected at a range of 800–83,000 pCi/kg (30–3,100 Bq/kg) (Livens and Baxter 1988). Core samples of surface soil at the Maxey Flats facility, Kentucky, where radioactive wastes were buried, were reported to contain a mean concentration of $1.9x10^{5}$ pCi/kg (7,000 Bq/kg) of ^{238}Pu and $2.2x10^{4}$ pCi/kg (810 Bq/kg) of ^{239,240}Pu (NEA/OECD 1981).

Maximum ^{239,240}Pu concentrations of 488 and 27,900 Bq/kg ($1.31x10^{4}$ and $7.54x10^{5}$ pCi/kg) have been reported in composite (0–20 cm) and surface (0–5 cm) soil samples, respectively, collected in the vicinity of ground zero of the first thermonuclear explosions at the Semipalatinsk Test Site (STS) (Carlsen et al.

2001). Maximum ^{239,240}Pu concentrations of 192 and 8,850 Bq/kg ($5.19x10^3$ and $2.39x10^5$ pCi/kg) have been reported in composite (0–20 cm) and surface (0–5 cm) soil samples, respectively, collected at a crater created by an underground nuclear explosions in 1965 along the Shagan River at the STS. Maximum ^{239,240}Pu concentration of 2.8 and 3.98 Bq/kg (76 and 108 pCi/kg) have been reported in composite (0–20 cm) and surface (0–5 cm) soil samples, respectively, from villages near the STS. The activities in soil from the villages are typical of levels associated with global fallout (Carlsen et al. 2001).

Michel et al. (2002) reported mean concentrations 101 and 4.5 Bq/m^2 ($2.8x10^3$ and 120 pCi/m^2), for ^{239,240}Pu and ^{238}Pu, respectively, for soil cores collected at seven sites adjacent to the catchment of Blelham Tarn, a small lake in Cumbria, United Kingdom. Sediment cores were collected from 14 locations in the lake during March 1997 and mean concentrations of ^{239,240}Pu and ^{238}Pu were 183 and 4.5 Bq/m^2 ($4.95x10^3$ and 120 pCi/m^2), respectively. Isotopic ratios indicated that the source of these plutonium isotopes was fallout from atmospheric weapons testing (Michel et al. 2002). ^{239,240}Pu concentrations in 96 surface soil samples (0–5 cm) collected from 32 areas in Iran ranged from 0.080 to 0.360 Bq/kg (2.2–9.7 pCi/kg) (Aliabadi et al. 2005). Luksiene et al. (2006) reported ^{239,240}Pu concentrations in beach and forest surface soils (0–5 cm) collected in 1996–2001 from the Baltic coastline in Lithuania ranging from 0.06 to 0.80 and from 0.09 to 0.4 Bq/kg (1.6–22 and 2.4–11 pCi/kg), respectively. Ivanova et al. (1995) reported concentration ranging from 0.05 to 2.73 Bq/kg (1–73.8 pCi/kg) for ^{238}Pu and from 0.37 to 5.04 Bq/kg (10–136 pCi/kg) for ^{239,240}Pu in surface soils (0–2 cm) collected in the Bryansk, Orel, and Tula regions of Russia in 1992.

^{239,240}Pu concentrations in surface (0–5 cm) soil samples collected in 1996 in the Gomel region of Belarus, near the Chernobyl nuclear plant, were reported as 3.7 and 0.8 Bq/kg (100 and 20 pCi/kg) dry weight from Chiepietovitach and Pecki, respectively (Michel et al. 1999). Concentrations of ^{239,240}Pu in soil samples from the 5–10 and 10–15 cm depths at Pecki were 0.52 and 0.45 Bq/kg (14 and 12 pCi/kg) dry weight, respectively. Soil concentrations of ^{238}Pu were 2.2 and 0.39 Bq/kg (59 and 11 pCi/kg) dry weight from Chiepietovitach and Pecki, respectively. ^{238}Pu concentrations in soil samples from the 5–10 and 10–15 cm depths at Pecki were 0.04 and 0.06 Bq/kg (1 and 2 pCi/kg) dry weight, respectively (Michel et al. 1999).

The Mayak PA, which processed weapons-grade plutonium from 1949 to 1952, discharged radioactive wastes into the Techa River. Contamination densities of ^{239,240}Pu in floodplain soil on the Techa River showed a decrease from approximately 2 to $4x10^{-2}$ kBq/m^2 (50–1 nCi/m^2) over a distance of 200 km starting from Dam 11, which is 30 km from the site of radioactive waste disposal. ^{239,240}Pu concentrations

in bottom soil along the river course decreased from approximately $5x10^{-2}$ to $2x10^{-2}$ Bq/kg (1.4–0.5 nCi/m^2) over the same distance (Akleyev et al. 2000). Børretzen et al. (2005) reported concentrations of $1.81x10^6$–$2.0x10^6$ and $1.22x10^5$–$1.35x10^5$ mBq/kg (48.9–54.1 and 3.30–3.65 nCi/kg) dry weight for ^{239}Pu and ^{240}Pu, respectively in surface soil samples from the Asanov Swamp at Mayak PA, collected on June 26, 1994.

In 1966, two nuclear weapons were accidentally detonated during a collision of two aircraft in the area of the village of Palomares, Spain. ^{239,240}Pu inventories in surface soil ranging from 8 to 57,900 Bq/m^2 (0.2–1,560 nCi/m^2) were reported in samples collected in the vicinity of the village of Palomares in October 2001 (Jimenez-Ramos et al. 2006). Concentrations in soil samples from Tabernas, 200 km away from Palomares, were reported as 0.36 Bq/kg (9.7 pCi/kg) for ^{239,240}Pu Bq/kg dry weight and <0.48 Bq/kg (<13 pCi/kg) dry weight for ^{238}Pu (Rubio Montero and Sanchez 2001).

Concentrations of ^{239,240}Pu in peat bog samples from the area of the Tomsk-Seversk nuclear facility (Siberia, Russia) were reported as 0.5, 0.6, and 10.5 Bq/kg (13, 16, and 284 pCi/kg) at depths of surface-5, 11–13, and 20 cm, respectively; reported concentrations for ^{238}Pu were 0.06, 0.01, and 0.34 Bq/kg (1.6, 0.3, and 9.2 pCi/kg), respectively. Concentrations of ^{239,240}Pu in forest soil samples from this area were reported as 0.052, 0.055, and 0.054 Bq/kg (1.4, 1.5, and 1.5 pCi/kg) at depths of surface, 3-6, and 32–40 cm, respectively, while concentrations in samples from an area river bank were 0.050, 0.049, and 0.050 Bq/kg (1.5, 1.4, and 1.5 pCi/kg) at depths of 0–3, 9–12, and 18–21 cm, respectively (Gauthier-Lafaye et al. 2008).

Yamamoto et al. (2008b) reported ^{239,240}Pu concentrations ranging from 0.16 to 51.87 Bq/kg (4.3–1,401 pCi/kg) in 26 soil samples collected in October 2005 from Dolon located 60 km northeast of the Semipalatinsk Nuclear Test Site in Kazakhstan, an area contaminated mainly by the first USSR nuclear test on August 29, 1949.

Yoshida et al. (2007) reported a ^{239,240}Pu soil (0–5 cm) concentration of 59.9 Bq/kg (1,620 pCi/kg) dry weight at 300 m west from the Nishiyama reservoir Nagasaki Japan. This concentration decreased with increasing distance for the Nishiyama reservoir. The ^{239,240}Pu concentration in the surface soil at farther sampling point was 1.82Bq/kg (49.2 pCi/kg) dry weight, a level within the range with global fallout plutonium concentrations in surface soil of Japanese forests (0.15–4.31 Bq/kg (3.8–116 pCi/kg, dry weight) (Yoshida et al. 2007).

Concentrations of ^{239,240}Pu in soils from counties throughout Hungary ranged from 0.020 to 0.61 Bq/kg (0.54–17 pCi/kg) and concentrations of ^{241}Pu in these same samples were reported to range from 0.043 to 1.70 Bq/kg (1.2–46 pCi/kg) (Varga and Tarján 2008). Isotopic ratio analysis indicated that the plutonium levels in Hungary arise from global fallout related to atmospheric testing of nuclear weapons.

^{239,240}Pu concentrations in sediment cores collected from Lake Michigan in 1972–1974 ranged from 0.003 to 0.401 pCi/g ($1x10^{-4}$–$1.48x10^{-2}$ Bq/g) dry weight. It was estimated in this report that radioactivity in the sediments was confined to the upper 6 cm of the sediments, and in many of the core samples, no radioactivity was detected below a depth of 3 cm (IAEA 1976g).

Rapiejko et al. (2001) reported ^{239,240}Pu median concentrations of 2.2 (59) (0.00–0.06 cm depth near sewage treatment plant), 1.3 (35) (0.06–0.15 cm depth), 1.1 (30) (0.15–0.24 cm depth), and 2.1 (57) (0.24–0.37 cm depth) Bq/kg (pCi/kg) in sediment samples collected in April 1999 from the Peconic River, downstream from the Brookhaven National Laboratory (BNL). Concentrations of ^{238}Pu in these same samples were 0.09, <0.07, <0.07, and <0.09 Bq/kg (2, <2, <2, and <2 pCi/kg), respectively. The median concentrations of ^{239,240}Pu in sediments from Donahues Pond and Forge Pond, further down stream from BNL, were 4.0 and 1.6 Bq/kg (108 and 43 pCi/kg), respectively; ^{238}Pu was not detected in these samples. Concentration ranges for ^{239,240}Pu in control samples from the Connetquot River were 1.7–3.7 Bq/kg (46–100 pCi/kg) at 0.0–0.06 cm depth and 0.13–0.48 Bq/kg (4–13 pCi/kg) at 0.06–0.15 cm depth; ^{238}Pu concentrations were reported as 0.15–0.26 Bq/kg (4–7 pCi/kg) at 0.0–0.06 cm depth and <0.07–0.074 Bq/kg (<2–2 pCi/kg) at 0.06–0.15 cm depth (Rapiejko et al. 2001).

Skipperud et al. (2009) reported average ^{239,240}Pu concentrations of 0.40, 0.24, and 0.55 Bq/kg (10, 6.5, and 15 pCi/kg), respectively, in sediments collected in 1996 from the Ob Estuary and Yenisey Estuary (both of which have weapons-grade plutonium sources in their catchment areas), and Kara Sea, Russia.

Surface sediment samples (0–1 cm) from the Rhone River collected in March 2001 at the input into the Gulf of Lions (Northwestern Mediterranean Sea) were reported to contain concentrations of ^{239,240}Pu and ^{238}Pu of 0.329–549 Bq/kg (8.89–41.86 pCi/kg) and 0.025–0.143 Bq/kg (0.68–3.86 pCi/kg), respectively (Lansard et al. 2007). Concentrations of ^{239,240}Pu in sediment cores collected in November 2001 ranged from 0.256 to 5.974 Bq/kg (6.92–161.5 pCi/kg) at 5–10 cm and 280–290 cm depth, respectively. Concentrations of ^{238}Pu in sediment cores collected in November 2001 ranged from 0.035 to 1.254 Bq/kg (0.95–33.89 pCi/kg) at 5–10 cm and 280–290 cm depth, respectively. Sources of plutonium isotopes in the Rhone River valley have been identified as weathering of the catchment basin contaminated by

atmospheric fallout and liquid effluents released from the Marcoule reprocessing plant (located upstream 120 km from the river mouth) since 1961 (Lansard et al. 2007).

Liao et al. (2008) reported ^{239}Pu concentrations in sediment from Lake Poyang, East China of 0.066, 0.395, and 0.062 mBq/g (1.8, 11, and 1.7 pCi/kg) at 0–1, 5–6, and 10–11 cm depth, respectively. ^{240}Pu concentrations of 0.046, 0.270, and 0.042 mBq/g (1.2, 7.3, and 1.1 pCi/kg) were reported at these same depths, respectively. The ^{240}Pu/^{239}Pu ratio (0.187) in sediment samples from Lake Poyang indicated that plutonium pollution was from global fallout.

6.4.4 Other Environmental Media

^{238,239,240}Pu was identified in imported food collected 2 weeks after the Chernobyl accident in an FDA/USDA-sponsored survey; however, concentrations were not provided. Generally, contamination levels for the radionuclides surveyed were below FDA's levels of concern (Cunningham et al. 1989). The FDA developed guidance levels for radionuclide activity concentration, called derived intervention levels (DILs), which help determine whether domestic food in interstate commerce or food offered for import into the United States present a safety concern (FDA 2005). The DIL for ^{238}Pu + ^{239}Pu + ^{241}Am is 2 Bq/Kg (FDA 2005). Various radionuclides were measured in 1996 on samples of mixed diet from regions throughout the United Kingdom (MAFF 1997b). Concentrations of all artificial radionuclides were reported to be low and of little significance. Concentrations of ^{238}Pu were generally <0.00030 Bq/kg (0.008 pCi/kg) and concentrations of ^{239,240}Pu ranged from 0.00011 to 0.00040 Bq/kg ($3x10^{-3}$–0.01 pCi/kg) (MAFF 1997b). Samples of milk, crops, bread, and meat collected from the United Kingdom in 1996 were analyzed for various natural and artificial radionuclides; concentrations of plutonium (^{238}Pu and ^{239,240}Pu) were generally <0.0002 Bq/L (<0.005 pCi/L) for milk and <0.0002 Bq/kg (<0.005 pCi/kg) for crops, bread, and meat (MAFF 1997b).

Seventy-two beverage brands available to the public in the United Kingdom were surveyed for natural and anthropogenic radionuclides. Beverages included in this survey were fruit juices, fruit juice drinks, fruit squashes, carbonated drinks, baby juices, flavored spring and mineral waters, ciders, wines, beers, and others beverages, such as powdered chocolate and malt drinks. Levels of all anthropogenic radionuclides surveyed, including ^{238}Pu and ^{239,240}Pu, were below the limits of detection (MAFF 1997a). Sanchez et al. (1999) studied doses of artificial radionuclides, including ^{239,240}Pu, in the diet of individuals living in Cumbria, United Kingdom. This investigation included three duplicate diet studies conducted in 1986, 1995, and 1996. In general, mean ^{239,240}Pu concentrations in diet samples from these surveys were

reported to range from <$1x10^{-4}$ (the detection limit) to <$2.8x10^{-3}$ Bq/kg (<$2.7x10^{-3}$–<$7.6x10^{-2}$ pCi/kg) fresh weight in both the control group from west Cumbria 1986 and the study group from Sellafield in 1995. The highest ^{239,240}Pu concentrations of $1.7x10^{4}$ and $1.2x10^{4}$ Bq/kg (0.46 and 0.32 pCi/kg) fresh weight were found in 1986 diet surveys, which contained crab (Sellafield) and cockles (west Cumbria) (Sanchez et al. 1999). Cooper et al. (1992) analyzed food and total diet samples for various radioactive isotopes that were collected from selected communities in areas of the former Union of the Soviet Socialist Republic (U.S.S.R.) that were contaminated with fallout from the accident at Chernobyl. Concentrations of ^{239,240}Pu in total diet samples ranged from $1.5x10^{-3}$ to $7.0x10^{-3}$ Bq/kg ($4.1x10^{-3}$–$2x10^{-2}$ pCi/kg) dry weight (Cooper et al. 1992).

Twenty Emmental cheese samples were collected from 6 European regions (Allgäu, Germany; Bretagne, France; Savoie, France; Switzerland; Finland; and Vorarlberg, Austria,) and analyzed for various radionuclides. ^{238}Pu and ^{239,240}Pu concentrations were determined in one sample from each location, except Finland, and were found to be less than the detection limit (0.3 Bq/kg [8 pCi/kg]; Froidevaux et al. 2004).

Samples of bottom-feeding fish, white sucker (*Catostomus commersoni*), channel catfish (*Ictalurus punctatus*), and carp (*Cyprinus carpio*) were collected along the Rio Grande upstream and downstream of the Los Alamos National Laboratory (LANL) in September 1997 and analyzed for various radionuclides (Fresquez et al. 1999b). Mean concentration of ^{239,240}Pu in samples collected downstream of LANL ranged from $4.8x10^{-5}$ to $47.5x10^{-5}$ pCi/g ($1.8x10^{-6}$ to $1.76x10^{-5}$ Bq/g) in muscle and bone, and from $27.5x10^{-5}$ to $135.0x10^{-5}$ pCi/g ($1.02x10^{-5}$ to $5.00x10^{-5}$ Bq/g) in viscera. In samples collected upstream of LANL, ^{239,240}Pu concentrations ranged from $5.5x10^{-5}$ to $33.1x10^{-5}$ pCi/g ($2.0x10^{-6}$ to $1.22x10^{-5}$ Bq/g) in muscle and bone, and a mean concentration of $85.1x10^{-5}$ pCi/g ($3.15x10^{-5}$ Bq/g) was determined in viscera. For most of the radionuclides, concentrations in fish collected downstream of LANL were not significantly higher than those in fish collected upstream of LANL (Fresquez et al. 1999b).

Børretzen et al. (2005) reported ^{239}Pu concentrations of 1,010, 12, 95, and 119 mBq/kg (27.30, 0.32, 2.6, and 3.22 pCi/kg) wet weight and ^{240}Pu concentrations reported of 1,150, 4, 6, and 44 Bq/kg (31.1, 0.11, 0.16, and 1.2 pCi/kg) wet weight in mussels, pike bone, pike filet, and roach, respectively, collected on June 26, 1994 from a reservoir adjacent to the Asanov Swamp, downstream from the Mayak PA.

Oikawa and Yamamoto (2007) reported ^{239}Pu and ^{240}Pu concentrations livers of Surume squid caught during the fishery season from September–December 2002 in the coastal seawaters off Japan.

Concentrations of ^{239}Pu and ^{240}Pu of 1.5–28 mBq/kg (0.041–0.76 pCi/kg) and 1.1–24 mBq/kg (0.030–0.65 pCi/kg), respectively; these concentrations were several thousand times higher than levels found in seawater.

Various metals and radionuclides, including ^{238}Pu and ^{239,240}Pu, were measured in birds and eggs from Amchitka and Kiska Islands in the Bering Sea/Northern Pacific Ocean. ^{238}Pu was not detected over the minimum detectable activity (MDA) in any samples. ^{239,240}Pu was only detected above the MDA at 0.31 Bq/kg (8.4 pCi/kg) wet weight in a guillemot composite (Burger and Gochfeld 2007).

Concentrations of ^{239,240}Pu ranged from 12 to 680 pCi/kg (0.44 –25 Bq/kg) dry weight in attic dust collected from communities surrounding the Nevada Test Site in southern Nevada and southern Utah during the summer 1996 and spring 1997. The activity ratios of radiocesium to plutonium in the dust samples suggest that the Nevada Test Site had a significant contribution to plutonium levels in this area as compared to global fallout (Cizdziel et al. 1998).

Plutonium concentrations in vegetation were monitored during 2004 on the Hanford Site. ^{239,240}Pu was not detected in vegetation samples collected on the Hanford Site in the 100-N Area and the 300 and 400 Areas (DOE 2005c). An average ^{239,240}Pu concentration of 0.003 pCi/g ($1x10^{-4}$ Bq/g) dry weight, was reported in vegetation samples collected from the 200 and 600 Areas. A ^{239,240}Pu concentration of 0.00033 pCi/g ($1.2x10^{-5}$ Bq/g) dry weight was reported in vegetation from distant communities. Average ^{239,240}Pu concentrations in vegetation samples collected in 1999–2002 in the 100-N Area and the 300 and 400 Areas ranged from 0.0004 to 0.024 and from 0.003 to 0.005 pCi/g ($1.5x10^{-5}$–$8.9x10^{-4}$ and $1x10^{-4}$–$2x10^{-4}$ Bq/g) dry weight and was not detected in the 2003 samples. Average ^{239,240}Pu concentrations in vegetation samples collected during 1999–2003 ranged from 0.003 to 0.033 pCi/g ($1x10^{-4}$–$1.2x10^{-3}$ Bq/g) dry weight (DOE 2005c). In 2004, mean ^{239,240}Pu concentrations of 0.0020, 0.0050, 0.0017, and 0.00022 pCi/g ($7x10^{-5}$, $2x10^{-4}$, $6.3x10^{-5}$, and $8.1x10^{-6}$ Bq/g) dry weight were reported in vegetation samples collected site-wide at the Hanford Site, at the perimeter, at the shoreline of the Hanford Reach of the Columbia River, and at a distant site, respectively. ^{238}Pu was only detected in one of five samples collected on-site at a concentration of $6.0x10^{-6}$ pCi/g ($2x10^{-7}$ Bq/g) dry weight. The results reported for the 2004 samples were similar to those reported in 1993, 1994, 1998, and 2001 (DOE 2005c).

Akleyev et al. (2000) reported that plutonium concentrations in grass samples from the Asanov Swamps and dams on the Techa River were estimated to be 7–80 Bq/kg (200–2,200 pCi/kg). Average values for plutonium concentrations in vegetation from the flood plain section from Dam 11 to the village of

Muslyumovo were reported as 7 Bq/kg (200 pCi/kg), and 1.1 Bq/kg (30 pCi/kg) in the section from Muslyumovo to Zarechnoye. These sites are in the area of the Mayak PA (Akleyev et al. 2000).

Børretzen et al. (2005) reported concentrations of 163 and 207 mBq/kg (4.41 and 5.59 pCi/kg) for ^{239}Pu and 23 and 24 mBq/kg (0.62 and 0.65 pCi/kg) for ^{240}Pu in two dried grass samples from the Asanov Swamp collected on June 26, 1994. ^{239}Pu and ^{240}Pu concentrations of 1,700 and 362 mBq/kg (46 and 9.78 pCi/kg) dry weight and 190 and 36 mBq/kg (5.1 and 0.97 pCi/kg) dry weight were also reported in two samples of water plants, respectively (Børretzen et al. 2005)

Plutonium concentrations in moss samples from counties in Hungary were reported as 1.06 and 0.007 Bq/kg (28.7 and 0.2 pCi/kg) for ^{239,240}Pu and 2.39 and 0.011 Bq/kg (64.6 and 0.30 pCi/kg) for ^{241}Pu in Komarom and Heves, respectively (Varga and Tarján 2008). ^{239,240}Pu concentrations in ashed fodder (Pest), hay (Bacs-Kiskun), and sedge (Tolna) were reported as 1.91, 0.004, and 0.038 Bq/kg (51.6, 0.1, and 1.03 pCi/kg), respectively. ^{241}Pu concentrations in these same samples were reported as 131, 0.22, and 0.69 Bq/kg (3540, 6.0, and 19 pCi/kg), respectively (Varga and Tarján 2008).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The estimated 50-year dose commitment from plutonium for people in the north temperate zone due to atmospheric nuclear weapons tests conducted before 1973 is 0.2 mrad (0.002 mGy) to the bone lining cells (Eisenbud 1987). The average annual dose equivalent from all background radiation to an individual residing in the United States is estimated to be 360 mrem (3.6 mSv) (NCRP 1987).

Sanchez et al. (1999) reported that ^{239,240}Pu contributed the lowest dose of radionuclides studied in a survey of the diets of individuals living in Cumbria, United Kingdom; the average dose was <0.04 µSv (0.004 mrem). Concentrations of ^{239,240}Pu in total diet samples collected from areas of the former U.S.S.R. that were contaminated by fallout from Chernobyl ranged from 1.5×10^{-7} to 7×10^{-7} Bq/g (4.1×10^{-6}–2×10^{-5} pCi/g) dry weight; a worst-case calculated dose of 0.2 µSv (0.02 mrem) was reported for ^{239,240}Pu (Cooper et al. 1992). Pietrzak-Flis and Orzechowska (1993) studied the content of ^{239,240}Pu in daily diet samples collected from a hospital in Bialystok, Poland from March 1987 to May 1992. The estimated annual intake of plutonium was 0.774 Bq/year (20.9 pCi/year) in the first year after the accident at Chernobyl; after the sixth year, the daily intake was 0.088 Bq/year (2.4 pCi/year) (Pietrzak-Flis and Orzechowska 1993). Daily ingestion of ^{239,240}Pu in food in Japan between 1978 and 1980 due to atmospheric fallout was estimated to be 4.5×10^{-3} pCi/day (1.7×10^{-4} Bq/day) (Hisamatsu et al. 1987).

Filipy et al. (2003) reported plutonium concentrations in bone samples collect at autopsy from eight individuals for the United States Transuranium and Uranium Registries (USTUR). The USTUR documents levels and distribution of uranium and transuranium isotopes in human tissues for occupationally exposed workers who donate their bodies to science (USTUR 2003). Plutonium levels were measured in various bone samples: clavicle; patella; ribs (5–10); sternum; and vertebrae (T5–L3). ^{238}Pu concentrations ranged from 0.146 (clavicle) to 82.7 (sternum) Bq/kg (3.95–2,240 pCi/kg) dry weight. ^{239}Pu concentrations ranged from 0.441 (patella) to 398.0 (vertebrae) Bq/kg (11.9–10,800 pCi/kg) dry weight. ^{241}Pu concentrations ranged from 0.850 (sternum) to 25.2 (sternum) Bq/kg (23–681 pCi/kg) dry weight (Filipy et al. 2003). Ivanova et al. (1995) measured plutonium concentrations in lungs, tracheobronchial lymph nodes (TLN), liver, and bone in 59 individuals who lived in the areas of the Bryansk region of Russia that was contaminated by the Chernobyl accident. Average concentrations of ^{238,239,240}Pu in lung, TLN, liver, and bone tissue were 0.060, 0.530, 0.070, and 0.070 Bq/kg (1.6, 14, 1.9, and 1.9 pCi/kg) dry weight, respectively (Ivanova et al. 1995).

Total plutonium deposition in five Manhattan Project workers exposed to plutonium in 1944–1945 ranged from 98 to 3,300 Bq (2,600–89,000 pCi) according to autopsy data (Voelz et al. 1997). Mean concentrations of ^{239,240}Pu in human tissues from autopsy specimens in Japan ranged from 2.5×10^{-4} pCi/g (9.3×10^{-6} Bq/g) (cerebrum) to 1.5×10^{-3} pCi/g (5.6×10^{-5} Bq/g) (gonads) wet weight (Takizawa 1982). Wrenn and Cohen (1977) reported ^{239}Pu levels in tissues derived from 12 autopsy cases in New York City from 1973 to 1976. Average levels for lung, liver, vertebrae, and gonads were 2.4×10^{-4}, 7×10^{-4}, 1.7×10^{-4}, and 4×10^{-4} pCi/g (8.9×10^{-6}, 3×10^{-5}, 6.3×10^{-6}, and 1×10^{-5} Bq/g), respectively. Tissue samples from autopsy cases of nonoccupationally exposed individuals from Great Britain showed median ^{239,240}Pu concentrations for ribs, vertebrae, femur, liver, and lungs of 1.6×10^{-4}, 1.2×10^{-4}, 9.5×10^{-5}, 7×10^{-4}, and 4.9×10^{-5} pCi/g (5.9×10^{-6}, 4.4×10^{-6}, 3.5×10^{-6}, 2.6×10^{-5}, and 1.8×10^{-6} Bq/g), respectively. Comparable samples taken from autopsy cases from a region in Great Britain located near a plutonium processing plant had median concentrations of 2.2×10^{-4}, 1.9×10^{-4}, 1.5×10^{-4}, 1.4×10^{-4}, and 1.8×10^{-4} pCi/g (8.1×10^{-6}, 7.0×10^{-6}, 5.5×10^{-6}, 5.2×10^{-6}, and 6.7×10^{-6} Bq/g) for ribs, vertebrae, femur, liver, and lungs, respectively (Popplewell et al. 1988).

Ibrahim et al. (1999) studied the excretion of ^{239}Pu in urine of residents living near the Rocky Flats Environmental Technology Site (RFETS). The Rocky Flats group consisted of two groups of individuals living near RFETS, who were not occupationally exposed to plutonium. Urine was collected from the first group during 1992–1993 and samples were collected from the second group in 1995. Background

samples were also collected during two periods from individuals living in Colorado least 16 km from the RFETS. Mean ^{239}Pu excretion rates of 1.1×10^{-6} and 8.5×10^{-7} Bq/day (3.0×10^{-5} and 2.3×10^{-5} piCi/day) were reported for the entire Rocky Flats group and the background group, respectively. Analysis indicated that these data were not statistically significantly different. Measured levels of ^{239}Pu in urine from the Rocky Flats group were within the range reported for background levels (Ibrahim et al. 1999).

Bolotov et al. (2003) reported ^{239}Pu concentrations in human hair ranging from 0.90 to 3.0 Bq/kg (20–80 pCi/kg) in samples from the area of the heavily damaged Semipalatinsk nuclear bomb test site region in Russia. ^{239}Pu concentrations in human gall stones collected from three individuals from Minsk, Belarus were 0.28–0.53 Bq/kg (7.5–14 pCi/kg); gall stones from another individual in Krakow, Poland contained <0.05 Bq/kg (<1 pCi/kg) ^{239}Pu (Bolotov et al. 2003).

Yamamoto et al. (2008a) reported plutonium concentrations human tissue samples, including bone (vertebra), lungs, liver, and kidneys, collected during 2000–2002 at autopsy from nine residents who died in some settlements and in Semipalatinsk City around the Semipalatinsk Nuclear Test Site. ^{239,240}Pu concentrations in four bone (vertebra) samples ranged from 0.049 to 0.13 mBq/g ashed weight. ^{239}Pu concentrations in six kidney samples ranged from 0.023 to 0.25 mBq/g ashed weight; ^{240}Pu was not detected in these kidney samples. In the nine liver samples ^{239}Pu and ^{240}Pu concentrations were 0.39–4.83 and 0.2–2.74 mBq/g ashed weight, respectively. In the nine lung samples ^{239}Pu and ^{240}Pu concentrations ranged from 0.044 to 1.56 and from not detected to 1.83 mBq/g ashed weight, respectively. In addition, bone samples, mainly vertebral bone, were collected from 23 deceased residents of this area. ^{239,240}Pu activity in these bone samples ranged from 0.020 to 0.107 mBq/g ashed weight, with a mean of 0.46 mBq/g ash weight. Yamamoto et al. (2008a) reported that the ^{239,240}Pu levels in bone, lung, and liver samples in this study did not seem to be largely different from ranges found for human tissue samples for residents from other countries that were due solely to global fallout during the 1970s–1980s. Human tissue autopsy samples were obtained for the period of 1975–2003 from non-occupationally exposed residents of Ozyorsk, Russia in the vicinity of the Mayak nuclear facility. Since the early 1950s, the plutonium body burden in the Ozyorsk population was shown to grow at a nearly constant rate and total accumulation amounted to 5.8 Bq at 35 years after the construction of the plant in the city (Suslova et al. 2007).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children would be exposed to plutonium from fallout by similar routes are adults, such as ingestion of food and water and breathing ambient air. However, levels would generally be low for children not living near areas with known plutonium contamination (e.g., areas where nuclear accidents or former plutonium processing plants). Limited data on exposures of children to plutonium were located.

Compared to adults, the potential for plutonium exposure is greater for children who consume foods (e.g., milk, grains) produced in areas with elevated concentrations of plutonium in the soil and for children with elevated concentrations of plutonium in their drinking water. Children are more likely to be exposed to plutonium in dairy products produced in contaminated areas.

O'Donnell et al. (1997) reported an average ^{239,240}Pu concentration in permanent teeth collected from children within the United Kingdom and Republic of Ireland of 5 mBq/kg (0.1 pCi/kg) ash weight. ^{239,240}Pu concentrations decreased with increasing distance from Sellafield; at 0–50, 50–150, and >150 miles from Sellafield, average ^{239,240}Pu concentrations were 7.1, 5.0, and 3.0 mBq/kg (0.20, 0.10, and 0.08 pCi/kg) ash weight, respectively. These levels are not considered to present a radiological hazard (O'Donnell et al. 1997). Urine collected during a 24-hour period from 17 school-aged children in North London contained 3.5 μBq/day of ^{239}Pu (Priest et al. 1999).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Total plutonium deposition in five Manhattan Project workers exposed to plutonium in 1944–1945 ranged from 98 to 3,300 Bq (2,600–89,000 pCi) according to autopsy data (Voelz et al. 1997).

Individuals living near facilities which utilize plutonium in their operations may have higher exposure potential due to regular releases through stack-emissions or waste water. In addition, atmospheric fallout to the soil can result in secondary releases due to dust generation while farming or due to uptake by crops and subsequent ingestion of contaminated crops (Corey et al. 1982).

Individuals living in Palomares, Spain, were exposed to plutonium after the dispersal of the plutonium in two bombs released during the midair collision of two airplanes (Iranzo et al. 1987). Exposure via inhalation due to the resuspension of contaminated soil was studied for 15 years following the release. Those individuals living near cultivated lands with the highest contamination received a cumulative total of 52.3 mrem ($5.2x10^{-1}$ mSv) from 1966 to 1980 while those in the urban area of Palomares, farther away from the source, received 5.4 mrem ($5.4x10^{-2}$ mSv) (Iranzo et al. 1987).

Kathren et al. (1987) determined levels of ^{239}Pu at autopsy in bones of an individual known to have had occupational exposure to plutonium. Values ranged from $1.9x10^{-4}$ to $1.14x10^{-2}$ pCi/g ash ($7.0x10^{-6}$–$5.0x10^{-5}$ Bq/g ash), with the highest value detected in the scapula.

Kawamura (1987) estimated the $^{239,240}Pu$ inhalation intake of visitors to Kiev after the Chernobyl accident to be 0.8 pCi/day (0.03 Bq/day) during peak fallout exposure.

6.8 ADEQUACY OF THE DATABASE

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

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would

reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Table 4-2 summarizes many of the relevant physical and chemical properties of plutonium and selected plutonium compounds. Table 4-3 summarizes the radiological properties of selected plutonium isotopes. There are adequate data for the physical, chemical, and radiological properties of plutonium and plutonium compounds. No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2004, became available in May of 2006. This database is updated yearly and should provide a list of industrial production facilities and emissions.

The potential for human exposure to plutonium is great due to its ubiquitous presence in the environment, resulting from releases from production facilities and from weapons testing, and its radiological half-life. However, the level of exposure to plutonium will generally be small. The production and use of plutonium 238–243 are well documented. There is little information regarding the production of ^{237}Pu. The amounts of these plutonium isotopes produced for various applications have been documented; however, the most current information is from 1974. More recent data are needed in order to compare past and present production and to project future production. The majority of information on the production and use of plutonium is classified in the nation's defense program. Information on past major releases of plutonium from weapons testing and from the explosion of a navigational satellite is available. However, current information on releases from production facilities is unavailable and is needed in order to monitor populations that might be exposed. The disposal of plutonium prior to 1970 is documented, but again, more recent information regarding amounts being held for mandated disposal in the proposed high-level disposal facility is needed. Rules and regulations for the disposal of plutonium have been established and these are reported in Chapter 8.

Environmental Fate. The major transport processes involved in the environmental fate of plutonium, as it relates to potential human exposure, have been fairly well defined. These processes include transport in the atmosphere when adsorbed to particulate matter and dry or wet deposition on land and water. Information on environmental compartments, such as flux rates, and the mechanisms and rates of several processes involved in the biogeochemical cycling of plutonium are still undefined. The data available regarding uptake of plutonium by plants are limited. There is some information regarding the conversion of the oxidized forms of plutonium to reduced forms followed by uptake into plants. Information regarding the influence of inorganic complexes on transport and regarding the media-specific effects of pH on the oxidation states of plutonium would be useful in order to more fully understand transport processes. The persistence of plutonium isotopes is well documented. Transformation of plutonium is through radioactive decay or chemical oxidation/reduction reactions. These processes have been well characterized.

Bioavailability from Environmental Media. Plutonium is known to be absorbed following inhalation exposure. Bioavailability following oral and dermal exposure is very low; however, plutonium can be absorbed from contaminated wounds. Bioassay data are available on absorption from contaminated air and water.

Food Chain Bioaccumulation. Plutonium has been shown to bioconcentrate in aquatic organisms at the lower end of the food chain (WHO 1983). However, data do not indicate that plutonium is bioconcentrated in plants, higher aquatic organisms, or animals. In addition, there is no indication that plutonium is biomagnified in terrestrial or aquatic food chains. No additional information on bioaccumulation appears to be necessary at this time.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of plutonium in contaminated media at hazardous waste sites are needed so that the information obtained on levels of plutonium in the environment can be used in combination with the known body burden of plutonium to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

A number of studies have been performed throughout the years on the fallout associated with the testing of nuclear weapons. Information is available on levels in air, water, soil, plant materials, and foodstuffs (Ahier and Tracy 1995; Arimoto et al. 2005; Dai et al. 2002; DOE 1999a, 2005a, 2005c, 2005d, 2005e, 2005f, 2006a; Hirose and Aoyama 2003; Ibrahim et al. 1997; Lee and Clark 2005; Lehto et al. 2006;

Litaor 1999; Mulsow et al. 1999; Struminska and Skwarzec 2004). In particular, information is very limited on levels in media associated with areas surrounding waste sites. Such information is needed in order to quantify the potential exposure via these sources. Limited data are available on estimates of human intake via specific media (e.g., food) (Cooper et al. 1992; Pietrzak-Flis and Orzechowska 1993; Sanchez et al. 1999). This information would be important in determining the impact of exposure through each of these media. In general, plutonium levels found in environmental media that resulted from fallout are low and exposure would also be expected to be low. Plutonium exposure would likely only be relevant to individuals living near areas with known plutonium contamination (e.g., nuclear accident sites or waste sites).

Exposure Levels in Humans. Plutonium concentrations have been reported in various tissues and biological fluids, including urine, and in lung, liver, and bone tissues obtained from autopsy (Filipy et al. 2003; Ibrahim et al. 1999; Ivanova et al. 1995; Popplewell et al. 1988; Takizawa 1982; Voelz et al. 1997; Wrenn and Cohen 1977). Occupationally exposed populations are likely routinely biomonitored through urinalysis. However, such data are not made available and are needed to quantify exposure to these individuals. In addition, no information is available on biomonitoring of individuals around NPL sites where plutonium has been found or of the general public.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children would be exposed to plutonium from fallout by similar routes are adults, such as ingestion of food and water and breathing ambient air. However, levels would generally be low for children not living near areas with known plutonium contamination (e.g., areas where nuclear accidents or former plutonium processing plants). Limited data on exposures of children to plutonium were located. O'Donnell et al. (1997) reported ^{239,240}Pu levels in permanent teeth collected from children in the United Kingdom and Republic of Ireland. Priest et al. (1999) reported ^{239}Pu content in urine in North London school children.

There do not appear to be any childhood-specific means to decrease exposure to plutonium. However, as levels of plutonium in food and ambient air are generally low, exposure to plutonium would also be expected to be low.

No data were located on plutonium concentrations in breast milk or infant formulas. Additional studies on daily intake of plutonium in children and infants would be useful to estimate the exposure of this

population to plutonium, particularly in areas contaminated with plutonium where exposure may be of greater concern.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for plutonium were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

USTUR established a database to document levels and distribution of uranium and transuranium isotopes in human tissues for occupationally exposed workers who donate their bodies to science (USTUR 2003). The Department of Energy (DOE) has developed the Comprehensive Epidemiologic Data Resource (CEDR) Program to provide public access to health and exposure data concerning DOE installations. In addition, studies relating to populations residing near DOE installations, as well as other studies of radiation exposures and health effects, such as atomic bomb survivors, are included in CEDR (CEDR 2007).

6.8.2 Ongoing Studies

No ongoing studies pertaining to the environmental fate of plutonium or plutonium compounds were identified in a search of the Federal Research in Progress database (FEDRIP 2007).

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring plutonium, its metabolites, and other biomarkers of exposure and effect to plutonium. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

The accurate and reliable determination of plutonium in biological and environmental samples is important because of the potential impact of this element on public health. Analytical methods used to measure plutonium in biological and environmental media are highly refined compared to other transuranics. Alpha spectrometry is the most widely used method for the determination of plutonium. However, this method typically cannot resolve the ^{239}Pu and ^{240}Pu peaks due to their similar energies (5.15 and 5.16 MeV). An independent mass spectrometric analysis is required in order to determine the individual concentrations of ^{239}Pu and ^{240}Pu (Muramatsu et al. 2001a; Wolf 2006). Mitchell et al. (1997) have described a deconvolution technique based on commercial software to resolve the ^{239,240}Pu peaks in alpha spectroscopy. Other methods such as thermal ionization mass spectrometry (TIMS) and accelerator mass spectrometry (AMS) have been used for the determination of plutonium. Inductively coupled plasma-mass spectrometry (ICP-MS) has advantages of ease of operation and rapid analysis. In addition, ICP-MS can provide information about the ^{239}Pu/^{240}Pu ratio in a sample, which can, in turn, provide important information about the source of plutonium contamination (Muramatsu et al. 2001a; Varga et al. 2007; Wolf 2006). Interferences that may be observed with ICP-MS are caused by polyatomic ions in the plasma, such as $^{238}UH^+$ and $^{238}UH_2^+$, which can interfere with ^{239}Pu and ^{240}Pu, respectively, in samples with high concentrations of uranium (Epov et al. 2005; Figg et al. 2000).

General environmental survey instruments (e.g., alpha particle meters) are available, but they are not specific for plutonium. The predominant analytical method for measuring plutonium present at or near background concentrations in both biological and environmental media requires radiochemical separation

and purification in conjunction with a quantitative measurement technique (e.g., alpha spectrometry, liquid scintillation, or mass spectrometry).

7.1 BIOLOGICAL MATERIALS

Methods for the determination of plutonium in biological materials are summarized in Table 7-1. The procedures that have been developed for the determination of small quantities of plutonium in biological samples, as well as in environmental samples, include the following steps:

- Release of plutonium from the sample's matrix into solution and the addition of plutonium tracers;
- Concentration by precipitation with a nonisotopic carrier (e.g., lanthanum or neodymium) or by solvent extraction;
- Purification by precipitation, liquid extraction, or ion exchange chromatography; and
- Determination of the plutonium content of the sample by alpha spectroscopy or other techniques.

Two common methods for releasing plutonium from the sample's matrix into solution are acid extraction and acid dissolution. Samples are wet- or dry-ashed prior to solubilization. Leaching the sample with a mixture of acids (e.g., nitric acid and hydrochloric acid) has the advantage of easily handling large sample volumes, but with the potential disadvantage of leaving plutonium compounds in the residue. The acid dissolution procedure includes the addition of excess hydrofluoric acid (HF) to the above mixture of acids and results in dissolution of much, if not all, of the sample matrix. Refractory plutonium compounds (e.g., PuO_2) are more likely to be dissolved upon addition of HF. However, dissolution of interfering elements, such as iron, phosphorous, and other rare earths (e.g., alpha-particle emitters) is also increased in acid dissolution.

A third example of a dissolution method is fusion, which is used primarily for decomposition of geological and solid environmental media and is suitable for large samples (several grams) (Wolf 2006). Fusion decomposition is performed by heating a sample with a flux reagent at atmospheric pressure in a graphite, zirconium, or platinum crucible. Common fluxes include hydroxides, peroxides, carbonates, bisulfates, hydrosulfates, pyrosulfates, tetraborates, and metaborates. Fusion with sodium hydroxide and sodium peroxide ($NaOH\text{-}Na_2O_2$) is an effective method for decomposition of silica-containing matrices. A disadvantage of fusion decomposition is that use of a large amount of flux material results in a solution

Table 7-1. Analytical Methods for Determining Plutonium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Tissue	Wet ashed with HNO_3/H_2O_2, separation by anion exchange,	ICP-MS	1 fg/mL	No data	Yamamoto et al. 2008a
Urine	Samples were spiked with a known amount of plutonium and digested with nitric acid/hydrogen peroxide Non-digested (raw) samples were also analyzed	ICP-MS	0.18 pg/L (digested samples after preconcentration) 1.9 pg/L (raw samples)	70–100% (raw samples)	Epov et al. 2005
Tissue	Wet ashed with HNO_3/H_2SO_4; collected on $Fe(OH)_2$; separation by ion exchange and electrodeposition or microprecipitation	α spectrometry	0.0007 Bq (400 minutes)	No data	DOE 1997 Pu-04-RC
Tissue	Wet ashed with HNO_3/HF; separation by solvent extraction; electrodeposition onto platinum disc	solid state α spectrometry	0.65 Bq (400 minutes)	No data	DOE 1997 Pu-05-RC
Urine	Wet ashing with H_2O_2/HNO_3/HCl/HF/H_2SO_4; separation by anion exchange chromatography; electrodeposition onto platinum disc	solid state α spectrometry	0.60 Bq (400 minutes)	No data	DOE 1997 Pu-06-RC
Urine	Wet ashed with HNO_3/H_2O_2/HCl; purified by ion exchange chromatography	α spectrometry	No data	No data	DOE 1997 Pu-07-RC; Pu-11-RC
Tissue	Ashed at 400 ºC; dissolved in HNO_3/HCl; filtered; decomposed with HF; purified by ion exchange chromatography	α spectrometry	No data	No data	DOE 1997 Pu-08-RC; Pu-11-RC
Tissue	Digested with HNO_3/H_2SO_4; coprecipitation of plutonium with $Fe(OH)_3$; purified by ion exchange chromatography	α spectrometry	No data	No data	DOE 1997 Pu-09-RC; Pu-11-RC
Tissue	Ashing; electrodeposition	α spectrometry	No data	No data	USTUR Method 600
Biological soft tissues	Wet ash; filter; extract; electrodeposition on platinum disk	α spectrometry	No data	No data	Singh and Wrenn 1988
Urine	Evaporate; wet ash; filter; extract; electrodeposit on platinum disk	α spectrometry	No data	No data	Singh and Wrenn 1988

Table 7-1. Analytical Methods for Determining Plutonium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fecal matter	Wet ash; filter; extract; electrodeposition on platinum disk	α spectrometry	No data	No data	Singh and Wrenn 1988
Bones	Dry ash; reduce valence state; extract; electrodeposition on platinum disk	α spectrometry	No data	No data	Singh and Wrenn 1988
Milk	Dry ashed; dissolution in HCl; extraction with triisooctylamine; coprecipitate with lanthanum fluoride; filtration	α spectrometry	No data	No data	EPA 1984 (Method 00-09)
Plant	Dissolve starch; filter; wet ash; extract; electrodeposition on platinum disk	α spectrometry	0.0027 pCi ($0.1x10^{-4}$ Bq)	No data	Bunzl and Kracke 1987

ICP-MS = inductively coupled plasma-mass spectrometry

with a high content of total dissolved solids, requiring chemical separation of the analyte from the dissolved flux material (Wolf 2006).

Plutonium solutions that contain: (1) other alpha-particle emitters (e.g., americium and neptunium); or (2) large amounts of fission products (e.g., cesium), or interfering amounts of other substances such as iron, calcium, uranium, and phosphorous need to undergo additional chemical separation procedures. Non-radioactive carriers, such as lanthanum fluoride (LaF_3), neodymium fluoride (NdF_3), and zirconium phenylphosphate ($ZrC_6H_6PO_4$), are used to selectively precipitate the lanthanides. Solvent extraction and ion exchange separation methods are preferred methods because of better separations. In addition, they do not involve the addition of nonvolatile substances resulting in an easier preparation of the co-precipitation source used for alpha-particle counting.

These extraction techniques can be made very efficient and selective by adjusting the oxidation state of the plutonium and other sample constituents. Common extraction methods specific for plutonium use 2-thenoyltrifluoroacetone (TTA), tetrapropylammonium trinitrate in isopropylacetone or triisooctylamine, cupferron in chloroform, tributylphosphate, and tri-octylphosphine dioxide. Anion exchange methods with either nitric or hydrochloric acid solutions are commonly used. Cation exchange column methods are less frequently used (Brouns 1980).

Prior to measurement, the separated and purified plutonium is typically deposited as a very thin layer on a highly polished metal plancet. Two techniques that are commonly used are: (1) electrodeposition; and (2) co-precipitation with a carrier. In electrodeposition, the plutonium is electrodeposited on a polished stainless steel, or platinum disk. In the co-precipitation technique, actinides can be co-precipitated from a large volume of solution using anions such as fluorides, hydroxides, and phosphate. Actinides in the tri- or tetravalent state can be removed from solution by the addition of lanthanide fluoride carriers, such as NdF_3 or LaF_3, which are used to co-precipitate the separated and purified plutonium from solution. Iron hydroxide can also be used to co-precipitate actinides from a carbonate-free solution. The precipitate is then prepared for counting by either filtration or by evaporation of a slurry of the precipitate onto a stainless steel disk (Hindman 1983; Mitchell 1960; Sill and Williams 1981; Talvitie 1972; Wolf 2006).

The U.S. Department of Energy Environmental Measurement Laboratory Procedures Manual and the U.S. Transuranium and Uranium Registries Radio Analysis Procedures Manual provide techniques for the determination of plutonium in biological samples using alpha spectroscopy (DOE 1997; USTUR 2001).

The other two alpha-particle emitting plutonium isotopes, ^{236}Pu and ^{242}Pu, are normally not found in environmentally significant quantities, and are not common constituents of nuclear fuels or waste waters. Therefore, they can be used as tracers to aid in the analysis of other isotopes. In this calibration procedure, a known quantity of a tracer is added to the sample being analyzed in order to determine the yield. This is the percentage of the total amount of plutonium in the sample that is actually measured in the electrodeposited amount after the separation, purification, and preparation of the source (Brouns 1980).

The most critical step in the analysis of biological samples is complete dissolution of the sample to assure solubilization of all plutonium compounds. Biological samples are generally dissolved by wet ashing or a combination of wet and dry ashing. High temperatures (700–1,000 °C) during ashing should be avoided in order to prevent the formation of an insoluble form of plutonium dioxide (Nielson and Beasley 1980; Sill 1975). Plutonium that has been distributed to urine, blood, or soft tissue as a result of metabolic processes is usually in a readily soluble form. Lung tissue, feces, and excised tissue from wound sites will likely contain insoluble forms of plutonium and will require treatment with HF and repeated ashings to effect solubilization. Tissues, feces, and vegetation require repeated treatment with a mixture of concentrated nitric acid (HNO_3), perchloric acid ($HClO_4$), and sulfuric acid (H_2SO_4) in order to oxidize the large amount of organic materials in these samples. If an insoluble residue remains after repeated ashings, then fusion of the residue with gram quantities of an inorganic flux (e.g., sodium carbonate, sodium pyrosulfate) can be used to effect solution. Known amounts of a plutonium isotope are commonly added subsequent to the dissolution step so that the percentage of plutonium recovered after separation and purification (i.e., the yield) may be determined. This added plutonium must be in the same chemical form as the plutonium in the sample or the yield estimates will not reflect the percentage of plutonium recovered from the dissolved sample (EPA 1976a; Nielson and Beasley 1980).

Methods used for concentrating plutonium in a sample by a carrier are often specific to one oxidation state of the plutonium. For example, the classical bismuth phosphate-lanthanum fluoride method of concentrating plutonium from urine samples is specific to plutonium in the tri- and tetravalent states and will leave plutonium(VI) in solution. The fate of the various oxidation states of plutonium in humans is not well understood and analysis procedures must insure reduction or oxidation of plutonium into appropriate oxidation states. Liver and kidney samples may contain metals (e.g., iron) that may greatly reduce chemical yields during the final electrodeposition step (EPA 1976a).

Sensitive methods for analysis of plutonium in urine are particularly important for estimating occupational plutonium body burdens. Routinely available instrumentation, such as the alpha spectrometer, can readily detect these low concentrations. More sensitive methods are commonly required for urine samples in order to assess chronic exposures to plutonium. These low detection limits were first achieved in the past by nuclear emulsion track counting. In this method, the electrodeposited sample is exposed to nuclear track film, subsequent to the isolation of plutonium. The alpha-particle emitting isotopes of plutonium will leave tracks on the film, which are counted to quantify the amount of plutonium. Nuclear emulsion track counting has been used in the past to measure plutonium concentrations in the urine of workers at a nuclear reactor plant (Nielson and Beasley 1980). A type of scintillation counting has been used to measure ^{239}Pu and americium-241 (^{241}Am) in animal tissues (NCRP 1985).

Epov et al. (2005) reported a method where nondigested urine samples could be analyzed with a detection limit of 1.9 pg/L. The authors noted that in the case of an emergency, urine analysis without digestion could provide a rapid determination (about 1 hour) of plutonium levels in urine. However, sample digestion would be needed if more precise and sensitive analysis is required. Four hours are required to analyze urine samples with digestion (Epov et al. 2005).

7.2 ENVIRONMENTAL SAMPLES

Methods for the determination of plutonium in environmental samples are summarized in Table 7-2. The separation and extraction methods used to prepare biological samples for plutonium analysis are commonly used for environmental samples. Large volumes of air samples (e.g., 10,000 m^3) should be collected in order to obtain detectable amounts of plutonium in particulate in air (EPA 1976a).

Field survey instruments for measuring photons of ^{241}Am in surface soils and on airborne particulates are available (e.g., Field Instrument for Detecting Low Energy Radiation or FIDLER) with a minimum detection limit of approximately twice the magnitude of a background level of ^{239}Pu ($1x10^3$–$2x10^3$ pCi/m^2; 37–74 Bq/m^2). The FIDLER uses a sodium iodide or calcium fluoride crystal and photon-height discrimination in order to detect the 17 keV x-rays emitted from the progeny of plutonium, or the 60 keV gamma photons of ^{241}Am. These instruments are useful for identifying areas of contamination, but cannot be used to accurately predict the concentration of plutonium in surface soils (EPA 1976a). This instrument has been used in aerial surveys of large area sources, such as the Nevada Test Site.

Table 7-2. Analytical Methods for Determining Plutonium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Recovery	Reference
Air filter, soil, water, vegetation	Fusion with KF and pyrosulfate; dissolution in HCl; coprecipitation on $BaSO_4$; dissolution of $BaSO_4$ and reprecipitation with DPTA	α spectrometry	No data	85–95%	DOE 1999c CHEM-TP-A.20
Water	Separation of radionuclides by Eichrom resins	α spectrometry	0.6 mBq (400 minutes)	93%	DOE 1997 Se-03
Soil	Plutonium isotopes are leached from soil using HNO_3/HCl	α spectrometry	1 mBq (400 minutes)	No data	DOE 1997 Pu-02-RC
Air filter	Digestion with HNO_3 followed by treatment with HF; decompose filters composed of organic polymer overnithe at 450 ºC prior to digestion	α spectrometry	No data	No data	DOE 1997 Pu-01-RC; Pu-11-RC; G-03
Soil, sediment	Plutonium isotopes are leached with HNO_3/HCl; purification by ion exchange chromatography; microprecipitation	α spectrometry	1 mBq (400 minutes)	No data	DOE 1997 Pu-12-RC
Water	Heated in HNO_3/HCl; evaporation and dissolution in HNO_3; purified by ion exchange; microprecipitation	α spectrometry	No data	No data	DOE 1997 Pu-07-RC; Pu-11-RC; G-03
Vegetation	Ashed at 400 ºC; dissolved in HNO_3/HCl; filtered; decomposed with HF; purified by ion exchange chromatography	α spectrometry	No data	No data	DOE 1997 Pu-08-RC; Pu-11-RC
Vegetation	Digested with HNO_3/H_2SO_4; coprecipitation of plutonium with $Fe(OH)_3$; purified by ion exchange chromatography	α spectrometry	No data	No data	DOE 1997 Pu-09-RC; Pu-11-RC

Table 7-2. Analytical Methods for Determining Plutonium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Recovery	Reference
Food	HNO_3, closed-vessel microwave digestion	ICP-MS	0.020 pg/g	100±20%	Evans et al. 2003
Air	Dry ash; filter; extract; reduce valence; coprecipitate with lanthanum fluoride	α spectrometry	No data	No data	EPA 1984 (EPA Method 00-04)
Soil, coal, fly ash, ores, vegetation, biotia, and water	Ashed or evaporated; dissolved with HF, $HClO_4$, and HCl; extraction with triisooctylamine/p-xylene; stripped with HNO_3; wet ashed; co-precipitated with lanthanum fluoride; filtration	α spectrometry	No data	No data	EPA 1984 (EPA Method Pu-01)
Water, soil, air, vegetation, and animal tissue	Ashing; ion exchange separation; electrodeposition	α spectrometry	0.02 pCi/sample	No data	EPA 1979
Water	Filter; extract; coprecipitate with lanthanum fluoride	α particle counter (either proportional or scintillation detectors)	No data	No data	EPA 1980 (EPA method 907.0)
Drinking water	Acidify; oxidation with sodium nitrite; precipitation; extraction with tri-isooctylamine; co-precipitated with lanthanum fluoride	α particle counter	No data	93%	EPA 1982 (EPA Method 911)

DPTA = diethylenetriamine-pentaacetic acid; ICP-MS = inductively coupled plasma-mass spectrometry

Since soil-adsorbed plutonium contamination exists as discrete particles of various sizes, analysis of larger soil volumes (25–100 g) is recommended (EPA 1976a). Commonly, soil samples with high amounts of carbonate are difficult to analyze. More rapid, efficient, and economical procedures have been developed to sequentially analyze a number of radioactive actinides (Hindman 1986).

The U.S. Department of Energy Environmental Measurement Laboratory provides techniques for the determination of plutonium in various biological and environmental samples using alpha spectroscopy. EPA methods are available for the determination of plutonium in air, soil, coal fly ash, ores, vegetation, biota, and water. APHA has standard methods for determination of gross alpha and beta radioactivity and gamma-emitting radionuclides in water, Methods 7110 and 7120, respectively; however, no methods that are specific to plutonium isotopes are reported (APHA 1998a, 1998b). No methods were reported by the AOAC for the determination of plutonium (AOAC 1990).

Anderson et al. (2001) reported that the U.S. Food and Drug Administration determines ^{239}Pu concentration using electroplating and alpha-spectroscopy, following sequential nitric acid/hydrofluoric acid and nitric acid/hydrofluoric acid/hydrochloric acid digestions of ashed food samples. A detection limit of 0.004 Bq/kg for ^{239}Pu is reported for this method.

Alpha spectrometry is the most common analytical method for measuring plutonium concentrations in environmental samples. Other measurement techniques available are liquid scintillation, mass spectrometry (MS), and gamma spectrometry. ICP-MS has been used increasingly for the determination of plutonium in environmental samples (Muramatsu et al. 2001a). Low concentrations of plutonium in environmental samples with high salt and organic matter content cause signal suppression and make it difficult to obtain an accurate plutonium determination. Preconcentration and matrix separation are typically required in these analyses (Epov et al. 2005; Figg et al. 2000).

MS is used by some research laboratories to determine the concentration of each plutonium isotope, including the naturally-occurring ^{244}Pu. MS determines the number of atoms of a given mass number and, therefore, can measure the concentration of all of the plutonium isotopes, not only the alpha-particle emitters as in alpha spectrometry. MS is several orders of magnitude more sensitive than alpha spectrometry in determining the quantities of plutonium isotopes with long half-lives, which also tend to be the heavier isotopes.

Quantities of ^{241}Pu, a beta-particle emitter, can be quantified from assumed isotopic abundance ratios; estimated in-growth of its progeny ^{241}Am by gamma spectrometry; or MS (EPA 1976a). ^{241}Am is produced from the beta decay of ^{241}Pu and, therefore, can be used to indirectly measure the concentration of ^{241}Pu (Metz and Waterbury 1962). Direct determination of ^{241}Pu by measurement of its low energy beta-particle decay has been reported using liquid scintillation analysis (Martin 1986).

7.3 ADEQUACY OF THE DATABASE

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

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

7.3.1 Identification of Data Needs

Analytical methods are available and are adequately sensitive to detect plutonium isotopes in biological materials (e.g., blood, urine, and bone) and in environmental samples (e.g., water, soil, air, and food). No data needs are identified at this time.

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. There are methods available for measuring the isotopes of plutonium in biological samples. The measurement of plutonium in the urine is considered a biomarker of exposure to plutonium. Methods are available to detect plutonium in the urine. However, no information was available concerning the reliability of these methods for determining plutonium levels in the urine. Plutonium can be determined sensitively and selectively by alpha spectrometry and ICP-MS in urine and tissues (DOE 1997; Epov et

al. 2005). Analytical methods with satisfactory sensitivity and precision are available to determine levels of plutonium in human tissues and body fluids.

Effect. Existing methods are sensitive enough to measure background levels for plutonium in the population and levels at which biological effects occur.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Environmental media are analyzed to identify contaminated areas and to determine if contaminant levels constitute a concern for human health. The detection of plutonium in air, water, and soil is of concern due to the potential for human exposure. There are many steps involved in the analysis of plutonium in environmental media. Alpha spectrometry a satisfactory method available for the determination of plutonium in water, air, and solid waste samples (DOE 1997, 1999c).

7.3.2 Ongoing Studies

No ongoing studies pertaining to analytical methods for plutonium were identified in a search of the Federal Research in Progress database (FEDRIP 2007).

8. REGULATIONS, ADVISORIES, AND GUIDELINES

International and national regulations and guidelines pertinent to human exposure to plutonium and to other radioactive substances are summarized in Table 8-1. Recommendations for radiation protection for people in the general population as a result of exposure to radiation in the environment are found in the International Commission on Radiological Protection (ICRP) Publication 60 (ICRP 1991). National guidelines for occupational radiation protection are found in the "Federal Radiation Protection Guidance for Occupational Exposure" (EPA 1987). The guidance presents general principles for the radiation protection of workers and specifies the numerical primary guides for limiting occupational exposure. These recommendations are consistent with the ICRP (ICRP 1991).

The basic philosophy of radiation protection is the concept of ALARA (As Low As Reasonably Achievable). ALARA requires that social and economic factors to be taken into consideration, and that further reductions in dose are not indicated where the costs of reducing exposure become disproportionate to the benefit achieved. As a rule, all exposure should be kept as low as reasonably achievable and the regulations and guidelines are meant to give an upper limit to exposure. Based on the primary guidelines (EPA 1987), guides for Annual Limits on Intake (ALIs) and Derived Air Concentrations (DACs) have been calculated (USNRC 2007a). The ALI is defined as "the annual intake of a given radionuclide by Reference Man which would result in a committed effective dose equivalent of 5 rems (stochastic) or 50 rems to an organ or tissue (non-stochastic)" (USNRC 2007a). The DAC is defined as "the concentration of a given radionuclide in air which, if breathed by the reference man for a working year of 2,000 hours under conditions of light work (inhalation rate of 1.2 m^3 of air/hour), results in the intake of one ALI" (USNRC 2009a). The ALIs and DACs refer to occupational situations, but may be converted to apply to exposure of persons in the general population by application of conversion factors (Table 8-1).

No inhalation or oral MRLs were derived for plutonium or plutonium compounds.

The EPA IRIS database has withdrawn its cancer classification for radionuclides, but the EPA Office of Air and Radiation believes that all radionuclides, including the plutonium isotopes, should be considered to be known carcinogens, and has assigned them to Group A. Carcinogenic toxicity values for plutonium isotopes are listed in EPA's Radionuclide Table: Radionuclide Carcinogenicity – Slope Factors (Federal Guidance Report No. 13 Morbidity Risk Coefficients, in Units of Picocuries) (EPA 2001). Lifetime excess total cancer risk per unit intake is included for water ingestion, food ingestion, soil ingestion,

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Plutonium and Plutonium Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2006
	^{239}Pu and its decay products (may contain ^{240}Pu and other isotopes), as aerosols	Group 1[a]	
ICRP	Occupational—whole body exposure	5 rem/year	ICRP 1977
	Individual—short-term, to critical populations	0.5 rem/year	
	Individual—chronic exposure	0.1 rem/year	
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	No data	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	Dose limits for exposure to ionizing radiation		ACGIH 2006
	Effective dose		
	In any single year	50 mSv	
	Averaged over 5 years	20 mSv per year	
	Annual equivalent dose to		
	Lens of the eye	150 mSv	
	Skin	500 mSv	
	Hands and feet	500 mSv	
	Embryo-fetus exposures once the pregnancy is known		
	Monthly equivalent dose	0.5 mSv	
	Dose to the surface of women's abdomen (lower trunk)	2 mSv for the remainder of the pregnancy	
	Intake of radionuclide	1/20 of ALI	
EPA	AEGL-1, -2, and -3	No data	EPA 2007b
	Occupational—the committed effective dose equivalent (internal) and annual effective dose equivalent (external) combined	5 rem/year	EPA 1987

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Plutonium and Plutonium Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
FRC	Individual—whole body exposure	5 rem/year	FRC 1960
	Individual—operational guide for "suitable sample of population" when individual whole body doses are not known	0.17 rem/year	
EPA	National emission standards for emissions of radionuclides other than radon from Department of Energy facilities	10 mrem/year	EPA 2002 40 CFR Part 61
NIOSH	REL (10-hour TWA)	No data	
OSHA	Exposure limits of individuals to ionizing radiation in restricted areas (rems per calendar quarter)		OSHA 2006 29 CFR 1910.1096
	Whole body: head and trunk; active blood-forming organs; lens of eyes; or gonads	1.25 rems	
	Hands and forearms; feet and ankles	18.75 rems	
	Skin of whole body	7.5 rems	
USNRC	Occupational values for oral ingestion ALI (µCi) of Class W		USNRC 2007a 10 CFR 20, Appendix B
	^{236}Pu	$2x10^{+0}$	
	^{237}Pu	$1x10^{+4}$	
	^{238}Pu	$9x10^{-1}$ (bone surface)	
	^{239}Pu	$8x10^{-1}$ (bone surface)	
	^{240}Pu	$8x10^{-1}$ (bone surface)	
	^{241}Pu	$4x10^{+1}$ (bone surface)	
	^{242}Pu	$8x10^{-1}$ (bone surface)	
	^{243}Pu	$2x10^{+4}$	
	^{244}Pu	$8x10^{-1}$ (bone surface)	
	Occupational values for inhalation ALI (µCi) of Class W[b]		
	^{236}Pu	$2x10^{-2}$	
	^{237}Pu	$3x10^{+3}$	
	^{238}Pu	$7x10^{-3}$ (bone surface)	
	^{239}Pu	$6x10^{-3}$ (bone surface)	
	^{240}Pu	$6x10^{-3}$ (bone surface)	
	^{241}Pu	$3x10^{-1}$ (bone surface)	
	^{242}Pu	$7x10^{-3}$ (bone surface)	
	^{243}Pu	$4x10^{+4}$	
	^{244}Pu	$7x10^{-3}$ (bone surface)	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Plutonium and Plutonium Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	Occupational values for inhalation ALI (µCi) of Class Y[b]		
	^{236}Pu	$4x10^{-2}$	
	^{237}Pu	$3x10^{+3}$	
	^{238}Pu	$2x10^{-2}$	
	^{239}Pu	$2x10^{-2}$ (bone surface)	
	^{240}Pu	$2x10^{-2}$ (bone surface)	
	^{241}Pu	$8x10^{-1}$ (bone surface)	
	^{242}Pu	$2x10^{-2}$ (bone surface)	
	^{243}Pu	$4x10^{+4}$	
	^{244}Pu	$2x10^{-2}$ (bone surface)	
USNRC	Occupational values for inhalation DAC (µCi/mL) of Class W[b]		USNRC 2007a 10 CFR 20, Appendix B
	^{236}Pu	$8x10^{-12}$	
	^{237}Pu	$1x10^{-6}$	
	^{238}Pu	$3x10^{-12}$	
	^{239}Pu	$3x10^{-12}$	
	^{240}Pu	$3x10^{-12}$	
	^{241}Pu	$1x10^{-10}$	
	^{242}Pu	$3x10^{-12}$	
	^{243}Pu	$2x10^{-5}$	
	^{244}Pu	$3x10^{-12}$	
	Occupational values for inhalation DAC (µCi/mL) of Class Y[b]		
	^{236}Pu	$2x10^{-11}$	
	^{237}Pu	$1x10^{-6}$	
	^{238}Pu	$8x10^{-12}$	
	^{239}Pu	$7x10^{-12}$	
	^{240}Pu	$7x10^{-12}$	
	^{241}Pu	$3x10^{-10}$	
	^{242}Pu	$7x10^{-12}$	
	^{243}Pu	$2x10^{-5}$	
	^{244}Pu	$7x10^{-12}$	
b. Water			
	Drinking water standards and health advisories for gross alpha particle activity		EPA 2006
	10^{-4} Cancer risk	15 pCi/L	
	National primary drinking water standards for alpha particles		EPA 2003
	MCLG	Zero	
	MCL	15 pCi/L	
	Public health goal	Zero	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Plutonium and Plutonium Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
c. Food		No data	
FDA	Guidance level for radionuclide in domestic and imported food		FDA 2004
	Derived intervention level	2 Bq/kg	
d. Other			
ACGIH	Carcinogenicity classification	No data	ACGIH 2006
EPA	Carcinogenicity classification	Group A[c]	EPA 2001
EPA	Superfund, emergency planning, and community right-to-know		EPA 2007c 40 CFR 302.4
	Designated CERCLA hazardous substance		
	Reportable quantity (Ci)		
	^{236}Pu	0.1	
	^{237}Pu	1,000	
	^{238}Pu	0.01	
	^{239}Pu	0.01	
	^{240}Pu	0.01	
	^{241}Pu	1	
	^{242}Pu	0.01	
	^{243}Pu	1,000	
	^{244}Pu	0.01	
NTP	Carcinogenicity classification	Known to be human carcinogens	NTP 2005

[a]Group 1: carcinogenic to humans
[b]The ALIs and DACs for inhalation are given for an aerosol with an activity median aerodynamic diameter (AMAD) of 1 μm and for three classes (D,W,Y) of radioactive material, which refer to their retention (approximately days, weeks, or years) in the pulmonary region of the lung. This classification applies to a range of clearance half-times of less than 10 days for D, for W from 10 to 100 days, and for Y greater than 100 days (USNRC 2007a).
[c]Group A: known human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Levels; ALI = Annual Limit on Intake; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DAC = Derived Air Concentration; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FRC = Federal Radiation Council; IARC = International Agency for Research on Cancer; ICRP = International Commission on Radiological Protection; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; USNRC = U.S. Nuclear Regulatory Commission; WHO = World Health Organization

inhalation, and external exposure. The risk values for selected plutonium isotopes are presented in Table 8-2. The EPA has not derived reference concentrations (RfCs) or reference doses (RfDs) for plutonium (IRIS 2009), but has derived a maximum contaminant level (MCL) of 15 pCi/L for total alpha-emitters (including plutonium), less uranium and radon (EPA 2003).

Table 8-2. Radionuclide Carcinogenicity—Slope Factors for Plutonium (Federal Guidance Report No. 13 Morbidity Risk Coefficients, in Units of Picocuries)[a]

	Slope factor (morbidity risk coefficient) lifetime excess total cancer risk per unit intake or exposure					
Isotope[b]	Gastro-intestinal absorption Fraction[c]	Water ingestion (risk/pCi)	Food ingestion (risk/pCi)	Soil ingestion (risk/pCi)	Inhalation (risk/pCi)	External exposure (risk/year per pCi/g)
Pu-234	5.00×10^{-4}	8.58×10^{-13}	1.25×10^{-12}	2.39×10^{-12}	6.85×10^{-11}	1.61×10^{-7}
Pu-235	5.00×10^{-4}	4.37×10^{-15}	6.03×10^{-15}	9.73×10^{-15}	2.39×10^{-15}	2.37×10^{-7}
Pu-236	5.00×10^{-4}	7.47×10^{-11}	9.92×10^{-11}	1.74×10^{-10}	2.28×10^{-8}	1.19×10^{-10}
Pu-237	5.00×10^{-4}	5.77×10^{-13}	8.40×10^{-13}	1.62×10^{-12}	1.27×10^{-12}	1.12×10^{-7}
Pu-238	5.00×10^{-4}	1.31×10^{-10}	1.69×10^{-10}	2.72×10^{-10}	3.36×10^{-8}	7.22×10^{-11}
Pu-239	5.00×10^{-4}	1.35×10^{-10}	1.74×10^{-10}	2.76×10^{-10}	3.33×10^{-8}	2.00×10^{-10}
Pu-240	5.00×10^{-4}	1.35×10^{-10}	1.74×10^{-10}	2.77×10^{-10}	3.33×10^{-8}	6.98×10^{-11}
Pu-241	5.00×10^{-4}	1.76×10^{-12}	2.28×10^{-12}	3.29×10^{-12}	3.34×10^{-10}	4.11×10^{-12}
Pu-242	5.00×10^{-4}	1.28×10^{-10}	1.65×10^{-10}	2.63×10^{-10}	3.13×10^{-8}	6.25×10^{-11}
Pu-243	5.00×10^{-4}	4.74×10^{-13}	6.92×10^{-13}	1.34×10^{-12}	2.94×10^{-13}	5.50×10^{-8}
Pu-244	5.00×10^{-4}	1.37×10^{-10}	1.80×10^{-10}	2.94×10^{-10}	2.93×10^{-8}	3.01×10^{-11}
Pu-245	5.00×10^{-4}	4.48×10^{-12}	6.55×10^{-12}	1.28×10^{-11}	2.07×10^{-12}	1.77×10^{-6}
Pu-246	5.00×10^{-4}	1.73×10^{-11}	2.53×10^{-11}	4.92×10^{-11}	1.73×10^{-11}	4.04×10^{-7}

[a]EPA classifies all radionuclides as Group A (known human) carcinogens. Radionuclide risk coefficients, or slope factors, are calculated by EPA's ORIA to assist HEAST users with risk-related evaluations and decision-making at various stages of the remediation process. Most values presented are taken from EPA (1999, 2000); risk estimates for the soil ingestion pathway are not addressed, but have been computed using similar methods. Ingestion and inhalation slope factors are central estimates in a linear model of the age-averaged, lifetime attributable radiation cancer incidence (fatal and nonfatal cancer) risk per unit of activity inhaled or ingested, expressed as risk/pCi. Slope factors can be converted into the SI units of becquerels (1 Bq=1 nuclear transformation per second) by dividing each inhalation, ingestion, or external exposure value by 0.037. Ci, the customary unit of activity is equal to 3.7x1,010 nuclear transformations per second (1 pCi=10–12 Ci). Inhalation values for particulates represent the indicated ICRP lung absorption type (medium, particulate). External exposure slope factors are central estimates of the lifetime attributable radiation cancer incidence risk for each year of exposure to external radiation from photon-emitting radionuclides uniformly distributed in a thick layer of soil (expressed as risk/year per pCi/g of soil).

[b]For each radionuclide listed, slope factors correspond to the risks per unit intake or exposure for that radionuclide only.

[c]Gastrointestinal absorption fractions are the fractional amounts of each radionuclide absorbed across the gastrointestinal tract into the bloodstream.

Bq = Becquerel; Ci = curie; EPA = Environmental Protection Agency; HEAST = Health Effects Assessment Summary Table; ICRP = International Commission on Radiological Protection; ORIA = Office of Radiation and Indoor Air; pCi = picocurie; SI = International System

Source: EPA 2001

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10. GLOSSARY

Absorbed dose—The amount of energy deposited by ionizing radiation in a unit mass of tissue. It is expressed in units of joule per kilogram (J/kg), and called "Gray" (Gy).

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

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.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical 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.

Dose Equivalent—A quantity used in radiation protection to place all radiation on a common scale for calculating tissue damage. Dose equivalent is the absorbed dose in grays multiplied by a radiation weighting factor. The radiation weighting factor accounts for differences in radiation effects caused by different types of ionizing radiation. Some radiation, including alpha particles, causes a greater amount of damage per unit of absorbed dose than other radiation. The sievert (Sv) is the unit used to measure dose equivalent.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Effective Dose—A dosimetric quantity useful for comparing the overall health effects of irradiation of the whole body. It takes into account the absorbed doses received by various organs and tissues and weighs them according to present knowledge of the sensitivity of each organ to radiation. It also accounts for the type of radiation and the potential for each type to inflict biologic damage. The effective dose is used, for example, to compare the overall health detriments of different radionuclides in a given mix. The unit of effective dose is the sievert (Sv); 1 Sv = 1 J/kg.

Embryotoxicity and Fetotoxicity—Any toxic effect on the concepts as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Equivalent Dose—The absorbed dose in an organ or tissue multiplied by the relevant radiation weighting factor w_R.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a

professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

MRLs were not derived for plutonium, as discussed in Section 2.3.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

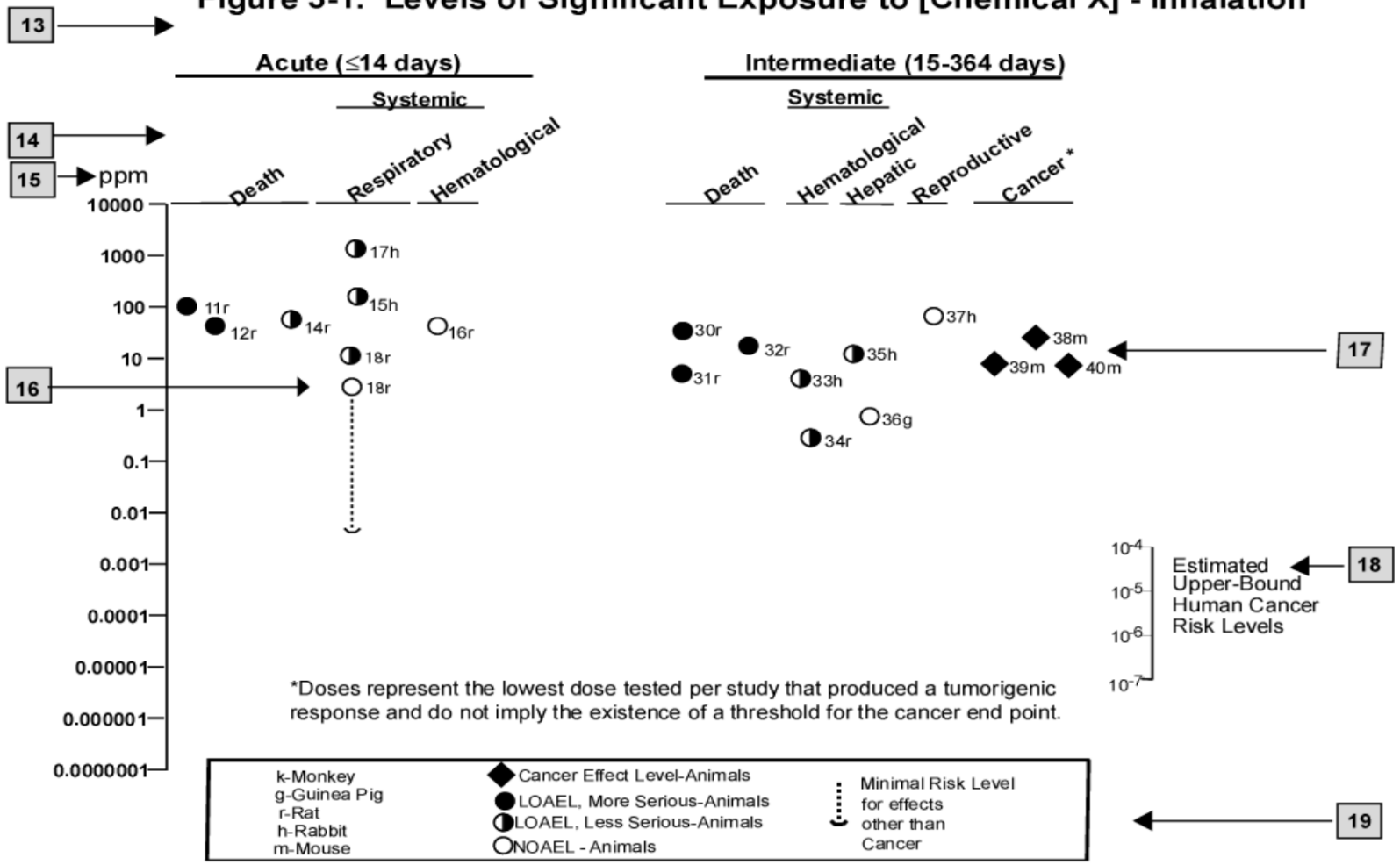
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALI	annual limits on intake
ALT	alanine aminotransferase
AMAD	activity median aerodynamic diameter
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
Bq	Becquerel
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CMAD	count median aerodynamic diameter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DAC	derived air concentration
DHEW	Department of Health, Education, and Welfare

DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
GSD	geometric standard deviation
Gy	gray
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
ITRI	Inhalation Toxicology Research Institute
kBq	kiloBequerel
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill

LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
MMD	mass median diameter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
NCRP	National Council on Radiation Protection
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards

NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBBK	physiologically based biokinetic
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
PNL	Pacific Northwest Laboratory
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval

Sv	sievert
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	United States Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. OVERVIEW OF BASIC RADIATION PHYSICS, CHEMISTRY, AND BIOLOGY

Understanding the basic concepts in radiation physics, chemistry, and biology is important to the evaluation and interpretation of radiation-induced adverse health effects and to the derivation of radiation protection principles. This appendix presents a brief overview of the areas of radiation physics, chemistry, and biology and is based to a large extent on the reviews of Mettler and Moseley (1985), Hobbs and McClellan (1986), Eichholz (1982), Hendee (1973), Cember (1996), and Early et al. (1979).

D.1 RADIONUCLIDES AND RADIOACTIVITY

The substances we call elements are composed of atoms. Atoms in turn are made up of neutrons, protons and electrons: neutrons and protons in the nucleus and electrons in a cloud of orbits around the nucleus. Nuclide is the general term referring to any nucleus along with its orbital electrons. The nuclide is characterized by the composition of its nucleus and hence by the number of protons and neutrons in the nucleus. All atoms of an element have the same number of protons (this is given by the atomic number) but may have different numbers of neutrons (this is reflected by the atomic mass numbers or atomic weight of the element). Atoms with different atomic mass but the same atomic numbers are referred to as isotopes of an element.

The numerical combination of protons and neutrons in most nuclides is such that the nucleus is quantum mechanically stable and the atom is said to be stable, i.e., not radioactive; however, if there are too few or too many neutrons, the nucleus is unstable and the atom is said to be radioactive. Unstable nuclides undergo radioactive transformation, a process in which a neutron or proton converts into the other and a beta particle is emitted, or else an alpha particle is emitted. Each type of decay is typically accompanied by the emission of gamma rays. These unstable atoms are called radionuclides; their emissions are called ionizing radiation; and the whole property is called radioactivity. Transformation or decay results in the formation of new nuclides some of which may themselves be radionuclides, while others are stable nuclides. This series of transformations is called the decay chain of the radionuclide. The first radionuclide in the chain is called the parent; the subsequent products of the transformation are called progeny, daughters, or decay products.

In general there are two classifications of radioactivity and radionuclides: natural and artificial (man-made). Naturally-occurring radioactive material (NORM) exists in nature and no additional energy is necessary to place them in an unstable state. Natural radioactivity is the property of some naturally occurring, usually heavy elements, that are heavier than lead. Radionuclides, such as radium and uranium, primarily emit alpha particles. Some lighter elements such as carbon-14 and tritium (hydrogen-3) primarily emit beta particles as they transform to a more stable atom. Natural radioactive atoms heavier than lead cannot attain a stable nucleus heavier than lead. Everyone is exposed to background radiation from naturally-occurring radionuclides throughout life. This background radiation is the major source of radiation exposure to man and arises from several sources. The natural background exposures are frequently used as a standard of comparison for exposures to various artificial sources of ionizing radiation.

Artificial radioactive atoms are produced either as a by-product of fission of uranium or plutonium atoms in a nuclear reactor or by bombarding stable atoms with particles, such as neutrons or protons, directed at the stable atoms with high velocity. These artificially produced radioactive elements usually decay by emission of particles, such as positive or negative beta particles and one or more high energy photons (gamma rays). Unstable (radioactive) atoms of any element can be produced.

Both naturally occurring and artificial radioisotopes find application in medicine, industrial products, and consumer products. Some specific radioisotopes, called fall-out, are still found in the environment as a result of nuclear weapons use or testing.

D.2 RADIOACTIVE DECAY

D.2.1 Principles of Radioactive Decay

The stability of an atom is the result of the balance of the forces of the various components of the nucleus. An atom that is unstable (radionuclide) will release energy (decay) in various ways and transform to stable atoms or to other radioactive species called daughters, often with the release of ionizing radiation. If there are either too many or too few neutrons for a given number of protons, the resulting nucleus may undergo transformation. For some elements, a chain of daughter decay products may be produced until stable atoms are formed. Radionuclides can be characterized by the type and energy of the radiation emitted, the rate of decay, and the mode of decay. The mode of decay indicates how a parent compound undergoes transformation. Radiations considered here are primarily of nuclear origin, i.e., they arise from nuclear excitation, usually caused by the capture of charged or uncharged nucleons by a nucleus, or by the radioactive decay or transformation of an unstable nuclide. The type of radiation may be categorized as charged or uncharged particles, protons, and fission products) or electromagnetic radiation (gamma rays and x rays). Table D-1 summarizes the basic characteristics of the more common types of radiation encountered.

D.2.2 Half-Life and Activity

For any given radionuclide, the rate of decay is a first-order process that is constant, regardless of the radioactive atoms present and is characteristic for each radionuclide. The process of decay is a series of random events; temperature, pressure, or chemical combinations do not effect the rate of decay. While it may not be possible to predict exactly which atom is going to undergo transformation at any given time, it is possible to predict, on average, the fraction of the radioactive atoms that will transform during any interval of time.

The *activity* is a measure of the quantity of radioactive material. For these radioactive materials it is customary to describe the activity as the number of disintegrations (transformations) per unit time. The unit of activity is the curie (Ci), which was originally related to the activity of one gram of radium, but is now defined as that quantity of radioactive material in which there are:

> 1 curie (Ci) = 3.7×10^{10} disintegrations (transformations)/second (dps) or 2.22×10^{12} disintegrations (transformations)/minute (dpm).

The SI unit of activity is the becquerel (Bq); 1 Bq = that quantity of radioactive material in which there is 1 transformation/second. Since activity is proportional to the number of atoms of the radioactive material, the quantity of any radioactive material is usually expressed in curies, regardless of its purity or concentration. The transformation of radioactive nuclei is a random process, and the number of transformations is directly proportional to the number of radioactive atoms present. For any pure radioactive substance, the rate of decay is usually described by its radiological half-life, T_R, i.e., the time it takes for a specified source material to decay to half its initial activity. The specific activity is an indirect measure of the rate of decay, and is defined as the activity per unit mass or per unit volume. The higher the specific activity of a radioisotope, the faster it is decaying.

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

$$A = A_o e^{-0.693t/Trad}$$

where A is the activity in dps or curies or becquerels, A_o is the activity at time zero, t is the time at which measured, and T_{rad} is the radiological half-life of the radionuclide (T_{rad} and t must be in the same units of time). The time when the activity of a sample of radioactivity becomes one-half its original value is the radioactive half-life and is expressed in any suitable unit of time.

Table D-1. Characteristics of Nuclear Radiations

Radiation	Rest mass[a]	Charge	Typical energy range	Path length[b]		Comments
				Air	Solid	
Alpha (α)	4.00 amu	+2	4–10 MeV	5–10 cm	25–80 μm	Identical to ionized He nucleus
Negatron (β^-)	$5.48x10^{-4}$ amu; 0.51 MeV	–1	0–4 MeV	0–10 m	0–1 cm	Identical to electron
Positron (β^+)	$5.48x10^{-4}$ amu; 0.51 MeV	+1	0-4 MeV	0–10 m	0–1 cm	Identical to electron except for sign of charge
Neutron	1.0086 amu; 939.55 MeV	0	0–15 MeV	b	b	Free half-life: 16 min
X ray (e.m. photon)	–	0	5 keV–100 keV	b	b	Photon from transition of an electron between atomic orbits
Gamma (γ) (e.m. photon)	–	0	10 keV–3 MeV	b	b	Photon from nuclear transformation

[a] The rest mass (in amu) has an energy equivalent in MeV that is obtained using the equation $E=mc^2$, where 1 amu = 932 MeV.
[b] Path lengths are not applicable to x- and gamma rays since their intensities decrease exponentially; path lengths in solid tissue are variable, depending on particle energy, electron density of material, and other factors.

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

The specific activity is a measure of activity, and is defined as the activity per unit mass or per unit volume. This activity is usually expressed in curies per gram and may be calculated by

$$\text{curies/gram} = 1.3x10^8 / (T_{rad})\ (\text{atomic weight}) \quad \text{or}$$

$$[3.577 \times 10^5 \times \text{mass(g)}] / [T_{rad} \times \text{atomic weight}]$$

where T_{rad} is the radiological half-life in days.

In the case of radioactive materials contained in living organisms, an additional consideration is made for the reduction in observed activity due to regular processes of elimination of the respective chemical or biochemical substance from the organism. This introduces a rate constant called the biological half-life (T_{biol}) which is the time required for biological processes to eliminate one-half of the activity. This time is virtually the same for both stable and radioactive isotopes of any given element.

Under such conditions the time required for a radioactive element to be halved as a result of the combined action of radioactive decay and biological elimination is the effective clearance half-time:

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

Table D-2 presents representative effective half-lives of particular interest.

Table D-2. Half-Lives of Some Radionuclides in Adult Body Organs

		Half-life[a]		
Radionuclide	Critical organ	Physical	Biological	Effective
Uranium 238	Kidney	4,460,000,000 y	4 d	4 d
Hydrogen 3[b] (Tritium)	Whole body	12.3 y	10 d	10 d
Iodine 131	Thyroid	8 d	80 d	7.3 d
Strontium 90	Bone	28 y	50 y	18 y
Plutonium 239	Bone surface	24,400 y	50 y	50 y
	Lung	24,400 y	500 d	500 d
Cobalt 60	Whole body	5.3 y	99.5 d	95 d
Iron 55	Spleen	2.7 y	600 d	388 d
Iron 59	Spleen	45.1 d	600 d	42 d
Manganese 54	Liver	303 d	25 d	23 d
Cesium 137	Whole body	30 y	70 d	70 d

[a]d = days, y = years
[b]Mixed in body water as tritiated water

D.2.3 Interaction of Radiation with Matter

Both ionizing and nonionizing radiation will interact with materials; that is, radiation will lose kinetic energy to any solid, liquid or gas through which it passes by a variety of mechanisms. The transfer of energy to a medium by either electromagnetic or particulate radiation may be sufficient to cause formation of ions. This process is called ionization. Compared to other types of radiation that may be absorbed, such as ultraviolet radiation, ionizing radiation deposits a relatively large amount of energy into a small volume.

The method by which incident radiation interacts with the medium to cause ionization may be direct or indirect. Electromagnetic radiations (x rays and gamma photons) are indirectly ionizing; that is, they give up their energy in various interactions with cellular molecules, and the energy is then utilized to produce a fast-moving charged particle such as an electron. It is the electron that then may react with a target molecule. This particle is called a “primary ionizing particle. Charged particles, in contrast, strike the tissue or medium and directly react with target molecules, such as oxygen or water. These particulate radiations are directly ionizing radiations. Examples of directly ionizing particles include alpha and beta particles. Indirectly ionizing radiations are always more penetrating than directly ionizing particulate radiations.

Mass, charge, and velocity of a particle, as well as the electron density of the material with which it interacts, all affect the rate at which ionization occurs. The higher the charge of the particle and the lower the velocity, the greater the propensity to cause ionization. Heavy, highly charged particles, such as alpha particles, lose energy rapidly with distance and, therefore, do not penetrate deeply. The result of these interaction processes is a gradual slowing down of any incident particle until it is brought to rest or "stopped" at the end of its range.

D.2.4 Characteristics of Emitted Radiation

D.2.4.1 Alpha Emission. In alpha emission, an alpha particle consisting of two protons and two neutrons is emitted with a resulting decrease in the atomic mass number by four and reduction of the atomic number of two, thereby changing the parent to a different element. The alpha particle is identical to a helium nucleus consisting of two neutrons and two protons. It results from the radioactive decay of some heavy elements such as uranium, plutonium, radium, thorium, and radon. All alpha particles emitted by a given radioisotope have the same energy. Most of the alpha particles that are likely to be found have energies in the range of about 4 to 8 MeV, depending on the isotope from which they came.

The alpha particle has an electrical charge of +2. Because of this double positive charge and their size, alpha particles have great ionizing power and, thus, lose their kinetic energy quickly. This results in very little penetrating power. In fact, an alpha particle cannot penetrate a sheet of paper. The range of an alpha particle (the distance the charged particle travels from the point of origin to its resting point) is about 4 cm in air, which decreases considerably to a few micrometers in tissue. These properties cause alpha emitters to be hazardous only if there is internal contamination (i.e., if the radionuclide is inside the body).

D.2.4.2 Beta Emission. A beta particle (β) is a high-velocity electron ejected from a disintegrating nucleus. The particle may be either a negatively charged electron, termed a negatron (β-) or a positively charged electron, termed a positron (β+). Although the precise definition of "beta emission" refers to both β- and β+, common usage of the term generally applies only to the negative particle, as distinguished from the positron emission, which refers to the β+ particle.

D.2.4.2.1 Beta Negative Emission. Beta particle (β-) emission is another process by which a radionuclide, with a neutron excess achieves stability. Beta particle emission decreases the number of neutrons by one and increases the number of protons by one, while the atomic mass number remains unchanged.[1] This transformation results in the formation of a different element. The energy spectrum of beta particle emission ranges from a certain maximum down to zero with the mean energy of the spectrum being about one-third of the maximum. The range in tissue is much less. Beta negative emitting radionuclides can cause injury to the skin and superficial body tissues, but mostly present an internal contamination hazard.

D.2.4.2.2 Positron Emission. In cases in which there are too many protons in the nucleus, positron emission may occur. In this case a proton may be thought of as being converted into a neutron, and a positron (β+) is emitted.[1] This increases the number of neutrons by one, decreases the number of protons by one, and again leaves the atomic mass number unchanged. The gamma radiation resulting from the annihilation (see glossary) of the positron makes all positron emitting isotopes more of an external radiation hazard than pure β emitters of equal energy.

D.2.4.2.3 Gamma Emission. Radioactive decay by alpha, beta, or positron emission, or electron capture often leaves some of the energy resulting from these changes in the nucleus. As a result, the

[1] Neutrinos also accompany negative beta particles and positron emissions

nucleus is raised to an excited level. None of these excited nuclei can remain in this high-energy state. Nuclei release this energy returning to ground state or to the lowest possible stable energy level. The energy released is in the form of gamma radiation (high energy photons) and has an energy equal to the change in the energy state of the nucleus. Gamma and x rays behave similarly but differ in their origin; gamma emissions originate in the nucleus while x rays originate in the orbital electron structure or from rapidly changing the velocity of an electron (e.g., as occurs when shielding high energy beta particles or stopping the electron beam in an x ray tube).

D.3 ESTIMATION OF ENERGY DEPOSITION IN HUMAN TISSUES

Two forms of potential radiation exposures can result: internal and external. The term exposure denotes physical interaction of the radiation emitted from the radioactive material with cells and tissues of the human body. An exposure can be "acute" or "chronic" depending on how long an individual or organ is exposed to the radiation. Internal exposures occur when radionuclides, which have entered the body (e.g., through the inhalation, ingestion, or dermal pathways), undergo radioactive decay resulting in the deposition of energy to internal organs. External exposures occur when radiation enters the body directly from sources located outside the body, such as radiation emitters from radionuclides on ground surfaces, dissolved in water, or dispersed in the air. In general, external exposures are from material emitting gamma radiation, which readily penetrate the skin and internal organs. Beta and alpha radiation from external sources are far less penetrating and deposit their energy primarily on the skin's outer layer. Consequently, their contribution to the absorbed dose of the total body dose, compared to that deposited by gamma rays, may be negligible.

Characterizing the radiation dose to persons as a result of exposure to radiation is a complex issue. It is difficult to: (1) measure internally the amount of energy actually transferred to an organic material and to correlate any observed effects with this energy deposition; and (2) account for and predict secondary processes, such as collision effects or biologically triggered effects, that are an indirect consequence of the primary interaction event.

D.3.1 Dose/Exposure Units

D.3.1.1 Roentgen. The roentgen (R) is a unit of x or gamma-ray exposure and is a measured by the amount of ionization caused in air by gamma or x radiation. One roentgen produces 2.58×10^{-4} coulomb per kilogram of air. In the case of gamma radiation, over the commonly encountered range of photon energy, the energy deposition in tissue for a dose of 1 R is about 0.0096 joules (J) /kg of tissue.

D.3.1.2 Absorbed Dose and Absorbed Dose Rate. The absorbed dose is defined as the energy imparted by the incident radiation to a unit mass of the tissue or organ. The unit of absorbed dose is the rad; 1 rad = 100 erg/gram = 0.01 J/kg in any medium. An exposure of 1 R results in a dose to soft tissue of approximately 0.01 J/kg. The SI unit is the gray which is equivalent to 100 rad or 1 J/kg. Internal and external exposures from radiation sources are not usually instantaneous but are distributed over extended periods of time. The resulting rate of change of the absorbed dose to a small volume of mass is referred to as the absorbed dose rate in units of rad/unit time.

D.3.1.3 Working Levels and Working Level Months. Working level (WL) is a measure of the atmospheric concentration of radon and its short-lived progeny. One WL is defined as any combination of short-lived radon daughters (through polonium-214), per liter of air, that will result in the emission of 1.3×10^5 MeV of alpha energy. An activity concentration of 100 pCi radon-222/L of air, in equilibrium with its daughters, corresponds approximately to a potential alpha-energy concentration of 1 WL. The WL unit can also be used for thoron daughters. In this case, 1.3×10^5 MeV of alpha energy (1 WL) is released by the thoron daughters in equilibrium with 7.5 pCi thoron/L. The potential alpha energy

exposure of miners is commonly expressed in the unit Working Level Month (WLM). One WLM corresponds to exposure to a concentration of 1 WL for the reference period of 170 hours, or more generally

WLM = concentration (WL) x exposure time (months) (one "month" = 170 working hours).

D.3.2 Dosimetry Models

Dosimetry models are used to estimate the dose from internally deposited to radioactive substances. The models for internal dosimetry consider the amount of radionuclides entering the body, the factors affecting their movement or transport through the body, distribution and retention of radionuclides in the body, and the energy deposited in organs and tissues from the radiation that is emitted during spontaneous decay processes. The dose pattern for radioactive materials in the body may be strongly influenced by the route of entry of the material. For industrial workers, inhalation of radioactive particles with pulmonary deposition and puncture wounds with subcutaneous deposition have been the most frequent. The general population has been exposed via ingestion and inhalation of low levels of naturally occurring radionuclides as well as radionuclides from nuclear weapons testing.

The models for external dosimetry consider only the photon doses (and neutron doses, where applicable) to organs of individuals who are immersed in air or are exposed to a contaminated object.

D.3.2.1 Ingestion. Ingestion of radioactive materials is most likely to occur from contaminated foodstuffs or water or eventual ingestion of inhaled compounds initially deposited in the lung. Ingestion of radioactive material may result in toxic effects as a result of either absorption of the radionuclide or irradiation of the gastrointestinal tract during passage through the tract, or a combination of both. The fraction of a radioactive material absorbed from the gastrointestinal tract is variable, depending on the specific element, the physical and chemical form of the material ingested, and the diet, as well as some other metabolic and physiological factors. The absorption of some elements is influenced by age, usually with higher absorption in the very young.

D.3.2.2 Inhalation. The inhalation route of exposure has long been recognized as being a major portal of entry for both nonradioactive and radioactive materials. The deposition of particles within the lung is largely dependent upon the size of the particles being inhaled. After the particle is deposited, the retention will depend upon the physical and chemical properties of the dust and the physiological status of the lung. The retention of the particle in the lung depends on the location of deposition, in addition to the physical and chemical properties of the particles. The converse of pulmonary retention is pulmonary clearance. There are three distinct mechanisms of clearance which operate simultaneously. Ciliary clearance acts only in the upper respiratory tract. The second and third mechanisms act mainly in the deep respiratory tract. These are phagocytosis and absorption. Phagocytosis is the engulfing of foreign bodies by alveolar macrophages and their subsequent removal either up the ciliary "escalator" or by entrance into the lymphatic system. Some inhaled soluble particles are absorbed into the blood and translocated to other organs and tissues.

D.3.3 Internal Emitters

An internal emitter is a radionuclide that is inside the body. The absorbed dose from internally deposited radioisotopes depends on the energy absorbed per unit tissue by the irradiated tissue. For a radioisotope 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 particle. All alpha and most beta radiation will be absorbed in the organ (or tissue) of reference. Gamma-emitting isotope emissions

are penetrating radiation, and a substantial fraction of gamma energy may be absorbed in tissue. The dose to an organ or tissue is a function of the effective retention half-time, the energy released in the tissue, the amount of radioactivity initially introduced, and the mass of the organ or tissue.

D.4 BIOLOGICAL EFFECTS OF RADIATION

When biological material is exposed to ionizing radiation, a chain of cellular events occurs as the ionizing particle passes through the biological material. A number of theories have been proposed to describe the interaction of radiation with biologically important molecules in cells and to explain the resulting damage to biological systems from those interactions. Many factors may modify the response of a living organism to a given dose of radiation. Factors related to the exposure include the dose rate, the energy of the radiation, and the temporal pattern of the exposure. Biological considerations include factors such as species, age, sex, and the portion of the body exposed. Several excellent reviews of the biological effects of radiation have been published, and the reader is referred to these for a more in-depth discussion (Brodsky 1996; Hobbs and McClellan 1986; ICRP 1984; Mettler and Moseley 1985; Rubin and Casarett 1968).

D.4.1 Radiation Effects at the Cellular Level

According to Mettler and Moseley (1985), at acute doses up to 10 rad (100 mGy), single strand breaks in DNA may be produced. These single strand breaks may be repaired rapidly. With doses in the range of 50–500 rad (0.5–5 Gy), irreparable double-stranded DNA breaks are likely, resulting in cellular reproductive death after one or more divisions of the irradiated parent cell. At large doses of radiation, usually greater than 500 rad (5 Gy), direct cell death before division (interphase death) may occur from the direct interaction of free-radicals with essentially cellular macromolecules. Morphological changes at the cellular level, the severity of which are dose-dependent, may also be observed.

The sensitivity of various cell types varies. According to the Bergonie-Tribondeau law, the sensitivity of cell lines is directly proportional to their mitotic rate and inversely proportional to the degree of differentiation (Mettler and Moseley 1985). Rubin and Casarett (1968) devised a classification system that categorized cells according to type, function, and mitotic activity. The categories range from the most sensitive type, "vegetative intermitotic cells, " found in the stem cells of the bone marrow and the gastrointestinal tract, to the least sensitive cell type, "fixed postmitotic cells," found in striated muscles or long-lived neural tissues.

Cellular changes may result in cell death, which if extensive, may produce irreversible damage to an organ or tissue or may result in the death of the individual. If the cell recovers, altered metabolism and function may still occur, which may be repaired or may result in the manifestation of clinical symptoms. These changes may also be expressed at a later time as tumors or cellular mutations, which may result in abnormal tissue.

D.4.2 Radiation Effects at the Organ Level

In most organs and tissues the injury and the underlying mechanism for that injury are complex and may involve a combination of events. The extent and severity of this tissue injury are dependent upon the radiosensitivity of the various cell types in that organ system. Rubin and Casarett (1968) describe and schematically display the events following radiation in several organ system types. These include: a rapid renewal system, such as the gastrointestinal mucosa; a slow renewal system, such as the pulmonary epithelium; and a nonrenewal system, such as neural or muscle tissue. In the rapid renewal system, organ injury results from the direct destruction of highly radiosensitive cells, such as the stem cells in the bone marrow. Injury may also result from constriction of the microcirculation and from edema and

inflammation of the basement membrane, designated as the histohematic barrier (HHB), which may progress to fibrosis. In slow renewal and nonrenewal systems, the radiation may have little effect on the parenchymal cells, but ultimate parenchymal atrophy and death over several months result from HHB fibrosis and occlusion of the microcirculation.

D.4.3 Low Level Radiation Effects

Cancer is the major latent harmful effect produced by ionizing radiation and the one that most people exposed to radiation are concerned about. The ability of alpha, beta, and gamma radiation to produce cancer in virtually every tissue and organ in laboratory animals has been well-demonstrated. The development of cancer is not an immediate effect. Radiation-induced leukemia has the shortest latent period at 2 years, while other radiation induced cancers have latent periods >20 years. The mechanism by which cancer is induced in living cells is complex and is a topic of intense study. Exposure to ionizing radiation can produce cancer at any site within the body; however, some sites appear to be more common than others, such as the breast, lung, stomach, and thyroid.

DNA is a major target molecule during exposure to ionizing radiation. Other macromolecules, such as lipids and proteins, are also at risk of damage when exposed to ionizing radiation. The genotoxicity of ionizing radiation is an area of intense study, as damage to the DNA is ultimately responsible for many of the adverse toxicological effects ascribed to ionizing radiation, including cancer. Damage to genetic material is basic to developmental or teratogenic effects, as well. However, for effects other than cancer, there is little evidence of human effects at low levels of exposure.

D.5 UNITS IN RADIATION PROTECTION AND REGULATION

D.5.1 Dose Equivalent (or equivalent dose)

Dose equivalent (as measured in rem or Sievert) is a special radiation protection quantity that is used, for administrative and radiation safety purposes only, to express the absorbed dose in a manner which considers the difference in biological effectiveness of various kinds of ionizing radiation. The dose equivalent concept is applicable only to doses that are not great enough to produce biomedical effects.

The NRC defines the dose equivalent, H, as the product of the absorbed dose, D, and the quality factor, Q, at the point of interest in biological tissue. This relationship is expressed as $H = D \times Q$. The NCRP defines equivalent dose, H, as the product of the absorbed dose, D, and the radiation weighting factor, w_r. This relationship is expressed as $H = Dw_r$.

The quality factor or radiation weighting factor is a dimensionless quantity that depends in part on the stopping power for charged particles, and it accounts for the differences in biological effectiveness found among the types of radiation. Originally relative biological effectiveness (RBE) was used rather than Q to define the quantity, rem, which was of use in risk assessment. The generally accepted values for quality factors and radiation weighting factors for various radiation types are provided in Table D-3. The dose equivalent rate is the time rate of change of the dose equivalent to organs and tissues and is expressed as rem/unit time or sievert/unit time.

Table D-3. Quality Factors (Q) and Radiation Weighting Factors

Type of radiation	Quality factor (Q)	Radiation Weighting Factor (w_r)
X, gamma, or beta radiation	1	1
Alpha particles, multiple-charged particles, fission fragments and heavy particles of unknown charge	20	20
Neutrons (100 keV to 2 MeV), protons, alpha particles, charged particles of unknown energy	7.5-11 depending on energy	20
Neutrons of unknown energy	10	
Thermal neutrons	2	5
High-energy protons	10	5

Source:
USNRC. 2004. Standards for the protection against radiation, tables 1004(b).1 and 1004(b).2. 10 CFR 20.1004. U.S. Nuclear Regulatory Commission, Washington, D.C.
NCRP 1993

D.5.2 Relative Biological Effectiveness

RBE is used to denote the experimentally determined ratio of the absorbed dose from one radiation type to the absorbed dose of a reference radiation required to produce an identical biologic effect under the same conditions. Gamma rays from cobalt-60 and 200–250 keV x-rays have been used as reference standards. The term RBE has been widely used in experimental radiobiology, and the term quality factor (or radiation weighting factor) used in calculations of dose equivalent for radiation safety purposes (ICRP 1977; NCRP 1971; UNSCEAR 1982). RBE applies only to a specific biological end point, in a specific exposure, under specific conditions to a specific species. There are no generally accepted values of RBE.

D.5.3 Effective Dose Equivalent (or effective dose)

The absorbed dose is usually defined as the mean absorbed dose within an organ or tissue. This represents a simplification of the actual problem. Normally when an individual ingests or inhales a radionuclide or is exposed to external radiation that enters the body (gamma), the dose is not uniform throughout the whole body. The simplifying assumption is that the detriment will be the same whether the body is uniformly or non-uniformly irradiated. In an attempt to compare detriment from absorbed dose of a limited portion of the body with the detriment from total body dose, the ICRP (1977) derived a concept of effective dose equivalent. ICRP (1990) changes this term to effective dose, but it has not yet been adopted by the NRC or DOE.

The effective dose equivalent, H_E, is

$$H_E = \sum W_t H_t$$

where H_t is the dose equivalent (or equivalent dose) in the tissue t, W_t is the tissue weighting factor in that tissue, which represents the estimated proportion of the stochastic risk resulting from tissue, t, to the

stochastic risk when the whole body is uniformly irradiated for occupational exposures under certain conditions (ICRP 1977). Tissue weighting factors for selected tissues are listed in Table D-4.

The ICRU (1980), ICRP (1984), and NCRP (1985) now recommend that the rad, roentgen, curie, and rem be replaced by the SI units: gray (Gy), Coulomb per kilogram (C/kg), Becquerel (Bq), and sievert (Sv), respectively. The relationship between the customary units and the international system of units (SI) for radiological quantities is shown in Table D-5.

Table D-4. Tissue Weighting Factors for Calculating Effective Dose Equivalent and Effective Dose for Selected Tissues

	Tissue Weighting factor	
Tissue	NCRP115/ ICRP60	NRC/ICRP26
Bladder	0.05	–
Bone marrow	0.12	0.12
Bone surface	0.01	0.03
Breast	0.05	0.15
Colon	0.12	–
Esophagus	0.05	–
Gonads	0.20	0.25
Liver	0.05	–
Lung	0.12	0.12
Ovary		–
Skin	0.01	–
Stomach	0.12	–
Thyroid	0.05	0.03
Remainder	0.05	0.30
Total	1.00	1.00

ICRP60 = International Commission on Radiological Protection, 1990 Recommendations of the ICRP
NCRP115 = National Council on Radiation Protection and Measurements. 1993. Risk Estimates for Radiation Protection, Report 115. Bethesda, Maryland
NRC = Nuclear Regulatory Commission, Title 10, Code of Federal Regulations, Part 20

Table D-5. Comparison of Common and SI Units for Radiation Quantities

Quantity	Customary units	Definition	SI units	Definition
Activity (A)	curie (Ci)	3.7×10^{10} transformations s^{-1}	becquerel (Bq)	s^{-1}
Absorbed dose (D)	rad (rad)	10^{-2} Jkg^{-1}	gray (Gy)	Jkg^{-1}
Absorbed dose rate ($\dot{D}$)	rad per second (rad s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	gray per second (Gy s^{-1})	Jkg^{-1} s^{-1}
Dose equivalent (H)	rem	10^{-2} Jkg^{-1}	sievert (Sv)	Jkg^{-1}
Dose equivalent rate ($\dot{H}$)	rem per second (rem s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	sievert per second (Sv s^{-1})	Jkg^{-1} s^{-1}
Effective dose	rem	10^{-2} Jkg^{-1}	sievert (Sv)	Jkg^{-1}
Equivalent dose (H)	rem	10^{-2} Jkg^{-1}	sievert (Sv)	Jkg^{-1}
Linear energy transfer (LET)	kiloelectron volts per micrometer (keV μm^{-1})	1.602×10^{-10} Jm^{-1}	kiloelectron volts per micrometer (keV μm^{-1})	1.602×10^{-10} Jm^{-1}

Jkg^{-1} = Joules per kilogram; $Jkg^{-1}s^{-1}$ = Joules per kilogram per second; Jm^{-1} = Joules per meter; s^{-1} = per second

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