TOXICOLOGICAL PROFILE FOR
URANIUM

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

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DISCLAIMER

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UPDATE STATEMENT

A Toxicology Profile for Uranium was released in September 1997. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the *Federal Register* on April 17, 1987, October 20, 1988, October 26, 1989, and on October 17, 1990.

Section 104 (I) (3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

   (A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order 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 which present a significant risk to human health of acute, subacute, and chronic health effects, and

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

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but 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.

Each toxicological profile begins with a public health statement, which 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 will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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

Pediatrics: 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 2.6	**Children's Susceptibility**
Section 5.6	**Exposures of Children**

Other Sections of Interest:

Section 2.7	**Biomarkers of Exposure and Effect**
Section 2.10	**Methods for Reducing Toxic Effects**

ATSDR Information Center
> *Phone:* 1-888-42-ATSDR or 404-639-6357   *Fax:*   404-639-6359
> *E-mail:* atsdric@cdc.gov   *Internet:* http://atsdr1.atsdr.cdc.gov:8080

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 •   Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com •   AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Sam Keith, M.S., CHP
ATSDR, Division of Toxicology, Atlanta, GA

Wayne Spoo, DVM, DABT
Research Triangle Institute, Research Triangle Park, NC

James Corcoran, Ph.D.
Research Triangle Institute, Research Triangle Park, NC

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

PEER REVIEW

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

1.   Herman Cember, Ph.D., CHP, Lafayette, Indiana

2.   Ron Kathren, Ph.D., CHP, Professor, Richland, Washington.

3.   Paul Morrow, Ph.D., Professor Emeritus, Rochester, New York.

4.   Richard Leggett, Ph.D., Research Scientist, Oak Ridge, Tennessee.

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

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

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

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

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1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Elevated uranium levels have been found in at least 54 of the 1,517 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which uranium is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are 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 uranium is radioactive, you can also be exposed to its radiation if you are near it.

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

1.1 WHAT IS URANIUM?

Uranium is a natural and commonly occurring radioactive element. It is found in very small amounts in nature in the form of minerals, but may be processed into a silver-colored metal. Rocks, soil, surface and underground water, air, and plants and animals all contain varying amounts of uranium. Typical concentrations in most materials are a few parts per million (ppm). This corresponds to around 4 tons of uranium in 1 square mile of soil 1 foot deep, or about half a teaspoon of uranium in a typical 8-cubic yard dump truck load of soil. Some rocks and soils may

also contain greater amounts of uranium. If the amount is great enough, the uranium may be
present in commercial quantities and can be mined. After the uranium is extracted, it is
converted into uranium dioxide or other chemical forms by a series of chemical processes known
as milling. The residue remaining after the uranium has been extracted is called mill tailings.
Mill tailings contain a small amount of uranium, as well as other naturally radioactive waste
products such as radium and thorium.

Natural uranium is a mixture of three types (or isotopes) of uranium, written as ^{234}U, ^{235}U, and
^{238}U, or as U-234, U-235, and U-238, and read as uranium two thirty-four, etc. All three isotopes
behave the same chemically, so any combination of the three would have the same chemical
effect on your body. But they are different radioactive materials with different radioactive
properties. That is why we must look at the actual percentages of the three isotopes in a sample
of uranium to determine how radioactive the uranium is. For uranium that has been locked
inside the earth for millions of years, we know the percentage of each isotope by weight and by
radioactivity. By weight, natural uranium is about 0.01% ^{234}U, 0.72% ^{235}U, and 99.27% ^{238}U.
About 48.9% of the radioactivity is associated with ^{234}U, 2.2% is associated with ^{235}U, and 48.9%
is associated with ^{238}U.

The weight and radioactivity percentages are different because each isotope has a different
physical half-life. Radioactive isotopes are constantly changing into different isotopes by giving
off radiation. The half-life is the time it takes for half of that uranium isotope to give off its
radiation and change into a different element. The half-lives of uranium isotopes are very long
(244 thousand years for ^{234}U, 710 million years for ^{235}U, and 4½ billion years for ^{238}U). The
shorter half-life makes ^{234}U the most radioactive, and the longer half-life makes ^{238}U the least
radioactive. If you have one gram of each isotope side by side, the ^{234}U will be about 20
thousand times more radioactive and the ^{235}U will be 6 times more radioactive than the ^{238}U.

Uranium is measured in units of mass (grams) or radioactivity (curies or becquerels), depending
on the type of equipment available or the level that needs to be measured. The becquerel (Bq) is
a new international unit, and the curie (Ci) is a traditional unit; both are currently used. A Bq is
the amount of radioactive material in which 1 billion atoms transform every second, and a Ci is

the amount of radioactive material in which 37 billion atoms transform every second. The mass and activity ratios given in the previous paragraph are those found in rocks inside the earth's crust, where 1.5 gram of uranium is equivalent to 1 millionth of a Ci (μCi). Although this ratio can vary in air, soil, and water, the conversions made in this profile use the 1.5-to-1 ratio unless the actual isotope ratios are known. When both mass and radioactivity units are shown, the first is normally the one reported in the literature. Some of the values may be rounded to make the text easier to read.

The uranium isotopes in the earth were present when the earth was formed. Both ^{235}U and ^{238}U have such long half-lives that part of the uranium originally on earth is still here, waiting to give off its radiation. The original ^{234}U would have decayed away by now, but new ^{234}U is constantly being made from the decay of ^{238}U. When ^{238}U gives off its radiation, it changes or decays through a series of different radioactive materials, including ^{234}U. This series, or decay chain, ends when a stable, non-radioactive substance is made. This element is lead. This toxicological profile deals with the uranium isotopes and not with the other radioactive decay products, like radium, thorium, and radon.

For uranium that has been in contact with water, the natural weight and radioactivity percentages can vary slightly from the percentages mentioned in the previous paragraphs. We don't fully understand why that happens in nature, but measurements show us that it does. The processing of uranium for industrial and governmental use can also change the ratios. We give these ratios special names if they were changed by human activities. If the fraction of ^{235}U is increased, we call it enriched uranium. However, if the portion of ^{235}U is decreased, we call it depleted uranium. The differences between the weight and radioactivity ratios matter when we want to convert between radioactivity and mass, and when we talk about how toxic uranium might be. Depleted uranium is less radioactive than natural uranium, and enriched uranium is more radioactive than natural uranium. This profile focuses on natural and depleted uranium, which are more likely to be chemical hazards than radiation hazards. The profile also discusses enriched uranium, which can be both a chemical and a radiation hazard.

1. PUBLIC HEALTH STATEMENT

The industrial process called enrichment is used to increase the amount of ^{234}U and ^{235}U and decrease the amount of ^{238}U in natural uranium. The product of this process is enriched uranium, and the leftover is depleted uranium. Enriched uranium is more radioactive than natural uranium, and natural uranium is more radioactive than depleted uranium. When enriched uranium is 97.5% pure ^{235}U, the same weight of enriched uranium has about 75 times the radioactivity as natural uranium. This is because enriched uranium also contains ^{234}U, which is even more radioactive than ^{235}U. The ^{235}U is responsible for most of the radioactivity in enriched uranium. Natural uranium is typically about two times more radioactive than depleted uranium. Other isotopes of uranium called ^{232}U and ^{233}U are produced by industrial processes. These are also much more radioactive than natural uranium.

The total amount of natural uranium on earth stays almost the same because of the very long half-lives of the uranium isotopes. The natural uranium can be moved from place to place by nature or by people, and some uranium is removed from the earth by mining. When rocks are broken up by water or wind, uranium becomes a part of the soil. When it rains, the soil containing uranium can be carried into rivers and lakes. Wind can blow dust that contains uranium into the air.

Natural uranium is radioactive but poses little radioactive danger because it gives off very small amounts of radiation. Uranium transforms into another element and gives off radiation. In this way uranium transforms into thorium and gives off a particle called an alpha particle or alpha radiation. Uranium is called the parent, and thorium is called the transformation product. When the transformation product is radioactive, it keeps transforming until a stable product is formed. During these decay processes, the parent uranium, its decay products, and their subsequent decay products each release radiation. Radon and radium are two of these products. Unlike other kinds of radiation, the alpha radiation ordinarily given off by uranium cannot pass through solid objects, such as paper or human skin. For more information on radiation, see Appendix D and the glossary at the end of this profile or the ASTDR *Toxicological Profile for Ionizing Radiation*.

The main civilian use of uranium is in nuclear power plants and on helicopters and airplanes. It is also used by the armed forces as shielding to protect Army tanks, parts of bullets and missiles

to help them go through enemy armored vehicles, as a source of power, and in nuclear weapons. Very small amounts are used to make some ceramic ornament glazes, light bulbs, photographic chemicals, and household products. Some fertilizers contain slightly higher amounts of natural uranium. For more information about the properties and uses of uranium, see Chapters 3, 4, and 5.

1.2 WHAT HAPPENS TO URANIUM WHEN IT ENTERS THE ENVIRONMENT?

Uranium is a naturally occurring radioactive material that is present to some degree in almost everything in our environment, including soil, rocks, water, and air. It is a reactive metal, so it is not found as free uranium in the environment. In addition to the uranium naturally found in minerals, the uranium metal and compounds that are left after humans mine and process the minerals can also be released back to the environment in mill tailings. This uranium can combine with other chemicals in the environment to form other uranium compounds. Each of these uranium compounds dissolves to its own special extent in water, ranging from not soluble to very soluble. This helps determine how easily the compound can move through the environment, as well as how toxic it might be.

The amount of uranium that has been measured in air in different parts of the United States by EPA ranges from 0.011 to 0.3 femtocuries (0.00002 to 0.00045 micrograms) per cubic meter (m^3). (One femtocurie is equal to 1 picocurie [pCi] divided by 1,000. A picocurie [pCi] is 1 one-trillionth of a curie and a microgram [μg] is one millionth of a gram Even at the higher concentration, there is so little uranium in a cubic meter of air that less than one atom transforms each day.

In the air, uranium exists as dust. Very small dust-like particles of uranium in the air fall out of the air onto surface water, plant surfaces, and soil either by themselves or when rain falls. These particles of uranium eventually end up back in the soil or in the bottoms of lakes, rivers, and ponds, where they stay and mix with the natural uranium that is already there.

Uranium in water comes from different sources. Most of it comes from dissolving uranium out of rocks and soil that water runs over and through. Only a very small part is from the settling of uranium dust out of the air. Some of the uranium is simply suspended in water, like muddy water. The amount of uranium that has been measured in drinking water in different parts of the United States by EPA is generally less than 1.5 μg (1 pCi) for every liter of water. EPA has found that the levels of uranium in water in different parts of the United States are extremely low in most cases, and that water containing normal amounts of uranium is usually safe to drink. Because of the nature of uranium, not much of it gets into fish or vegetables, and most of that which gets into livestock is eliminated quickly in urine and feces.

Uranium is found naturally in soil in amounts that vary over a wide range, but the typical concentration is 3 μg (2 pCi) per gram of soil. Additional uranium can be added by industrial activities. Soluble uranium compounds can combine with other substances in the environment to form other uranium compounds. Uranium compounds may stay in the soil for thousands of years without moving downward into groundwater. When large amounts of natural uranium are found in soil, it is usually soil with phosphate deposits. The amount of uranium that has been measured in the phosphate-rich soils of north and central Florida ranges from 4.5 to 83.4 pCi of uranium in every gram of soil. In areas like New Mexico, where uranium is mined and processed, the amount of uranium per gram of soil ranges between 0.07 and 3.4 pCi (0.1–5.1 micrograms [μg]) of uranium per gram soil). The amount of uranium in soil near a uranium fuel fabrication facility in the state of Washington ranges from 0.51 to 3.1 pCi/gram (0.8–4.6 μg uranium/gram soil), with an average value of 1.2 pCi/gram (1.7 μg uranium/gram soil). These levels must be carefully compared with the levels in uncontaminated soil in that area, since they are within the normal ranges for uncontaminated soil.

Plants can absorb uranium from the soil onto their roots without absorbing it into the body of the plant. Therefore, root vegetables like potatoes and radishes that are grown in uranium-contaminated soil may contain more uranium than if the soil contained levels of uranium that were natural for the area. Washing the vegetable or removing its skin often removes most or all of the uranium. For more information about what happens to uranium in the environment, see Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO URANIUM?

Since uranium is found everywhere in small amounts, you always take it into your body from the air, water, food, and soil. Food and water have small amounts of natural uranium in them. People eat about 1–2 micrograms (0.6–1.0 picocuries) of natural uranium every day with their food and take in about 1.5 micrograms (0.8 picocuries) of natural uranium for every liter of water they drink, but they breathe in much lower amounts. Root vegetables, such as beets and potatoes, tend to have a bit more uranium than other foods. In a few places, there tends to be more natural uranium in the water than in the food. People in these areas naturally take in more uranium from their drinking water than from their foods. It is possible that you may eat and drink more uranium if you live in an area with naturally higher amounts of uranium in the soil or water or if you live near a uranium-contaminated hazardous waste site. You can also take in (or ingest) more uranium if you eat food grown in contaminated soil, or drink water that has unusually high levels of uranium. Normally, very little of the uranium in lakes, rivers, or oceans gets into the fish or seafood we eat. The amounts in the air are usually so small that they can be safely ignored. People who are artists, art or craft teachers, ceramic hobbyists, or glass workers who still use certain banned uranium-containing glazes or enamels may also be near to higher levels of uranium, but they will not necessarily take any into their bodies.   People who work at factories that process uranium, work with phosphate fertilizers, or live near uranium mines have a chance of taking in more uranium than most other people. People who work on gyroscopes, helicopter rotor counterbalances, or control surfaces of airplanes may work with painted uranium metal, but the coating normally will keep them from taking in any uranium. People who work with armor-piercing weapons that contain uranium will be exposed to low levels of radiation while close to these weapons, but are not likely to take in any uranium. Those who fire uranium weapons, work with weapons with damaged uranium, or on equipment which has been bombarded with these weapons can be exposed to uranium and may wear protective clothes and masks to limit their intake. Larger-than-normal amounts of uranium might also enter the environment from erosion of tailings from mines and mills for uranium and other metals. Accidental discharges from uranium processing plants are possible, but these compounds spread out quickly into the air. For more information about how you may be exposed to uranium, see Chapter 5.

1.4 HOW CAN URANIUM ENTER AND LEAVE MY BODY?

We take uranium into our bodies in the food we eat, water we drink, and air we breathe. What we take in from industrial activities is in addition to what we take in from natural sources.

When you breathe uranium dust, some of it is exhaled and some stays in your lungs. The size of the uranium dust particles and how easily they dissolve determines where in the body the uranium goes and how it leaves your body. Uranium dust may consist of small, fine particles and coarse, big particles. The big particles are caught in the nose, sinuses, and upper part of your lungs where they are blown out or pushed to the throat and swallowed. The small particles are inhaled down to the lower part of your lungs. If they do not dissolve easily, they stay there for years and cause most of the radiation dose to the lungs from uranium. They may gradually dissolve and go into your blood. If the particles do dissolve easily, they go into your blood more quickly. A small part of the uranium you swallow will also go into your blood. The blood carries uranium throughout your body. Most of it leaves in your urine in a few days, but a little stays in your kidneys and bones.

When you eat foods and drink liquids containing uranium, most of it leaves within a few days in your feces and never enters your blood. A small portion will get into your blood and will leave your body through your urine within a few days. The rest can stay in your bones, kidneys, or other soft tissues. A small amount goes to your bones and may stay there for years. Most people have a very small amounts of uranium, about 1/5,000th of the weight of an aspirin tablet, in their bodies, mainly in their bones.

Although uranium is weakly radioactive, most of the radiation it gives off cannot travel far from its source. If the uranium is outside your body, such as in soil, most of its radiation cannot penetrate your skin and enter your body. To be exposed to radiation from uranium, you have to eat, drink, or breathe it, or get it on your skin. If uranium transformation products are also present, you can be exposed to their radiation at a distance. For more information about how uranium can leave your body, see Chapter 2.

1.5 HOW CAN URANIUM AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists must determine what the harmful effects are, how to test for them, how much of the chemical is required to produce each of the harmful effects, how we recognize an overexposure, and how to treat it.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as kidney or liver damage, cancer, or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Uranium is a chemical substance that is also radioactive. Scientists have never detected harmful radiation effects from low levels of natural uranium, although some may be possible. However, scientists have seen chemical effects. A few people have developed signs of kidney disease after intake of large amounts of uranium. Animals have also developed kidney disease after they have been treated with large amounts of uranium, so it is possible that intake of a large amount of uranium might damage your kidneys. There is also a chance of getting cancer from any radio-active material like uranium. Natural and depleted uranium are only weakly radioactive and are not likely to cause you to get cancer from their radiation. No human cancer of any type has ever been seen as a result of exposure to natural or depleted uranium. Uranium can decay into other radionuclides, which can cause cancer if you are exposed to enough of them for a long enough period. Doctors that studied lung and other cancers in uranium miners did not think that uranium radiation caused these cancers. The miners smoked cigarettes and were exposed to other substances that we know cause cancer, and the observed lung cancers were attributed to large exposures to radon and its radioactive transformation products.

The chance of getting cancer is greater if you are exposed to enriched uranium, because it is more radioactive than natural uranium. Cancer may not become apparent until many years after a person is exposed to a radioactive material (from swallowing or breathing it). Just being near uranium is not dangerous to your health because uranium gives off very little of the penetrating gamma radiation. However, uranium is normally accompanied by the other transformation products in its decay chain, so you would be exposed to their radiation as well.

The Committee on the Biological Effects of Ionizing Radiation (BEIR IV) reported that eating food or drinking water that has normal amounts of uranium will most likely not cause cancer or other health problems in most people. The Committee used data from animal studies to estimate that a small number of people who steadily eat food or drink water that has larger-than-normal quantities of uranium in it could get a kind of bone cancer called a sarcoma. The Committee reported calculations showing that if people steadily eat food or drink water containing about 1 pCi of uranium every day of their lives, bone sarcomas would be expected to occur in about 1 to 2 of every million people after 70 years, based on the radiation dose alone. However, we do not know this for certain because people normally ingest only slightly more than this amount each day, and people who have been exposed to larger amounts have not been found to get cancer.

We do not know if exposure to uranium causes reproductive effects in people. Very high doses of uranium have caused reproductive problems (reduced sperm counts) in some experiments with laboratory animals. Most studies show no effects. For more information about how uranium can affect your health, see Chapter 2.

1.6 HOW CAN URANIUM AFFECT CHILDREN?

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

Like adults, children are exposed to small amounts of uranium in air, food, and drinking water.
However, no cases have been reported where exposure to uranium is known to have caused
health effects in children. It is possible that if children were exposed to very high amounts of
uranium they might have damage to their kidneys like that seen in adults. We do not know
whether children differ from adults in their susceptibility to health effects from uranium
exposure.

It is not known if exposure to uranium has effects on the development of the human fetus. Very
high doses of uranium in drinking water can affect the development of the fetus in laboratory
animals. One study reported birth defects and another reported an increase in fetal deaths.
However, we do not believe that uranium can cause these problems in pregnant women who take
in normal amounts of uranium from food and water, or who breathe the air around a hazardous
waste site that contains uranium.

Very young animals absorb more uranium into their blood than adults when they are fed
uranium. We do not know if this happens in children.

Measurements of uranium have not been made in pregnant women, so we do not know if
uranium can cross the placenta and enter the fetus. In an experiment with pregnant animals, only
a very small amount (0.03%) of the injected uranium reached the fetus. Even less uranium is
likely to reach the fetus in mothers exposed by inhaling, swallowing, or touching uranium. No
measurements have been made of uranium in breast milk. Because of the chemical properties of
uranium, it is unlikely that it would concentrate in breast milk.

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

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

It is possible that higher-than-normal levels of uranium may be in the soil at a hazardous waste site. Some children eat a lot of dirt. You should prevent your children from eating dirt. Make sure they wash their hands frequently, and before eating. If you live near hazardous waste site, discourage your children from putting their hands in their mouths or from engaging in other hand-to-mouth activities.

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

Yes, there are medical tests that can determine whether you have been exposed by measuring the amount of uranium in your urine, blood, and hair. Urine analysis is the standard test. If you take into your body a larger-than-normal amount of uranium over a short period, the amount of uranium in your urine may be increased for a short time. Because most uranium leaves the body within a few days, normally the amount in the urine only shows whether you have been exposed to a larger-than-normal amount within the last week or so. If the intake is large or higher-than-normal levels are taken in over a long period, the urine levels may be high for a longer period of time. Many factors can affect the detection of uranium after exposure. These factors include the type of uranium you were exposed to, the amount you took into your body, and the sensitivity of the detection method. Also, the amount in your urine does not always accurately show how much uranium you have been exposed to. If you think you have been exposed to elevated levels of uranium and want to have your urine tested, you should do so promptly while the levels may still be high. In addition to uranium, the urine could be tested for evidence of kidney damage, by looking for protein, glucose, and nonprotein nitrogen, which are some of the chemicals that can appear in your urine because of kidney damage. Testing for these chemicals could determine whether you have kidney damage. However, since kidney damage is also caused by several common diseases, such as diabetes, it would not tell you if the damage was caused by the presence of uranium in your body.

A radioactivity counter can tell if your skin is contaminated with uranium, because uranium is radioactive. If you inhale large amounts of uranium, it may be possible to measure the amount

of radioactivity in your body with special radiation measurement instruments. See Chapters 2
and 6 for more information.

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

International and national organizations like the International Commission on Radiological
Protection (ICRP) and the National Council on Radiation Protection and Measurements (NCRP)
provide recommendations for protecting people from materials, like uranium, that give off
ionizing radiation. The federal government considers these recommendations and develops
regulations and guidelines to protect public health. Regulations <u>can</u> be enforced by law. Federal
agencies that develop regulations for toxic substances include the EPA, the Nuclear Regulatory
Commission (NRC), the Occupational Safety and Health Administration (OSHA), and the Food
and Drug Administration (FDA). Recommendations provide valuable guidelines to protect
public health but <u>cannot</u> be enforced by law. Federal organizations that develop
recommendations for toxic substances include the Agency for Toxic Substances and Disease
Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

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

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

EPA has not set a limit for uranium in air, but it has set a goal of no uranium in drinking water.
EPA calls this the Maximum Contaminant Level Goal (MCLG), but recognizes that, currently,
there is no practical way to meet this goal. Because of this, EPA proposed in 1991 to allow up to

20 μg of uranium per liter (20 μg/L) in drinking water, and states began regulating to achieve this level. EPA calls this the Maximum Contaminant Level (MCL). The MCL for uranium is based on calculations that if 150,000 people drink water that contains 20 μg/L of uranium for a lifetime, there is a chance that one of them may develop cancer from the uranium in the drinking water. In 1994, EPA considered changing the MCL to 80 μg per liter based on newer human intake and uptake values and the high cost of reducing uranium levels in drinking water supplies. In 1998, EPA temporarily dropped its 1991 limit, but is currently working to develop an appropriate limit based on a broader range of human and animal health studies. ATSDR, other federal agencies, Canada, and other professionals are advising EPA regarding a new MCL. Canada is currently developing its own national guideline value because that country has the richest known uranium ore deposits in the world and high uranium concentrations in some of its well water.

EPA has also decided that any accidental uranium waste containing 0.1 curies of radioactivity (150 kilograms) must be cleaned up. EPA calls this the Reportable Quantity Accidental Release. EPA also has established a standard for uranium mill tailings. In the workplace, NIOSH/OSHA has set a Recommended Exposure Limit (REL) and a Permissible Exposure Limit (PEL) of 0.05 mg/m^3 (34 pCi/m^3) for uranium dust, while the NRC has an occupational limit of 0.2 mg/m^3 (130 pCi/m^3). The NRC has set uranium release limits at 0.06 pCi/m^3 (0.09 μg/m^3) of air and 300 pCi/liter (450 μg/liter) of water. NRC and OSHA expect that the public will normally be exposed to much lower concentrations. For more information about recommendations the federal government has made to protect your health, see Chapter 7.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

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

1. PUBLIC HEALTH STATEMENT

* Information line and technical assistance

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

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

* To order toxicological profiles, contact

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

2. HEALTH EFFECTS

2.1   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 of the toxicology of uranium. It contains descriptions and evaluations of toxicological studies and epidemiologic 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.

The health effects associated with oral or dermal exposure to natural and depleted uranium appear to be solely chemical in nature and not radiological, while those from inhalation exposure may also include a slight radiological component, especially if the exposure is protracted. A comprehensive review by the Committee on the Biological Effects of Ionizing Radiation (BEIR IV) concluded that ingesting food or water containing normal uranium concentrations will most likely not be carcinogenic or cause other health problems in most people. Inhaled uranium is associated with only a low cancer risk, with the main risk being associated with the co-inhalation of other toxic and/or carcinogenic agents, such as the radioactive transformation products of radon gas and cigarette smoke. Very high oral doses of uranium have caused renal damage in humans. Animal studies in a number of species and using a variety of compounds confirm that uranium is a nephrotoxin and that the most sensitive organ is the kidney. Hepatic and developmental effects have also been noted in some animal studies. This profile is primarily concerned with the effects of exposure to natural and depleted uranium, but does include limited discussion regarding enriched uranium, which is considered to be more of a radiological than a chemical hazard. Also, whenever the term "radiation" is used, it applies to ionizing radiation and not to non-ionizing radiation.

Although natural and depleted uranium are primarily chemical hazards, the next several paragraphs describe the radiological nature of the toxicologically-important uranium isotopes, because individual isotopes are addressed in some of the health effects studies. Uranium is a naturally occurring radioactive element and a member of the actinide series. Radioactive elements are those that undergo spontaneous transformation (decay), in which energy is released (emitted) either in the form of particles, such as alpha or beta particles, or electromagnetic radiation with energies sufficient to cause ionization, such as gamma or X-rays. This transformation or decay results in the formation of different elements, some of which

may themselves be radioactive, in which case they will also decay. The process continues until a stable (nonradioactive) state is reached (see Appendix D for more information).

Uranium exists in several isotopic forms, all of which are radioactive. The most toxicologically important of the 22 currently recognized uranium isotopes are anthropogenic uranium-232 (^{232}U) and uranium-233 (^{233}U) and naturally occurring uranium-234 (^{234}U), uranium-235 (^{235}U), and uranium-238 (^{238}U). When an atom of any of these five isotopes decays, it emits an alpha particle (the nucleus of a helium atom) and transforms into a radioactive isotope of another element. The process continues through a series of radionuclides until reaching a stable, non-radioactive isotope of lead. The radionuclides in these transformation series (such as radium and radon), emit alpha, beta, and gamma radiations with energies and intensities that are unique to the individual radionuclide.

Natural uranium consists of isotopic mixtures of ^{234}U, ^{235}U, and ^{238}U. There are three kinds of mixtures (based on the percentage of the composition of the three isotopes): natural uranium, enriched uranium, and depleted uranium. Natural uranium, including uranium ore, is comprised of 99.284% ^{238}U, 0.711% ^{235}U, and 0.005% ^{234}U by mass. Combining these mass percentages with the unique half-life of each isotope converts mass into radioactivity units and shows that uranium ore contains 48.9% ^{234}U, 2.25% ^{235}U, and 48.9% ^{238}U by radioactivity, and has a very low specific activity of 0.68 µCi/g (Parrington et al. 1996). Enriched and depleted uranium are the products of a process which increases (or enriches) the percentages of ^{234}U and ^{235}U in one portion of a uranium sample and decreases (or depletes) their percentages in the remaining portion. Enriched uranium is quantified by its ^{235}U percentage Uranium enrichment for nuclear energy produces uranium that typically contains 3% ^{235}U. Uranium enrichment for a number of other purposes, including nuclear weapons, can produce uranium that contains as much as 97.3% ^{235}U and has a higher specific activity (. 50 µCi/g). The residual uranium after the enrichment process is called "depleted uranium" (DU), which possesses even less radioactivity (0.36 µCi/g) than natural uranium. The Nuclear Regulatory Commission (NRC) considers the specific activity of depleted uranium to be 0.36 µCi/g (10 CFR 20), but more aggressive enrichment processes can drive this value slightly lower (0.33 µCi/g). In this profile, both natural and depleted uranium are referred to as "uranium." The higher specific-activity mixtures and isotopes are described in the profile as "enriched uranium," or as ^{232}U, ^{233}U, or ^{234}U, as applicable, in the summary of the studies in which these mixtures and isotopes were used.

Because uranium is a predominantly alpha-emitting radionuclide, there is a concern for potential DNA damage and fragmentation if alpha particles reach cell nuclei. Attempts by cells to repair this

fragmentation, if it occurs, may result in repair errors, producing gene mutations or chromosomal aberrations. These effects, when sufficiently severe, may be manifested as cancer and possibly as developmental malformations. However, the genetic effects of radiation have not been observed in humans with exposure to radiation, including that from uranium. Ionizing radiation may also promote carcinogenesis by an apoptotic mechanism by which radiation-induced cell death in tissues or organs elicits an increased cell proliferation response to replace the lost cells. Increased mitotic activity may afford cancer cells a preferential advantage in clonal expansion.

Although radiation exposure has been generally assumed to be carcinogenic at all dose levels, no correlation has been established at low doses such as occur from exposure to natural radiation background levels. This is largely attributable to two factors: (1) it is difficult to construct and obtain meaningful data from epidemiological studies where exposure is near background exposure levels, and (2) the data are not statistically significant enough to substantiate a detectable health impact. Recent risk assessment reviews of carcinogenicity and exposure to hazardous chemicals, including radiation, have been questioning the non-threshold assumption. With specific reference to radiation, there is increasing biological evidence that there is a threshold for radiation-induced carcinogenicity (Clark 1999).

The National Research Council Committee on the Biological Effects of Ionizing Radiation BEIR IV report stated that ingesting uranium in food and water at the naturally occurring levels will not cause cancer or other health problems in people. However, based on the zero-threshold linear dose-response model (a conservative model that is inherently unverifiable and is intended to be used as an aid to risk-benefit analysis and not for predicting cancer deaths), the BEIR IV committee calculated that the ingestion of an additional 1 pCi/day (0.0015 mg/day) of soluble natural uranium would lead to a fractional increase in the incidence rate of osteogenic sarcoma (bone cancer) of 0.0019. This means that over a period of 70 years (the nominal lifetime length), if everyone were exposed at that level, the number of bone cancer cases in a U.S. population of 250 million would increase from 183,750 to about 184,100. Currently, there are no unequivocal studies that show that intake of natural or depleted uranium can induce radiation effects in humans or animals. The available information on humans and animals suggests that intake of uranium at the low concentrations usually ingested by humans or at levels found at or near hazardous waste sites is not likely to cause cancer. The BEIR IV committee, therefore, concluded that "...exposure to natural uranium is unlikely to be a significant health risk in the population and may well have no measurable effect."

2. HEALTH EFFECTS

Exposure to enriched uranium, used as uranium fuel in nuclear energy production, may present a radiological health hazard. Although uranium-associated cancers have not been identified in humans, even following exposure to highly enriched uranium, higher doses associated with highly enriched, high specific activity uranium may be able to produce bone sarcomas in humans. Evidence from animal studies suggests that high radiation doses associated with large intakes of ^{234}U and ^{235}U-enriched uranium compounds can be hazardous. Adverse effects reported from such exposures include damage to the interstitium of the lungs (fibrosis) and cardiovascular abnormalities (friable vessels). However, access to ^{235}U-enriched or other high specific-activity uranium is strictly regulated by the NRC and the U.S. Department of Energy (DOE). Therefore, the potential for human exposure to this level of radioactivity is limited to rare accidental releases in the workplace.

The potential for adverse noncancerous radiological health effects from uranium is dependent on several factors, including physicochemical form and solubility, route of entry, distribution in the various body organs, the biological retention time in the various tissues, and the energy and intensity of the radiation. The potential for such effects is generally thought to be independent of the known chemical toxicity of uranium. While the chemical properties affect the distribution and biological half-life of a radionuclide, the damage from radiation is independent of the source of that radiation. In this profile, there is little, or equivocal, specific information regarding the influence of radiation from uranium on certain biological effect end points in humans, such as reproductive, developmental, or carcinogenic effects. There is evidence, however, from the large body of literature concerning radioactive substances that alpha radiation can affect these processes in humans (see Appendix D for additional information on the biological effects of radiation). However, because the specific activities of natural and depleted uranium are low, no radiological health hazard is expected from exposure to natural and depleted uranium. Since the radiological component of natural uranium has essentially been discounted as a significant source of health effects, this leaves only the chemical effects of uranium to contend with. The chemical (non-radiological) properties of natural uranium and depleted uranium are identical; therefore, the health effects exerted by each are expected to be the same. The results of the available studies in humans and animals are consistent with this conclusion. The potential health impacts of depleted uranium are specifically addressed in a recent Department of Energy publication (DOE 1999).

Uranium is a heavy metal that forms compounds and complexes of different varieties and solubilities. The chemical action of all isotopes and isotopic mixtures of uranium is identical, regardless of the specific activity (i.e., enrichment), because chemical action depends only on chemical properties. Thus, the chemical toxicity of a given amount or weight of natural, depleted, and enriched uranium is identical.

2. HEALTH EFFECTS

The toxicity of uranium varies according to its chemical form and route of exposure. On the basis of the toxicity of different uranium compounds in animals, it was concluded that the relatively more water-soluble compounds (uranyl nitrate hexahydrate, uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranium pentachloride) were the most potent renal toxicants. The less water-soluble compounds (sodium diuranate, ammonium diuranate) were of moderate-to-low renal toxicity, and the insoluble compounds (uranium tetrafluoride, uranium trioxide, uranium dioxide, uranium peroxide, triuranium octaoxide) had little potential to cause renal toxicity but could cause pulmonary toxicity when exposure was by inhalation. *The terms soluble, moderately soluble, and insoluble are often used in this profile without relisting the specific compounds.* Generally, hexavalent uranium, which tends to form soluble compounds, is more likely to be a systemic toxicant than tetravalent uranium, which forms insoluble compounds. Ingested uranium is less toxic than inhaled uranium, which may be partly attributable to the relatively low gastrointestinal absorption of uranium compounds. Only <0.1–6% of even the more soluble uranium compounds are absorbed in the gastrointestinal tract (Leggett 1989). The available data on a variety of uranium compounds are sufficient to conclude that uranium has a low order of metallotoxicity (chemical toxicity) in humans. This low order results from the high exposures to which animals in these studies were exposed without adverse effects in many cases. The ICRP (1995) recommends a gastrointestinal absorption fraction of 0.02 (i.e. 2%) for uranium ingested in relatively stable form.

The hazard from inhaled uranium aerosols, or any noxious agent, is determined by the likelihood that the agent will reach the site of its toxic action. Two main factors that influence the degree of hazard from toxic airborne particles are the site of deposition in the respiratory tract of the particles and the fate of the particles within the lungs. The deposition site within the lungs depends mainly on the particle size of the inhaled aerosol, while the subsequent fate of the particle depends mainly on the physical and chemical properties of the inhaled particles and the physiological status of the lungs.

Human and animal studies have shown that long-term retention in the lungs of large quantities of inhaled insoluble uranium particles (e.g., carnotite dust [4% uranium as uranium dioxide and triuranium octaoxide, 80–90% quartz, and <10% feldspar]) can lead to serious respiratory effects. However, animals exposed to high doses of purified uranium (as uranyl nitrate hexahydrate, uranium tetrachloride, uranium dioxide, uranium trioxide, uranium tetraoxide, uranium fluoride, or uranium acetate) through the inhalation or oral route in acute-, intermediate-, or chronic-duration exposures failed to develop these respiratory ailments. The lack of significant pulmonary injury in animal studies with insoluble compounds indicates that other factors, such as diverse inorganic particle abrasion or chemical reactions, may contribute to these effects.

Highly soluble forms of uranium clear the lungs quickly and are less likely to react with or affect the normal physiology of lung parenchymal tissue. In animal studies and in studies following intense accidental human exposure to uranium hexafluoride, hydrogen fluoride gas (a hydrolysis product of uranium hexafluoride) was suggested to have caused the observed pulmonary injury. Longer-term inhalation exposures to tolerable levels of uranium hexafluoride in animals, however, have caused renal toxicity.

Because natural uranium produces very little radioactivity per mass of uranium, the renal and respiratory effects from exposure of humans and animals to uranium are usually attributed to the chemical properties of uranium. However, in exposures to more radioactive uranium isotopes (e.g., ^{232}U and ^{233}U, and naturally occurring ^{234}U and ^{235}U), it has been suggested that the chemical and radiological toxicity may be additive or may potentiate in some instances. In these instances, this dual mode of uranium toxicity may not be distinguishable by end point because of the overlap of etiology and manifested effects. The mechanism of this interaction is as yet unclear.

In animals, kidney damage is the principal toxic effect of uranium, especially to its soluble compounds. The kidneys have been identified as the most sensitive target of uranium toxicosis, consistent with the metallotoxic action of a heavy metal. The toxic action is mediated by accumulation of uranium in the renal tubular epithelium which induces cellular necrosis and atrophy in the tubular wall resulting in decreased reabsorption efficiency in the renal tubule in humans and animals. Heavy metal ions, such as uranyl ions, are also effective in delaying or blocking the cell division process, thereby magnifying the effects of cell necrosis. These renal effects observed in animals can also occur in humans if the uranium dose is high enough. However, these effects have only been seen in certain acute poisoning incidents in humans. Epidemiological studies of uranium miners and mill workers have not demonstrated unusual rates of kidney disease. A recent comparison of kidney tissue obtained at autopsy from 7 uranium workers and 6 referents with no known exposure to uranium showed that the groups were indistinguishable by pathologists experienced in uranium-induced renal pathology. One study in humans found a dose-response nephrotoxicity, indicated by the presence of β_2-microglobulinuria and aminoaciduria from decreased tubular reabsorption, in 39 male uranium mill workers exposed for more than a year to uranium concentrations exceeding the then current occupational standard of 1.0×10^{-10} μCi/mL (3.7 Bq/m^3) (0.15 mg/m^3) by up to 8-fold.   However, the negative findings regarding renal injury among current uranium miners and mill workers exposed to dusts of both soluble and insoluble uranium compounds are particularly significant in view of the high levels of exposure.

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A histological kidney study of chronically exposed workers found no pathological differences at the low kidney concentrations (~0.3 µg/g) when compared to unexposed workers (Russell et al. 1996). In animal studies, observations in acute- and intermediate-duration exposures to uranium compounds conclusively show that high doses of uranium are nephrotoxic. Histopathological examination of the kidneys of these animals following oral, inhalation, or parenteral exposure revealed a thickened glomerular capsular wall, shrinkage of the glomerular capillary network, and decreased glomerular filtration rates. The damage in animals is histologically manifested as glomerular and tubular wall pathology. A mechanism involving bicarbonate uptake in the kidneys and subsequent precipitation of uranium in the tubule was proposed for uranium-induced renal toxicity. An alternative mechanism involving the inhibition of both sodium transport-dependent and transport-independent adenosine triphosphate (ATP) utilization and of mitochondrial oxidative phosphorylation in the renal proximal tubule has also been proposed.

Respiratory diseases have been associated with human exposure to the atmosphere in uranium mines. Respiratory diseases in uranium miners (fatal in some cases) have been linked to exposure to silica dust, oxide dusts, diesel fumes, and radon and its daughters, in conjunction with cigarette smoking. In several of these studies, the investigators concluded that, although uranium mining clearly elevates the risk for respiratory disease, uranium contributes minimally, if at all, to this risk. The mine air also contained radon and its daughters, and cigarette smoke, which are proven carcinogens. As in human studies, several animal studies in which uranium-containing dusts, such as carnotite uranium dust, were used reported the occurrence of respiratory diseases.

Epidemiologic studies among workers who had been exposed to uranium aerosols in strip and underground mines, mills, and processing facilities found more than the expected number of lung cancers only among underground miners and especially among miners who were cigarette smokers. No significant difference in the incidence rate of lung cancer was found between other workers who had been occupationally exposed to uranium and control populations. In addition to uranium dust, the mine air contained many other noxious aerosols (including silica, oxides of nickel, cobalt, and vanadium), radon and its daughters, diesel fumes, and cigarette smoke. Excess cancers were found among those underground miners whose radon daughter exposure exceeded 120 working level months (WLM). The rate of cancer incidence increased with increasing exposure to radon daughters.

No significant difference in cancer (of the lungs) was found between workers who are occupationally exposed to uranium and control populations. Other detailed studies conducted between 1950 and 1967 on the association between uranium mining and an increased incidence of cancer found lung cancer in the

miners over six times the rate expected. However, some of the miners were exposed to other potentially cancer-causing substances such as radon and its progeny, tobacco smoke, diesel smoke, and solvents (carbon tetrachloride and trichloroethylene). These studies and a review of 11 uranium miner studies attributed the increased incidence of lung cancer to radon and its progeny and not to uranium.

The evidence for the cancer-inducing potential of uranium in animals is also inconclusive. Animals exposed to very high doses of uranyl nitrate hexahydrate, uranium tetrachloride, uranium dioxide, uranium trioxide, uranium tetroxide, uranyl fluoride, uranium tetrafluoride, or uranium acetate, through the inhalation or oral route in acute-, intermediate-, or chronic-duration exposures, failed to develop these respiratory cancers. The lack of significant pulmonary injury in oral animal studies indicates that other factors such as diverse inorganic dust or radon daughters may contribute to these effects. Because uranium is a predominantly alpha-emitting radionuclide, current theories on cellular necrosis by high linear energy transfer (LET) alpha radiation also imply a contributory role to the cellular degenerative pulmonary changes. In studies in which human subjects and animals were exposed to uranium hexafluoride, hydrogen fluoride was probably responsible for, or aggravated, the observed respiratory effects. Uranium hexafluoride is hydrolyzable to uranyl fluoride and hydrogen fluoride, and death occurred shortly after intake with signs and symptoms of acute acid-induced cellular damage.

2.2   DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites or potential hazardous wastes sites containing uranium, the information in this section is organized first by route of exposure—inhalation, oral, and dermal; by health effects— death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and cancer effects; and then by chemical and radiation effects. Regarding the last aggregation of the data, the chemical and radiological identities of uranium are discussed, for the purpose of presentation only, as separate concerns. 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. For noncancer radiological effects, the actual dose or exposure at which the
effects occurred or were observed is designated the radiation effect level.

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 (LOAEL) or exposure levels below which no
adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans
(Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with health effects by route of exposure to uranium are indicated in
Tables 2-1 and 2-2 and Figures 2-1 and 2-2. Data permitting, the cancer effects of uranium are discussed
separately with respect to chemical and radiation etiology.

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

Although methods have been established to derive the MRLs (Barnes and Dourson 1988; EPA 1990),
uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional
uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an

example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

2.2.1 Inhalation Exposure

The toxicity of uranium compounds to the lungs and distal organs varies when exposed by the inhalation route. In general, the more soluble compounds (uranyl fluoride,[1] uranium tetrachloride, uranyl nitrate hexahydrate) are less toxic to the lungs but more toxic systemically by the inhalation route due to easier absorption from the lungs into the blood and transportation to distal organs (Tannenbaum and Silverstone 1951). A study summary of the data for inhalation toxicity (lethality) studies in mice exposed to equivalent uranium concentrations of uranium tetrafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate, or triuranium octaoxide concluded that the order of decreasing systemic toxicity for these compounds may be as follows: very toxic, uranyl fluoride; toxic, uranyl nitrate hexahydrate; and nontoxic (at the levels tested in companion studies), uranium tetrachloride, uranium tetrafluoride, and triuranium octaoxide (Stokinger et al. 1953; Tannenbaum and Silverstone 1951). Although uranium tetrachloride is highly soluble in water, it is easily hydrolyzed and oxidized into less soluble uranyl chloride and insoluble

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[1] Uranium hexafluoride is hydrolyzed to uranyl fluoride and hydrogen fluoride. Hydrogen fluoride is highly toxic in acute exposures and causes pulmonary edema, which may be immediately life-threatening.

uranium dioxide. For this reason, inhaled uranium tetrachloride tends not to behave as if it is a highly soluble uranium compound. Conversely, the more common insoluble salts and oxides (uranium tetrafluoride, uranium dioxide, uranium trioxide, triuranium octaoxide) are generally more toxic to the lungs through inhalation exposure because of the longer retention time in the lung tissue but they are less toxic to distal organs.

On the basis of the available data, the rabbit appears to be unusually susceptible to the lethal effects of uranium's metallotoxicity. The order of animal species susceptibility to acute uranium toxicity has been suggested as follows: rabbit > rat > guinea pig > pig > mouse (Orcutt 1949).

2.2.1.1 Death

The lethal effects of inhalation exposure to uranium have been investigated in humans in epidemiological studies and in animal studies under controlled conditions. Epidemiological studies indicate that routine exposure of humans (in the workplace and the environment at large) to airborne uranium is not associated with increased mortality. Brief accidental exposures to very high concentrations of uranium hexafluoride have caused fatalities in humans. Laboratory studies in animals indicate that inhalation exposure to certain uranium compounds can be fatal. These deaths are believed to result from renal failure caused by absorbed uranium. The low specific activity of uranium precludes the possibility of absorbing enough uranium to deliver a lethal dose of radiation.

No definitive evidence has been found in epidemiologic studies that links human deaths to uranium exposure. Among uranium miners, death rates from diseases of the cardiovascular system and the urogenital system were decreased compared to other populations. Uranium miners have higher-than-expected rates of death from lung cancer; however, this finding is attributed to the radiological effects of radon and its decay products, which are progeny of uranium and, therefore, present in uranium mines. In addition, the role of tobacco smoking in these deaths was not evaluated (Archer et al. 1973a; Gottlieb and Husen 1982; Lundin et al. 1969; Samet et al. 1984, 1986). Epidemiologic studies of workers at uranium mill and metal processing plants (where there is little or no exposure to radon in excess of normal environmental levels) showed no increase in overall deaths attributable to exposure to uranium (Archer et al. 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Cragle et al. 1988; Hadjimichael et al. 1983; Polednak and Frome 1981; Scott et al. 1972; Waxweiler et al. 1983).

Deaths occurred after accidental releases of uranium hexafluoride at uranium-processing facilities in 1944 and 1986, but these deaths were not attributed to the uranium component of this compound (Kathren and

Moore 1986; Moore and Kathren 1985; USNRC 1986). These releases resulted in the generation of concentrated aerosols of highly toxic hydrofluoric acid and uranyl fluoride[2]. In the 1944 incident exposure time was estimated to be only 17 seconds, deaths occurred in 2 of 20 workers within an hour and were attributed to severe chemical burns of the lungs. In the 1986 incident, 1 of 23 workers died from massive pulmonary edema, indicating that inhalation of hydrofluoric acid was responsible for death. Estimated airborne concentrations were 20 mg uranium hexafluoride/m^3 for a 1-minute exposure and 120 mg uranium hexafluoride/m^3 for a 60-minute exposure (15.2 and 91 mg U/m^3, respectively).

Mortality can be induced in animals exposed to sufficiently high concentrations of pure uranium compounds. The acute-duration LC_{50} (lethal concentration, 50% death) for uranium hexafluoride has been calculated for Long-Evans rats and Hartley guinea pigs (Leach et al. 1984). The animals were exposed to uranium hexafluoride in a nose-only exposure apparatus for periods of up to 10 minutes and then observed for 14 days. Total mortality in rats was 34% (157/460): 25% of the deaths occurred during exposure or within 48 hours, 59% between days 3 and 7, and 17% between days 7 and 14. Guinea pigs were more sensitive than rats; total mortality was 46% (36/78), and 64% of deaths occurred within 48 hours. In guinea pigs, the LC_{50} was estimated as 35,011 mg U/m^3 for a 2-minute exposure limit. For a 5-minute inhalation exposure, the LC_{50} in Long-Evans rats was estimated as 26,098 mg U/m^3; the LC_{50} for a 10-minute inhalation was estimated as 8,114 mg U/m^3. The animals that died showed some damage to the respiratory tract, probably due to hydrofluoric acid, but this damage was not judged to be the cause of death, at least in the animals that died more than 2 days postexposure. Urinalysis and histopathological examination indicated that renal injury was the primary cause of death (Leach et al. 1984). In other acute lethality studies, rats, mice, and guinea pigs suffered 10, 20, and 13% mortality, respectively, following a 10-minute inhalation of uranium hexafluoride corresponding to 637 mg U/m^3 (Spiegl 1949).

In intermediate-duration studies, rabbits and cats were generally the most sensitive species to uranium lethality. Deaths in these studies generally occurred beginning 2 weeks after exposure started and continued to the end of the experiment. Exposure to 2 mg U/m^3 (as uranium hexafluoride) 6 hours a day for 30 days caused 5, 20, and 80% mortality in guinea pigs, dogs, and rabbits, respectively (Spiegl 1949). An exposure to 9.5 mg U/m^3 (as uranyl nitrate hexahydrate) for 8 hours per day, 5 days per week for 30 days caused 10% mortality in rats and guinea pigs, and 75% mortality in dogs. Exposure to 2 mg U/m^3 killed all four cats tested (Roberts 1949). Exposure to 9.2 mg U/m^3 (as uranyl fluoride) 6 hours a day, 5.5 days a week for 5 weeks caused 0%, 100%, 83%, and 55% mortality in rats, mice, rabbits and guinea pigs, and deaths in two dogs and two cats tested at this concentration (Rothstein

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[2] Uranium hexafluoride rapidly dissociates into hydrofluoric acid and uranyl fluoride on contact with moisture in the air.

1949a). The lowest exposure causing death with uranyl fluoride was 0.15 mg U/m^3 in mice and rabbits and 2.2 mg U/m^3 in guinea pigs. Exposure to 15.4 mg U/m^3 (as uranium peroxide) 5 hours a day, 5 days a week for 23 days caused 10, 63, 40, 80, and 100% mortality in rats, mice, guinea pigs, rabbits, and cats, respectively, while 9.2 mg U/m^3 killed all the dogs tested (Dygert 1949d). Inhalation of air containing 15 mg U/m^3 (as sodium diuranate) for 6 hours a day, 5.5 days a week for 5 weeks caused 13 and 28% mortality in guinea pigs and rabbits, respectively (Rothstein 1949d).

Insoluble uranium compounds were also lethal to animals by the inhalation route, but at higher concentrations than with soluble compounds. Exposure to 15.8 mg U/m^3 (as uranium trioxide) 6 hours a day, 5.5 days a week for 4 weeks caused 10, 9, 17, and 67% mortality in rats, guinea pigs, dogs, and rabbits, respectively (Rothstein 1949c). Inhalation of air containing 19.4 mg U/m^3 (as uranium dioxide) for 6 hours a day, 5.5 days a week for 5 weeks, caused 60% mortality in rabbits but no mortality in rats, mice, guinea pigs, or dogs (Rothstein 1949b). Inhalation of air containing 18 mg U/m^3 (as uranium tetrafluoride) for 5 hours a day for 30 days caused 15, 32, 33, and 100% mortality in guinea pigs, rats, rabbits, and cats, respectively, and death in a single dog tested at this concentration. Inhalation at 4 mg U/m^3 caused no deaths in a group of 18 dogs, and one death in a group of 30 rats (Dygert 1949a). A mortality of 4% was observed among rabbits given 3 mg U/m^3 (Stokinger et al. 1953). Exposure to 6.8 mg U/m^3 (as ammonium diuranate) 6 hours a day for 30 days caused 20 and 100% mortality in guinea pigs and rabbits, respectively (Dygert 1949b).

In chronic-duration experiments, inhalation of 2 mg U/m^3 as uranyl nitrate hexahydrate for 6 hours a day, 5.5 days a week for 92–100 weeks resulted in 1% mortality in rats (Stokinger et al. 1953). This is not an unusual mortality rate for rats, so it is unlikely that these deaths can be attributed to uranium exposure. Dogs exposed to uranyl nitrate hexahydrate for 2 years suffered 4% mortality (Stokinger et al. 1953). One dog died at 0.25 mg U/m^3, and another at 2 mg U/m^3 out of 25 exposed dogs. Death may or may not have been attributable to uranium, according to the study investigator.

In several other inhalation-exposure animal studies, no deaths were observed when either soluble or insoluble uranium compounds were administered. In one of these animal studies, no mortality was observed in monkeys exposed by inhalation to uranium dioxide dust at a concentration of 5 mg U/m^3 for 5 years. The death of Beagle dogs similarly exposed could not be attributed to uranium by the investigators (Leach et al. 1970).

The percent mortality values for each species and other LOAEL values for mortality from exposure to uranium by the inhalation route are presented in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

No human studies were located regarding the cardiovascular, musculoskeletal, endocrine, metabolic, dermal, ocular, body weight, or other systemic effects of elemental uranium following acute-duration inhalation exposure. Nor were any human studies located regarding the respiratory, hematological, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, metabolic, dermal, ocular, body weight, or other systemic effects of uranium following intermediate-duration inhalation exposure. No studies were found regarding the cardiovascular, gastrointestinal, musculoskeletal, renal, endocrine, metabolic, dermal, ocular, body weight, or other systemic effects in humans following chronic-duration inhalation exposure. The existing human data on the respiratory and hepatic effects of uranium are limited to acute- and chronic-duration inhalation exposures, hematological effects are limited to chronic-duration inhalation exposure, and gastrointestinal and renal effects are limited to acute-duration inhalation exposure.

No animal studies were located regarding the endocrine, metabolic, dermal, or ocular effects of uranium in animals following acute-duration inhalation exposures to uranium. Nor were any studies located regarding the metabolic, dermal, ocular, or other systemic effects in animals following intermediate-duration inhalation exposure to uranium. There are animal data for acute-, intermediate-, and chronic-duration inhalation exposures to uranium for respiratory, hematological, cardiovascular, gastrointestinal, renal, or body weight effects. However, animal data on hepatic effects are limited to acute- and chronic-duration inhalation exposures to uranium.

The highest NOAEL values and all reliable LOAEL values in each species and duration category for systemic effects from chemical exposure to uranium by the inhalation route are presented in Table 2-1 and plotted in Figure 2-1. The radiation effect level values in each species and duration category for systemic effects from radiation exposure to uranium by the inhalation route are presented in Table 2-2 and plotted in Figure 2-2.

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation

Key to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Long-Evans)	10 min				630 M (1/10 died)	Leach et al. 1984 *** UF6
2	Rat (Long-Evans)	5 min				6470 M (1/10 died on day 7 postexposure)	Leach et al. 1984 *** UF6
3	Rat (NS)	1 d 10 min				637 (10% mortality 30 days post-exposure)	Spiegl 1949 UF6
4	Mouse (NS)	1 d 10 min				637 (20% mortality 30 days post-exposure)	Spiegl 1949 UF6
5	Gn Pig (Hartley)	2 min				23040 M (2/6 died 48 hrs postexposure)	Leach et al. 1984 *** UF6
6	Gn Pig (NS)	1 d 10 min				637 (13% mortality 30 days post-exposure)	Spiegl 1949 UF6
Systemic							
7	Rat (Long-Evans)	10 min	Renal		426 M (proteinuria, glucosuria, and polyuria)		Leach et al. 1984 *** UF6
8	Rat (Long-Evans)	2 min	Renal	920 M	1430 M (proteinuria)		Leach et al. 1984 *** UF6
9	Rat (Long-Evans)	5 min	Resp	9131		54503 M (severe nasal congestion, hemorrhage)	Leach et al. 1984 *** UF6
			Renal		392 M (glucosuria)		

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation   (continued)

Key to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
10	Rat (NS)	1 d 10 min	Resp			637 (gasping in 100% of rats; severe irritation of nasal passages)	Spiegl 1949 UF6
			Renal			637 (severe degeneration of renal cortical tubules 5-8 days post-exposure)	
			Ocular		637 (conjunctivitis)		
11	Mouse (NS)	1 d 10 min	Resp			637 (gasping in 100% of mice; severe irritation of nasal passages)	Spiegl 1949 UF6
			Ocular		637 (conjunctivitis)		
12	Gn Pig (Hartley)	2 min	Renal		23040 M (glucosuria and polyuria)		Leach et al. 1984 *** UF6
13	Dog [Beagle]	once 0.5-1 hr	Resp	270			Morrow et al. 1982 *** UO2F2
			Renal			250 (extensive degeneration in kidney cortex and tubules)	
Immunological/Lymphoreticular							
14	Rat (Fischer-344)	once			44 M (increased macrophage activity)		Morris et al. 1989 *** UO2
15	Rat (Fischer-344)	once			132 M (increased macrophage activity)		Morris et al. 1992 *** UO2

INTERMEDIATE EXPOSURE

Death

| 16 | Rat (NS) | 30 d 6 hr/d | | | | 4 (3% mortality) | Dygert 1949a UF4 |

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL		Reference Chemical Form
					Less serious mg U/m3	Serious mg U/m3	
17	Rat (NS)	23 d 5 d/wk 5 hr/d				15.4 (10% mortality)	Dygert 1949d UO4
18	Rat (NS)	30 d Cont.				9.5 (10% mortality)	Roberts 1949 UO2(NO3)2*6H2O
19	Rat (NS)	4 wk 6 d/wk 6 hr/d				15.8 (10% mortality)	Rothstein 1949c UO3
20	Mouse (NS)	23 d 5 d/wk 5 hr/d				15.4 (63% mortality)	Dygert 1949d UO4
21	Gn Pig (NS)	30 6 hr/d				18 (15% mortality)	Dygert 1949a UF4
22	Gn Pig (NS)	30 d 6 hr/d				6.8 (20% mortality)	Dygert 1949b (NH4)2U2O7
23	Gn Pig (NS)	23 d 5 d/wk 5 hr/d				15.4 (40% mortality)	Dygert 1949d UO4
24	Gn Pig (NS)	30 d Cont.				9.5 (10% mortality)	Roberts 1949 UO2(NO3)2*6H2O
25	Gn Pig (NS)	5 wk 6 d/wk 6 hr/d				2.2 (3% mortality)	Rothstein 1949a UO2F2
26	Gn Pig (NS)	4 wk 6 d/wk 6 hr/d				15.8 (9% mortality)	Rothstein 1949c UO3

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL		Reference Chemical Form
					Less serious mg U/m3	Serious mg U/m3	
27	Gn Pig (NS)	5 wk 5.5 d/wk 6 hr/d				15 (13% mortality)	Rothstein 1949d Na2U2O7
28	Gn Pig (NS)	30 d 6 hr/d				2 (5% mortality)	Spiegl 1949 UF6
29	Dog (NS)	30 d 6 hr/d				18 (lethal dose)	Dygert 1949a UF4
30	Dog (NS)	30 d Cont.				9.5 (75% mortality)	Roberts 1949 UO2(NO3)2*6H2O
31	Dog (NS)	5 wk 6 d/wk 6 hr/d				9.2 (100% mortality)	Rothstein 1949a UO2F2
32	Dog (NS)	4 wk 6 d/wk 6 hr/d				15.8 (17% mortality)	Rothstein 1949c UO3
33	Dog (NS)	30 d 6 hr/d				2 (20% mortality)	Spiegl 1949 UF6
34	Rabbit (NS)	30 d 6 hr/d				18 (33% mortality)	Dygert 1949a UF4
35	Rabbit (NS)	30 d 6 hr/d				6.8 (100% mortality)	Dygert 1949b (NH4)2U2O7
36	Rabbit (NS)	23 d 5 hr/d 5 d/wk				15.4 (80% mortality)	Dygert 1949d UO4
37	Rabbit (NS)	5 wk 6 d/wk				19.4 (60% mortality)	Rothstein 1949b UO2

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
38	Rabbit (NS)	4 wk 6 d/wk 6 hr/d					15.8	(67% mortality)	Rothstein 1949c UO3
39	Rabbit (NS)	5 wk 5.5 d/wk 6 hr/d					15	(28% mortality)	Rothstein 1949d Na2U2O7
40	Rabbit (NS)	30 d 6 hr/d					2	(80% mortality)	Spiegl 1949 UF6
41	Rabbit	34 wk 5.5 d/wk 6 hr/d					3	(4% mortality)	Stokinger et al. 1953 UF4
42	Cat (NS)	30 d 6 hr/d					18	(100% mortality)	Dygert 1949a UF4
43	Cat (NS)	23 d 5 d/wk 5 hr/d					15.4	(100% mortality)	Dygert 1949d UO4
44	Cat (NS)	30 d Cont.					2	(100% mortality)	Roberts 1949 UO2(NO3)2*6H2O

Systemic

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
45	Rat (NS)	30 d 6 hr/d	Gastro		0.4	(ulceration of cecum)			Dygert 1949a UF4
			Hemato	18					
			Hepatic		0.4	(focal necrosis of liver)			
			Renal	4	18	(slight azotemia)			
			Bd Wt	4			18	(26% decrease body weight)	

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation   (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL		Reference Chemical Form
					Less serious mg U/m3	Serious mg U/m3	
46	Rat (NS)	30 d 6 hr/d	Resp		6.8 (intersitial bronchopneumonia in 25% of animals; nasal irritation)		Dygert 1949b (NH4)2U2O7
			Hemato		6.8 (decreased RBC, hemoglobin)		
			Renal		6.8 (minimal necrosis of tubular epithelium followed by regeneration)		
			Bd Wt	6.8			
47	Rat (NS)	26 d 4-6 hr/d	Resp	4.8			Dygert 1949c U3O8
			Cardio	4.8			
			Hemato	4.8			
			Hepatic	4.8			
			Renal		4.8 (renal degeneration indicated by moderate regeneration)		
			Bd Wt	4.8			
48	Rat (NS)	30 d Cont.	Hemato	2.1	9.5 (decreased RBC, hemoglobin)		Roberts 1949 UO2(NO3)2*6H2O
			Renal		0.13 (slight renal tubular degeneration in 33% after 28 days exposure)		
			Bd Wt	2.1	9.5 (5.6-12.6% decreased body weight)		
49	Rat (NS)	5 wk 6 d/wk 6 hr/d	Hemato	9.2			Rothstein 1949a UO2F2
			Renal	0.5	2.2 (minimal renal tubular degeneration)		
			Bd Wt	2.2	9.2 (unspecified moderate weight loss)		

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation   (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL				Reference Chemical Form
					Less serious mg U/m3		Serious mg U/m3		
50	Rat (NS)	4 wk 6 d/wk 6 hr/d	Resp		16	(very slight degenerative changes in the lungs)			Rothstein 1949c UO3
			Hemato		16	(increased percentage of myeloblasts and lymphoid cells of bone marrow)			
			Hepatic	16					
			Renal	16					
			Bd Wt	16					
51	Rat (NS)	5 wk 5.5 d/wk 6 hr/d	Hemato	15					Rothstein 1949d Na2U2O7
			Renal		15	(moderate renal degeneration and necrosis)			
52	Rat (NS)	30 d 6 hr/d	Resp	2			13	(pulmonary edema, hemorrhage, emphysema; inflammation of bronchi, alveoli and alveolar interstices)	Spiegl 1949 UF6
			Hemato	13					
			Ocular	2	13	(eye irritation)			
			Bd Wt	13					
53	Rat (NS)	30 d 6 hr/d	Hemato	0.2					Spiegl 1949 UF6
			Renal	0.2					
			Bd Wt	0.2					

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL				Reference Chemical Form
					Less serious mg U/m3		Serious mg U/m3		
54	Mouse (NS)	30 d 4.4-6 hr/d	Resp	2.9					Pozzani 1949 Carnotite U ore
			Hepatic	2.9					
			Renal		2.9	(slight renal tubular degeneration)			
			Bd Wt	2.9					
55	Mouse (NS)	5 wk 6 d/wk	Resp	19.4					Rothstein 1949b UO2
			Hemato	19.4					
			Renal	19.4					
			Bd Wt	19.4					
56	Mouse (NS)	30 d 6 hr/d	Resp	2			13	(lung edema, hemorrhage, and emphysema; inflammation of bronchi, alveoli, and alveolar interstitices)	Spiegl 1949 UF6
			Renal	2			13	(severe renal-tubular degeneration followed by regeneration, and necrosis, and the presence of casts in the tubules)	
			Ocular	2	13	(eye irritation)			
			Bd Wt	2	13	(unspecified weight loss)			
57	Gn Pig (NS)	30 d 6 hr/d	Hemato	18					Dygert 1949a UF4
			Renal	4			18	(moderate to severe necrosis of corticomedullary tubular epithelium)	

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL				Reference Chemical Form
					Less serious mg U/m3		Serious mg U/m3		
58	Gn Pig (NS)	30 d 4.4-6 hr/d	Resp	2.9					Pozzani 1949 Carnotite U ore
			Hepatic	2.9					
			Renal	0.8	2.9	(micoscopic focal lesions in renal tubular epithelium in 1/5 guinea pigs)			
			Bd Wt	2.9	22	(14% decreased body weight in animals that died)			
59	Gn Pig (NS)	30 d Cont.	Bd Wt	2.1			9.5	(2.9-27.9% decreased body weight)	Roberts 1949 UO2(NO3)2*6H2O
60	Gn Pig (NS)	5 wk 6 d/wk 6 hr/d	Renal	2.2			9.2	(severe degeneration of renal tubular epithelium)	Rothstein 1949a UO2F2
			Bd Wt		2.2	(unspecified moderate weight loss)			
61	Gn Pig (NS)	30 d 6 hr/d	Resp	2			13	(lung edema, hemorrhage, and emphysema, acute inflammation was seen in the bronchi, alveoli, and alveolar interstitices)	Spiegl 1949 UF6
			Renal	2			13	(severe renal-tubular degeneration, necrosis, regeneration; casts in the tubules)	
			Bd Wt	2	13	(13% decreased body weight)			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		Serious mg U/m3		Reference Chemical Form
62	Gn Pig (NS)	30 d 6 hr/d	Resp	2			13	(lung edema, hemorrhage, and emphysema, acute inflammation was seen in the bronchi, alveoli, and alveolar interstitices)	Spiegl 1949 UF6
			Renal	2			13	(severe renal-tubular degeneration, necrosis, regeneration; casts in the tubules)	
			Bd Wt	2	13	(13% decreased body weight)			
63	Gn pig	30 wk 5.5 d/wk 6 hr/d	Renal		0.2	(minimal microscopic lesions in tubular epithelium)			Stokinger et al. 1953 UCl4
64	Gn pig (NS)	28 wk 5.5 d/wk 6 hr/d	Renal	10					Stokinger et al. 1953 UO2
			Bd Wt	10					
65	Gn pig (NS)	26 wk 5.5 d/wk 6 hr/d	Hemato	2 M					Stokinger et al. 1953 UO2(NO3)2*6H2O
			Renal	2 M					
			Bd Wt	2 M					
66	Gn pig	34 wk 5.5 d/wk 6 hr/d	Hemato	3					Stokinger et al. 1953 UF4
			Renal		3	(minimal microscopic lesions in renal tubule)			
			Bd Wt	3					

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL		Reference Chemical Form
					Less serious mg U/m3	Serious mg U/m3	
67	Gn pig	36 wk 5.5d/wk 6 hr/d	Renal	0.2			Stokinger et al. 1953 UF6
			Bd Wt	0.2			
68	Dog (NS)	30 d 6 hr/d	Resp	4	18 (rhinitis)		Dygert 1949a UF4
			Gastro	4		18 (vomited blood)	
			Hemato	18			
			Renal	0.5	3 (very slight degenerative changes in tubular epithelium)		
			Ocular	4	18 (conjunctivitis)		
			Bd Wt	4		18 (26% decreased body weight)	
69	Dog (NS)	23 d 5 d/wk 5 hr/d	Hemato	15.4			Dygert 1949d UO4
			Bd Wt	15.4			
70	Dog (NS)	30 d 4.4-6 hr/d	Resp	0.8	2.9 (hemorrhagic lungs)		Pozzani 1949 Carnotite U ore
			Hemato	2.9			
			Hepatic	2.9			
			Renal		0.8 (mild renal tubular degeneration)		
			Bd Wt	2.9			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL				Reference Chemical Form
					Less serious mg U/m3		Serious mg U/m3		
71	Dog (NS)	30 d Cont.	Resp	2.1	9.5	(rales; slight degeneration in lung epithelium)			Roberts 1949 UO2(NO3)2*6H2O
			Gastro	2.1	9.5	(vomiting, anorexia)			
			Hemato		0.13	(slightly decreased fibrinogen)			
			Renal		0.13	(proteinuria, transient increase in bromosulfalein retention)			
			Bd Wt	2.1			9.5	(approximately 25% decreased body weight in 3/4 that died)	
			Other	2.1					
72	Dog (NS)	5 wk 6 d/wk 6 hr/d	Resp	2.2	9.2	(rhinitis)			Rothstein 1949a UO2F2
			Gastro	2.2			9.2	(vomited blood)	
			Hemato	9.2					
			Renal		0.15[b]	(very slight renal degeneration in approximately 50% of dogs)			
			Bd Wt	2.2			9.2	(unspecified severe weight loss)	
73	Dog (NS)	5 wk 6 d/wk	Resp	9.2					Rothstein 1949b UO2
			Hemato	9.2					
			Renal	1.1[c]	8.2	(slight renal tubular degeneration in 2/6)			
			Bd Wt	9.2					

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL				Reference Chemical Form
					Less serious mg U/m3		Serious mg U/m3		
74	Dog (NS)	4 wk 6 d/wk 6 hr/d	Resp		16	(very slight pulmonary degenerative changes)			Rothstein 1949c UO3
			Hemato	16					
			Hepatic	16					
			Renal		16	(mild degeneration in glomerulus; diuresis)			
			Bd Wt	16					
75	Rabbit (NS)	30 d 6 hr/d	Hemato	18					Dygert 1949a UF4
			Renal		0.4	(increased urinary catalase and phosphatase)			
			Bd Wt	3			18	(24% decreased body weight)	
76	Rabbit (NS)	30 d 6 hr/d	Resp				6.8	(pulmonary edema, hemorrhage, and necrosis)	Dygert 1949b (NH4)2U2O7
			Hemato		6.8	(increased neutrophils, decreased lymphocytes)			
			Renal				6.8	(severe necrosis of the tubular epithelium)	
77	Rabbit (NS)	23 d 5 d/wk 5 hr/d	Resp				15.4	(edematous alveoli, alveolar hemorrhage, hyperemia, and atelectasis)	Dygert 1949d UO4
			Hemato	15.4					
			Hepatic	15.4					
			Renal		15.4	(moderate corticomedullary tubule necrosis with regeneration of tubular cells; azotemia)			
			Bd Wt	15.4					

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
78	Rabbit (NS)	30 d 4.4-6 hr/d	Resp	2.9			22	(moderate to severe pulmonary lesions)	Pozzani 1949 Carnotite U ore
			Hemato	22					
			Hepatic	22					
			Renal	0.8	2.9	(moderate kidney tubular degeneration)			
			Bd Wt	2.9	22	(11% decreased body weight in dying rabbits)			
79	Rabbit (NS)	30 d Cont.	Resp	0.2					Roberts 1949 UO2(NO3)2*6H2O
			Hemato		0.13	(increased plasma prothrombin and fibrinogen)			
			Renal		0.13	(increased urinary catalase)			
			Bd Wt	0.13	0.2	(unspecified decrease in body weight)			
80	Rabbit (NS)	5 wk 6 d/wk	Resp	19.4					Rothstein 1949b UO2
			Hemato	19.4					
			Renal	9.2			19	(severe tubular necrosis in dying animals)	
			Bd Wt	8.2	9.2	(unspecified decreased body weight)			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL			Reference Chemical Form
					Less serious mg U/m3		Serious mg U/m3	
81	Rabbit (NS)	4 wk 6 d/wk 6 hr/d	Resp				16 (hemorrhage and consolidation in lungs of animals that died)	Rothstein 1949c UO3
			Hemato	16				
			Hepatic		16	(moderate fatty livers in 5/8 animals that died)		
			Renal		16	(mild to severe necrosis of the tubular epithelium with degeneration and regeneration; increased NPN)		
			Bd Wt	16				
82	Rabbit (NS)	5 wk 5.5 d/wk 6 hr/d	Hepatic		15	(slight decrease in lactate)		Rothstein 1949d Na2U2O7
			Renal		15	(progressive degeneration and necrosis followed by regeneration of tubular epithelium; increased NPN)		
			Bd Wt	15				
83	Rabbit (NS)	30 d 6 hr/d	Hemato	13				Spiegl 1949 UF6
			Bd Wt	0.2	2	(12% decreased body weight)		

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL		Reference Chemical Form
					Less serious mg U/m3	Serious mg U/m3	
84	Rabbit (NS)	26 wk 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 UO2(NO3)2*6H2O
			Hepatic	2			
			Renal		0.25 (increased urinary catalase; minimal microscopic lesions in renal tubule)		
			Bd Wt	2			
85	Rabbit	34 wk 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 UF4
			Renal		2 (minimal microscopic lesions in renal tubule)		
			Bd Wt	2			
86	Rabbit (NS)	30 wk 5.5 d/wk 6 hr/d	Hemato	1			Stokinger et al. 1953 UO2
			Renal		1 (minimal microscopic lesions in renal tubule)		
			Bd Wt	1			
87	Rabbit	36 wk 5.5 d/wk 6 hr/d	Hemato	0.25			Stokinger et al. 1953 UF6
			Renal		0.25 (minimal microscopic lesions in renal tubule)		
			Bd Wt	0.25			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation   (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
88	Cat (NS)	30 d 6 hr/d	Resp		18	(rhinitis)			Dygert 1949a UF4
			Gastro				18	(vomited blood)	
			Hemato	18					
			Renal				18	(moderate to severe typical renal injury in 2/3 dying cats; azotemia)	
			Ocular		18	(conjunctivitis)			
			Bd Wt		18	(18% decreased body weight)			
89	Cat (NS)	23 d 5 d/wk 5 hr/d	Hemato	15.4					Dygert 1949d UO4
			Renal				15.4	(azotemia)	
			Bd Wt	15.4					
90	Cat (NS)	5 wk 6 d/wk 6 hr/d	Resp	2.2	9.2	(rhinitis)			Rothstein 1949a UO2F2
			Gastro	2.2			9.2	(vomited blood prior to death)	
			Renal	2.2			9.2	(severe degeneration of renal tubular epithelium)	
91	Cat (NS)	4 wk 6 d/wk 6 hr/d	Hemato	16					Rothstein 1949c UO3
			Renal		16	(diuresis; proteinuria; increased NPN)			
			Bd Wt	16					
Immunological/Lymphoreticular									
92	Rat (NS)	30 d 6 hr/d			0.4	(edematous cecal lymph nodes; focal necrosis of spleen)			Dygert 1949a UF4

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation   (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL				Reference Chemical Form
					Less serious mg U/m3		Serious mg U/m3		
93	Rat (NS)	30 d 6 hr/d			6.8	(rise in neutrophils, decreased lymphocytes, moderate fall in the white blood count, rise in the eosinophils)			Dygert 1949b (NH4)2U2O7
94	Rat (NS)	30 d Cont.		2.1	9.5	(decreased absolute number of lymphocytes and neutrophils)			Roberts 1949 UO2(NO3)2*6H2O
Neurological									
95	Dog (NS)	30 d 6 hr/d		4	18	(weakness and unsteady gait)			Dygert 1949a UF4
96	Dog (NS)	5 wk 6 d/wk 6 hr/d		2.2			9.2	(anorexia, severe muscle weakness, lassitude)	Rothstein 1949a UO2F2
97	Cat (NS)	30 d 6 hr/d			18	(weakness and unsteady gait)			Dygert 1949a UF4
98	Cat (NS)	5 wk 6 d/wk 6 hr/d		2.2			9.2	(anorexia, severe muscle weakness, lassitude)	Rothstein 1949a UO2F2
CHRONIC EXPOSURE									
Death									
99	Rat (NS)	92-100 wk 5.5 d/wk 6 hr/d					2	(1% mortality)	Stokinger et al. 1953 UO2(NO3)2*6H2O
100	Dog (Beagle)	5 yr 5 d/wk 5.4 hr/d					5	(4.5% mortality)	Leach et al. 1970 UO2

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL		Reference Chemical Form
					Less serious mg U/m3	Serious mg U/m3	
101	Dog (NS)	2 yr 5.5 d/wk 6 hr/d				2 (9% mortality)	Stokinger et al. 1953 UO2(NO3)2*6H2O
Systemic							
102	Monkey	5 yr 5 d/wk 5.4 hr/d	Resp		5.1 (minimal pulmonary hyaline fibrosis)		Leach et al. 1970 UO2
			Hepatic	5.1			
			Renal	5.1			
			Bd Wt	5.1			
103	Monkey	1-5 yr 5 d/wk 5.4 hr/d	Resp		5.1 (minimal pulmonary fibrosis)		Leach et al. 1973 UO2
			Hemato	5.1			
			Hepatic	5.1			
			Renal	5.1			
			Bd Wt	5.1			
104	Rat (NS)	1 yr 5.5 d/wk 6 hr/d	Resp	0.2			Stokinger et al. 1953 UCl4
			Gastro	0.2			
			Hepatic	0.2			
			Renal		0.2 (minimal microscopic lesions in renal tubule)		
			Endocr	0.2			
			Bd Wt	0.2			
105	Rat (NS)	1 yr 5.5 d/wk 6 hr/d	Renal	0.15	0.25 (mild renal tubular atrophy)		Stokinger et al. 1953 UO2(NO3)2*6H2O
			Bd Wt	2			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
106	Rat (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	3			Stokinger et al. 1953 UF4
			Renal		0.5 (minimal microscopic lesions in renal tubule)		
			Bd Wt	3			
107	Rat	1 yr 5.5 d/wk 6 hr/d	Hemato	10			Stokinger et al. 1953 UO2
			Renal	1	10 (slight degenerative changes)		
			Bd Wt	10			
108	Rat (NS)	2 yr 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 UO2(NO3)2*6H2O
			Renal		2 (mild, acute tubular necrosis and regeneration)		
			Bd Wt	2			
109	Rat (NS)	1 yr 5.5 d/wk 6 hr/d	Resp	0.2			Stokinger et al. 1953 UF6
			Cardio	0.2			
			Gastro	0.2			
			Hepatic	0.2			
			Renal	0.05	0.2 (mild renal tubular degeneration)		
			Endocr	0.2			
			Dermal	0.2			
			Bd Wt	0.2			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL		Reference Chemical Form
					Less serious mg U/m3	Serious mg U/m3	
110	Dog (Beagle)	1-5 yrs 5 d/wk 5.4 hr/d	Resp	5.1			Leach et al. 1970 UO2
			Hemato	5.1			
			Renal	5.1			
			Bd Wt	5.1			
111	Dog (NS)	1-5 yr 5 d/wk 5.4 hr/d	Resp		5.1 (minimal pulmonary fibrosis)		Leach et al. 1973 UO2
			Hemato	5.1			
			Renal	5.1			
			Bd Wt	5.1			
112	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	0.2			Stokinger et al. 1953 UCl4
			Hepatic	0.2			
			Renal	0.05[d]	0.2 (minimal microscopic lesions in renal tubule)		
			Bd Wt	0.2			
113	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 UO2(NO3)2*6H2O
			Hepatic	2			
			Renal	0.15	0.25 (minimal microscopic lesions in renal tubule; transient increase in NPN)		
			Bd Wt	2			
114	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Renal	0.15	0.25 (minimal degeneration in renal tubule)		Stokinger et al. 1953 UO2(NO3)2*6H2O

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL				Reference Chemical Form
					Less serious mg U/m3		Serious mg U/m3		
115	Dog (NS)	2 yr 5.5 d/wk 6 hr/d	Hemato	2					Stokinger et al. 1953 UO2(NO3)2*6H2O
			Renal		2	(mild tubular necrosis)			
116	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	0.05	0.2	(lengthened blood clotting time; decreased blood fibrinogen)			Stokinger et al. 1953 UF6
			Hepatic		0.2	(increased bromosulfalein retention)			
			Renal		0.05	(minimal microscopic lesions in renal tubule)			
			Bd Wt	0.2					
117	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	2					Stokinger et al. 1953 UO2(NO3)2*6H2O
			Hepatic	2					
			Renal	0.15	0.25	(minimal microscopic lesions in renal tubule; transient increase in NPN)			
			Bd Wt	2					
Immunological/Lymphoreticular									
118	Dog (Beagle)	5 yr 5 d/wk 5.4 hr/d			5.1	(minimal lymph node fibrosis)			Leach et al. 1970 UO2

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL		Reference Chemical Form
					Less serious mg U/m3	Serious mg U/m3	
Cancer							
119	Dog (NS)	1-5 yr 5 d/wk 5.4 hr/d				5.1 (CEL: lung cancer)	Leach et al. 1973 UO2

[a]The number corresponds to entries in Figure 2-1.

[b] Used to derive an intermediate-duration inhalation MRL for soluble uranium compounds of 0.0004 mg/m^3: concentration adjusted from intermittent to continuous exposure and divided by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

[c]Used to derive an intermediate-duration inhalation MRL for insoluble uranium compounds of 0.008 mg/m^3: concentration adjusted from intermittent to continuous exposure and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans, and 10 for human variability).

[d] Used to derive a chronic-duration inhalation MRL for soluble uranium compounds of 0.0003 mg/m^3: concentration adjusted from intermittent to continuous exposure and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

*** Enriched uranium; natural and depleted uranium are without asterisks.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; Cont. = continuous; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LC$_{50}$ = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observable-adverse-effect level; NPN = nonprotein nitrogen; NS = not specified; RBC = red blood cell; Resp = respiratory; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation
Chemical Toxicity - Acute (≤14 days)

Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)
Chemical Toxicity - Intermediate (15-364 days)

Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Intermediate (15-364 days)

Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Intermediate (15-364 days)

Systemic

(mg/m^3)

Hematological

Hepatic

Key
k monkey
r rat
m mouse
g guinea pig
d dog
h rabbit
c cat

● LOAEL for serious effects (animals)

◑ LOAEL for less serious effects (animals)

○ NOAEL (animals)

◆ CEL: cancer effect level (animals)

▲ LOAEL for less serious effects (humans)

△ NOAEL (humans)

Minimal risk level for effects other than cancer

The number next to each point corresponds to entries in Table 2-1.

* 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 end point.

Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Intermediate (15-364 days)

Systemic

Renal

(mg/m³)

100000

10000

1000

100

10

1

0.1

0.01

0.001

0.0001

0.00001

0.000001

0.0000001

45r 46r 47r 50r 51r 55m 56m 57g 60g 61g 62g 64g 65g 66g 68d 73d 74d 76h 77h 78h 80h 81h 82h 85h 86h 88c 89c 90c 91c
45r 48r 49r 53r 54m 56m 57g 58g 60g 61g 62g 63g 67g 68d 70d 71d 72d 73d 75h 78h 79h 84h 87h 90c
49r

Key		
k monkey	● LOAEL for serious effects (animals)	┃ Minimal risk level for effects other than cancer
r rat	◐ LOAEL for less serious effects (animals)	
m mouse	○ NOAEL (animals)	
g guinea pig	◆ CEL: cancer effect level (animals)	The number next to each point corresponds to entries in Table 2-1.
d dog	▲ LOAEL for less serious effects (humans)	
h rabbit	△ NOAEL (humans)	
c cat		

* 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 end point.

Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)
Chemical Toxicity - Intermediate (15-364 days)

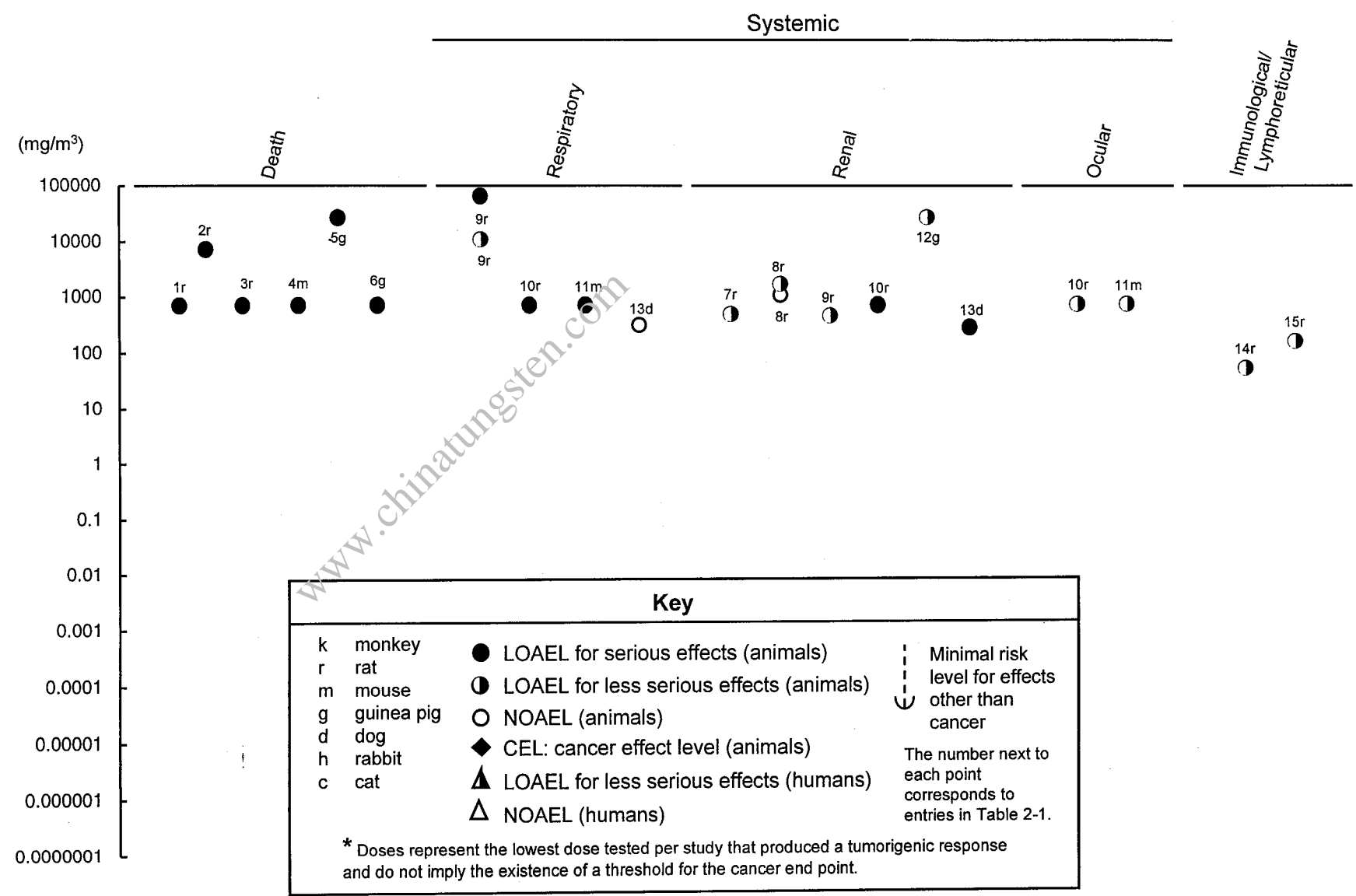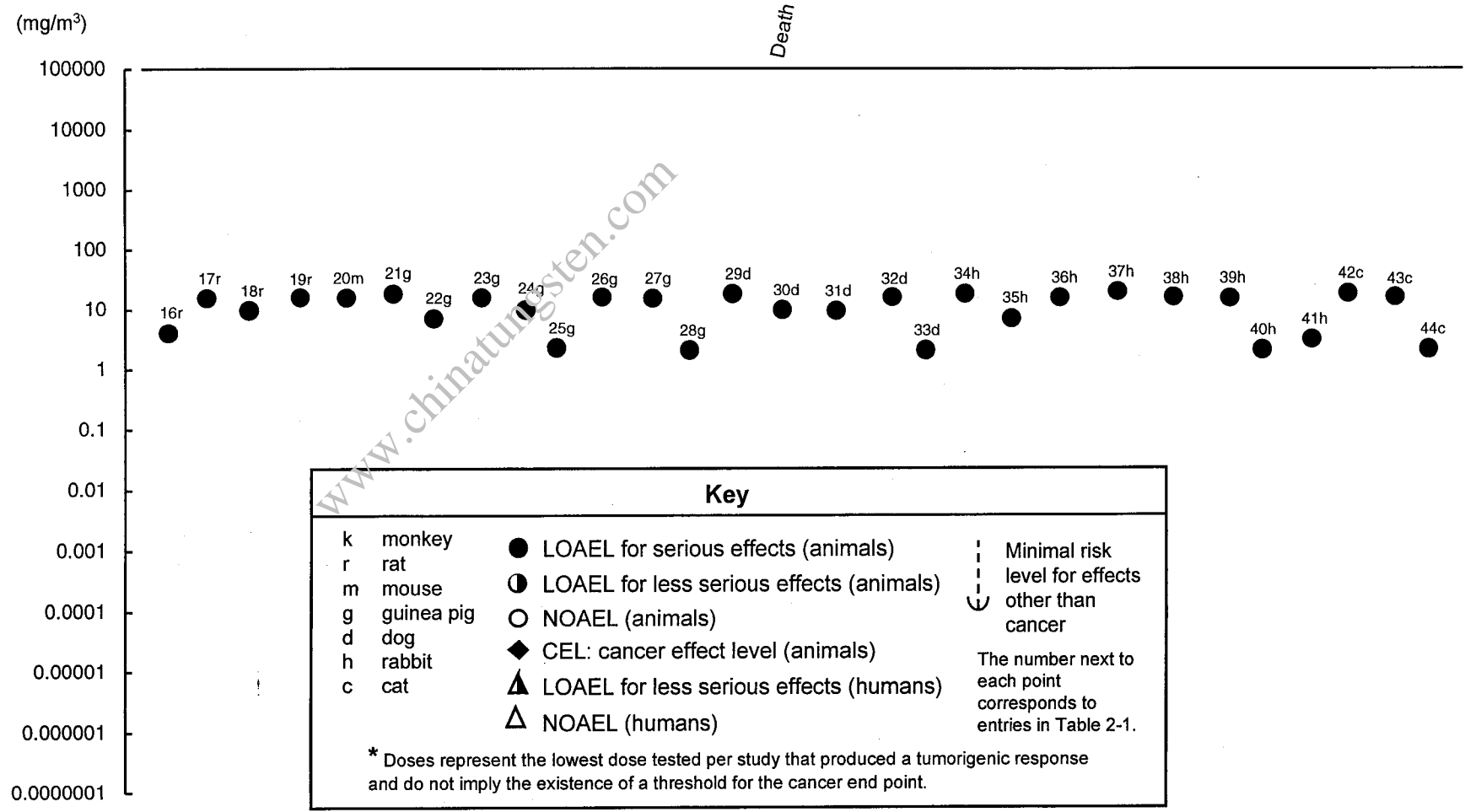# Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Intermediate (15-364 days)

Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Chronic (≥365 days)

Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)
Chemical Toxicity - Chronic (≥365 days)
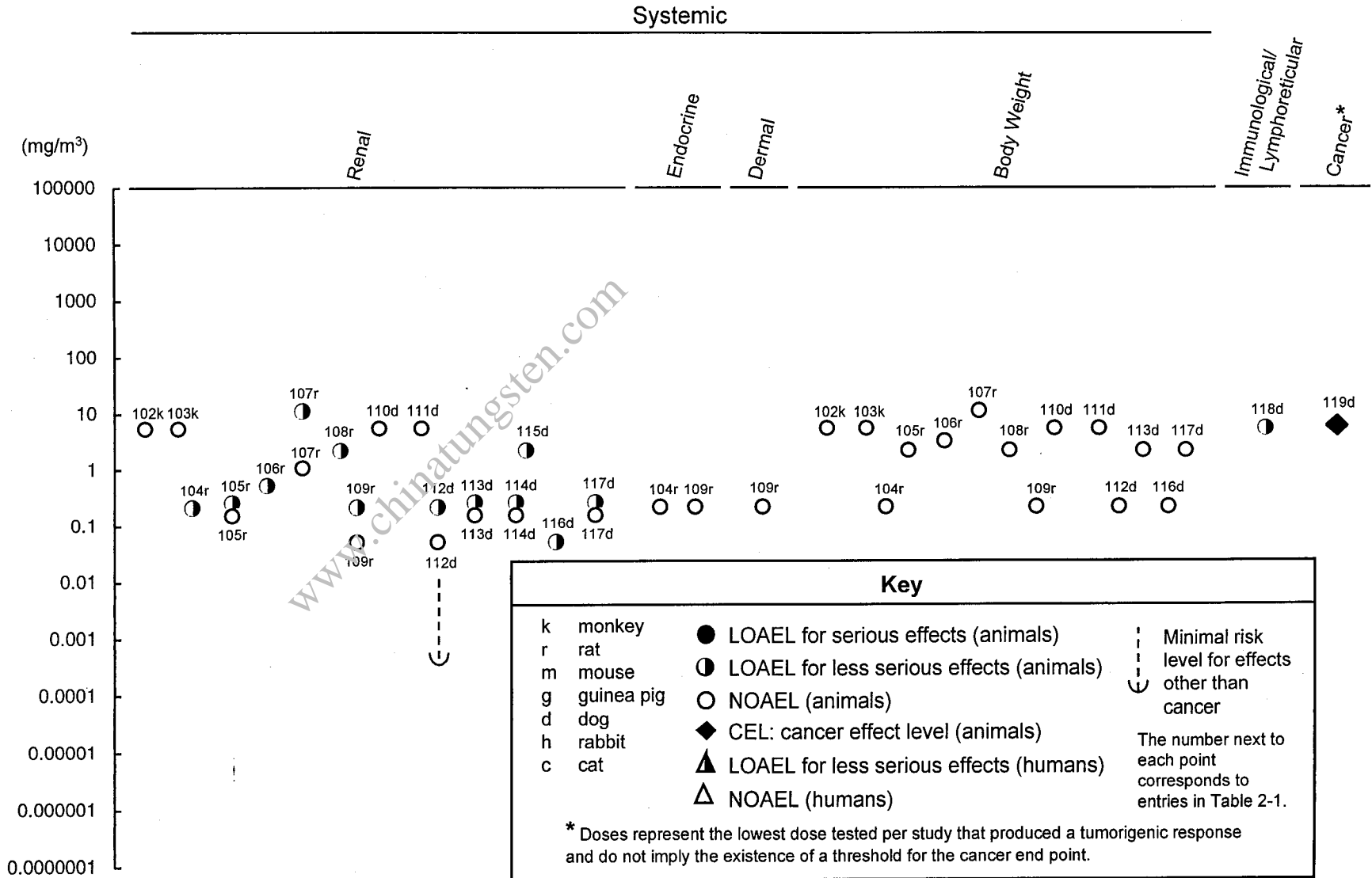
Table 2-2. Levels of Significant Exposure to Uranium - Radiation Toxicity - Inhalation

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (nCi/m3)	LOAEL		Reference Chemical Form
					Less serious (nCi/m3)	Serious (nCi/m3)	
ACUTE EXPOSURE							
Systemic							
1	Rat (Fischer-344)	once 100 min	Resp			5051 M (severe alveolar fibrosis) ***	Morris et al. 1990 UO2
CHRONIC EXPOSURE							
Cancer							
2	Human	occup				20 rad M (CEL: lung cancer)	Cookfair et al. 1983 *** Uranium dust

[a] The number corresponds to entries in Figure 2-2.

*** Enriched uranium; natural and depleted uranium are without asterisks.

CEL = cancer effect level; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); NOAEL = no-observable-adverse-effect level; occup = occupational; Resp = respiratory

Figure 2-2. Levels of Significant Exposure to Uranium - Inhalation

Radiation Toxicity - Acute (≤14 days) and Chronic (≥365 days)
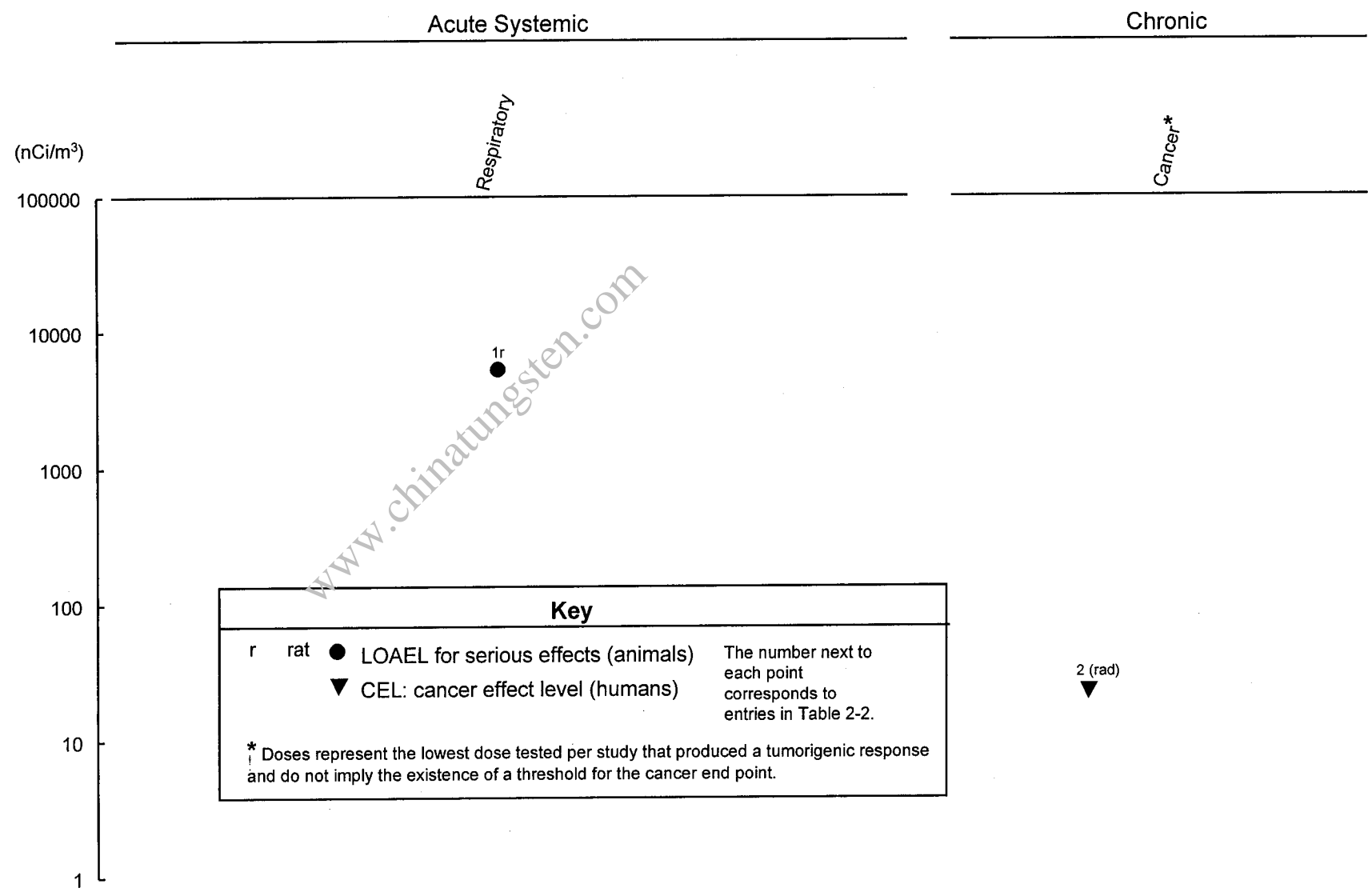
Respiratory Effects.   The hazard from inhaled uranium aerosols, or from any noxious agent, is the likelihood that the agent will reach the site of its toxic action. Two of the main factors that influence the degree of hazard from toxic airborne particles are 1) the site of deposition in the respiratory tract of the particles and 2) the fate of the particles within the lungs. The deposition site within the lungs depends mainly on the particle size of the inhaled aerosol, while the subsequent fate of the particle depends mainly on the physical and chemical properties of the inhaled particles and the physiological status of the lungs.

Small particles (about 2 micrometers [µm] or smaller in diameter) tend to be deposited in the alveoli. The alveoli, frequently called the "deep respiratory tract," form the functional part of the lungs where gas exchange occurs. As the particle size increases, progressively fewer particles penetrate into the deep respiratory tract, and increasingly greater fractions of the inhaled particles are deposited in the upper respiratory tract. The respiratory tract is a system of ducts that starts at the nares and includes the pharynx, larynx, trachea, and a complex series of bronchi and bronchioles that terminate in several thousand alveoli. Three different mechanisms are involved in the removal of particles from the respiratory tract. The first is mucociliary action in the upper respiratory tract (trachea, bronchi, bronchioles, and terminal bronchioles), which sweeps particles deposited there into the throat, where they are either swallowed into the gastrointestinal tract or spat out. The two other clearance mechanisms, dissolution (which leads to absorption into the bloodstream) and phagocytosis (removal by specialized cells in the process), deal mainly with the particles deposited in the deep respiratory tract (respiratory bronchioles, alveolar ducts, and alveolar sacs) (ICRP 1994; NCRP 1997). The less soluble uranium particles may remain in the lungs and in the regional lymph nodes for weeks (uranium trioxide, uranium tetrafluoride, uranium tetrachloride) to years (uranium dioxide, triuranium octaoxide).

In acute exposures, respiratory disease may be limited to interstitial inflammation of the alveolar epithelium, leading eventually to emphysema or pulmonary fibrosis (Cooper et al. 1982; Dungworth 1989; Stokinger 1981; Wedeen 1992). In studies of the pulmonary effects of airborne uranium dust in uranium miners and in animals, the respiratory diseases reported are probably aggravated by the inhalable dust particles' (the form in which uranium is inhaled) toxicity because most of the respiratory diseases reported in these studies are consistent with the effects of inhaled dust (Dockery et al. 1993). In some of these instances, additional data from the studies show that the workers were exposed to even more potent respiratory tract irritants, such as silica and vanadium pentaoxide (Waxweiler et al. 1983).

The effects of massive acute exposures to uranium in humans, as well as epidemiologic or clinical studies of uranium mine workers chronically exposed to mine atmospheres (containing other noxious agents that include silica, diesel fumes, cigarette smoke, and radon and its daughters), have been investigated. Several epidemiologic studies have reported respiratory diseases in uranium mine and mill workers, who are also exposed to significant amounts of dust and other pulmonary irritants, but not in uranium-processing workers, who are not exposed to these potential aggravants.

Accidental exposure of workers to estimated airborne concentrations of 20 mg uranium hexafluoride/m^3 for a 1-minute exposure and 120 mg uranium hexafluoride/m^3 for a 60-minute exposure (15.2 and 91 mg U/m^3, respectively) resulted in acute respiratory irritation, which is attributed to the hydrofluoric acid decomposition product. One worker died of pulmonary edema a few hours after the accident (Fisher et al. 1990; USNRC 1986). In another report, 20 men who were seriously injured following accidental exposure to a stream of uranium hexafluoride when a transportation cask ruptured showed signs of pulmonary edema, which also was attributed to hydrofluoric acid. After 3 weeks, most had normal clinical findings and were considered to be in excellent health. A follow-up examination 38 years later on three of the injured workers showed no detectable uranium deposition and no respiratory findings attributable to the exposure (Kathren and Moore 1986). No clinical signs of pulmonary toxicity were found in about 100 uranium-processing workers exposed to insoluble uranium dust at levels of 0.5–2.5 mg U/m^3 for about 5 years (Eisenbud and Quigley 1955). Other reports of workers in the uranium processing industry did not show increased deaths due to diseases of the respiratory system related to exposure to uranium (Brown and Bloom 1987; Cragle et al. 1988; Polednak and Frome 1981; Scott et al. 1972).

A 30-year follow-up study in which ionizing radiation hazard was assessed for a study cohort consisting of 995 workers in a uranium-processing facility that operated between 1943 and 1949 found statistically significant increases in death from all causes. Significantly increased mortality was observed for cancer of the larynx and for pneumonia, but not for lung cancer. The workers were exposed to internal radiation from the inhaled uranium dust, with an upper limit of 1,000 mSv. The data (external radiation badge) for the last 24 months of operation indicated that the highest cumulative external gamma dose for a worker was about 20 mSv. Long-term occupational exposure was evaluated in a subcohort that received 150 mSv/year or more. Because the workers were also exposed to radon-222 (^{222}Ra), chlorine, hydrofluoric acid, lead sulfate, nickel, nitric acid and nitrogen oxides, silicon dioxide, and sulfuric acid,

the etiology of the reported laryngeal disease is uncertain (Dupree et al. 1987). An increased incidence of deaths (Standard Mortality Ratio [SMR] =2.29) from obstructive pulmonary disease was found in 4,106 workers in a nuclear fuels fabrication plant who were employed for more than 6 months from 1956 to 1978 (Hadjimichael et al. 1983). However, the overall death rate and rate of all cancers combined were lower than expected. The association of disease with exposure to uranium was not confirmed.

The pulmonary toxicity of uranium compounds varies in animals. Reports of pulmonary toxicity in animals after acute-duration exposure to uranium are limited to experiments with uranium hexafluoride. Gasping and severe irritation to the nasal passages were reported after 10 minute exposures at 637 mg U/mg^3 in rats and mice (Spiegl 1949) and nasal hemorrhage in rats after a 5 minute exposure to 54,503 mg/m^3 (Leach et al. 1984). Uranium hexafluoride promptly hydrolyzes on contact with water to uranyl fluoride and hydrofluoric acid. Thus, the animals were potentially exposed to hydrofluoric acid, a potent toxicant to respiratory tract epithelium, which probably contributed to pulmonary tissue destruction (Leach et al. 1984; Spiegl 1949; Stokinger et al. 1953). In addition, exposure to fluoride ions can result in hypocalcemia, hypomagnesemia, pulmonary edema, metabolic acidosis, ventricular arrhythmia, and death (Meditext 1998).

Intermediate-duration exposure to uranium compounds also caused pulmonary toxicity, particularly when exposure was to uranium hexafluoride. Exposure of rats, mice, and guinea pigs to this compound for 6 hours/day for 30 days at 13 mg U/m^3 resulted in pulmonary edema, hemorrhage, emphysema, and inflammation of the bronchi and alveoli (Spiegl 1949). Milder effects were observed with other uranium compounds in a series of experiments where exposure conditions were similar to those found in the workplace (i.e., 5–6 hours/day, 5–6 days/week). For example, rhinitis was observed in cats and dogs after 30 days exposure to 18 mg U/m^3 as uranium tetrafluoride (Dygert 1949a) and after 5 weeks exposure to 9.2 mg U/m^3 as uranyl fluoride (Rothstein 1949a). Histopathological evidence of toxicity was observed in several studies, including slight degenerative changes in rats and dogs exposed to 16 mg U/m^3 as uranium trioxide (Rothstein 1949c) and dogs exposed to 9.5 mg U/m^3 as uranyl nitrate (Roberts 1949). Uranium dioxide and triuranium octaoxide did not cause toxicity (Dygert 1949c; Rothstein 1949b). Carnotite uranium ore did not cause toxicity in mice or guinea pigs, but hemorrhagic lungs were observed in dogs (Pozzani 1949). The species differences may reflect deeper penetration of this material into the dog respiratory tract. Rabbits were more sensitive to respiratory effects of uranium compounds than other species. Severe respiratory effects (pulmonary edema, hemorrhage) were observed in this species with

exposure to 6.8 mg U/m^3 as ammonium diuranate (Dygert 1949b), 15.4 mg U/m^3 as uranium peroxide (Dygert 1949d), 16 mg U/m^3 as uranium trioxide (Rothstein 1949c) and 22 mg U/m^3 as carnotite uranium ore (Pozzani 1949). Uranium dioxide at 19.4 mg U/m^3 did not cause respiratory effects in rabbits (Rothstein 1949b).

In chronic-duration exposure tests, a total of 3,100 test animals, including rats, rabbits, guinea pigs, and dogs were exposed to aerosols containing 0.05–10 mg U/m^3 of various uranium compounds for 7–13 months. Histological examination of the lungs revealed no signs of injury attributable to uranium exposure. In chronic-duration exposure tests, no histological damage attributable to uranium exposure to the lungs was observed. There was an absence of any other type of histological damage outside the kidneys (Cross et al. 1981a, 1981b; Stokinger et al. 1985). Dogs exposed to 15 mg/m^3 of carnotite ore dust containing 0.6 mg U/m^3 with a particle size activity median aerodynamic diameter (AMAD) of 1.5–2.1 μm for 1–4 years, 5 days a week, 4 hours a day, showed very slightly increased pulmonary resistance, which may not have been statistically significant. Histological findings included vesicular emphysema, which was present to a lesser degree in control animals. Fibrosis was not noted at this concentration (Cross et al. 1981a, 1982).

Exposure of 200 rats, 110 dogs, and 25 monkeys to 5 mg U/m^3 as uranium dioxide dust for 1–5 years for 5.4 hours a day, 5 days a week did not result in histological damage in the lungs of the dogs or rats. Minimal patchy hyaline fibrosis was occasionally seen in the tracheobronchial lymph nodes of dogs and monkeys exposed for more than 3 years. No atypical epithelial changes were noted (Leach et al. 1970).

Because particles containing insoluble uranium compounds can reside in the lung for years, it is likely that radiotoxicity as well as chemical toxicity can result from inhalation exposure to highly enriched uranium compounds. Radiation effects on tissues from the alveolar regions of the lungs were examined in Albino HMT (Fischer 344) male rats exposed, nose-only, for 100 minutes to an aerosol of to 92.8% [235]U-enriched uranium dioxide with a concentration of 2,273 nCi/m^3 (84.1 kBq/m^3) to 5,458 nCi/m^3 (202 kBq/m^3). Increases in the sizes and numbers of lung macrophages and type II[3] cells, the numbers of

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[3]Type I cells are alveolar lining cells that are involved with the transfer of substances from the alveolus through the wall to the blood. Type II cells are alveolar cells with two functions: oxidative enzymes for lung metabolism, and the production and secretion of the surfactant coating the alveolar surface.

macrophages and type I cells, and a significant increase in the size of lysosomal granules within the macrophages were reported 8 days postexposure. At 7 days postexposure, 35 of the rats were further exposed to thermalized neutrons at a fluence of $1.0x10^{12}$ neutrons/cm^2 over 2.5 minutes in order to study the combined effects of radiation and chemical toxicity. The radiation dose due to the neutrons and the fission fragments was about 600 rads, which is about 300 times greater than the radiation dose from the uranium dioxide alpha particles. No significant difference was found between the uranium dioxide-only group and those that were subsequently irradiated with neutrons, indicating that the extra radiation exposure caused no immediate pulmonary cellular reaction above that produced by uranium dioxide alone. This finding implies that the observed acute pulmonary effects were due to the metallotoxicity of the uranium dioxide rather than to the alpha radiation from the uranium (Morris et al. 1989). General damage to pulmonary structures, usually noncancerous alveolar epithelium damage of type II cells, can occur upon inhalation of insoluble reactive chemicals such as uranium salts and oxides. The main responses of epithelial cells to chronic injury are hyperplasia, hypertrophy, and transdifferentiation (metaplasia). These changes occur predominantly in proximal acinar regions where chronic injury often causes persistent lining of alveolar spaces by enlarged cuboidal cells that are derived from pre-existing type II cells, nonciliated epithelial cells from adjacent bronchioles, or a mixture of the two.

There is evidence that exposure to highly enriched uranium through inhaled or intratracheally instilled enriched uranium compounds adversely affect the epithelium of the lungs. Severe alveolar fibrosis or metaplasia was found in 72% of the sampled lung tissues from Fischer 344 rats exposed for 100 minutes to an aerosol of 92.8% enriched uranium dioxide at a radioactivity concentration of 5 µCi/m^3 (137 kBq/m^3) (- 150 mg U/m^3) to 10 µCi/m^3 (270 kBq/m^3) (- 300 mg U/m^3). Extensive lung disease of an unspecified nature was observed only in animals sacrificed at 720 days postexposure. The radioactivity concentration of the mixture was estimated as 1.91 kBq/g (51.6 nCi/mg), and the AMAD of the particles ranged from 2.7 to 3.2 µm (Morris et al. 1990).

In other animal studies, changes suggestive of damage from either radiation or diverse inorganic dust (fibrosis) were reported in lungs and tracheobronchial lymph nodes in Rhesus monkeys exposed by inhalation to 5.1 mg/m^3 (as uranium dioxide) corresponding to a radioactivity concentration of 3.4 nCi/m^3 (126 Bq/m^3) for periods >3 years. Estimated cumulative alpha-radiation tissue doses were >500 rads (5 Gy) for the lungs and 7,000 rads (70 Gy) for the lymph nodes. Similarly exposed dogs also developed slight interstitial and vascular fibrosis of the lungs at lung alpha-radiation tissue doses of 760–1,280 rads (7.6–12.8 Gy) (Leach et al. 1970). The effect on the tracheobronchial lymph nodes in animals exposed for

an additional 2 years ranged from involvement of a single node to complete destruction of all nodes, was dose-dependent, and showed a similarity to changes seen after inhalation exposure to plutonium as [238,239]Pu dioxide (Leach et al. 1973). Renal damage was not observed in either dogs or monkeys, but fibrosis was found in monkey lung and both necrosis and fibrosis were found in dog and monkey lymph nodes. It was not clear whether the damage was chemically or radiologically induced, but the magnitude of the radiation doses and the presence of lung and lymph node damage in the absence of renal effects was suggestive to the authors of long-term radiation damage (Leach et al. 1970). However, such degenerative changes in the lungs have also been observed following prolonged exposure to diverse inorganic dust.

For more information about lung effects from plutonium and a review of the hazards associated with alpha-emitting radionuclide exposure, see the ATSDR *Toxicological Profile for Plutonium* (ATSDR 1990e) or Appendix D of this profile.

Cardiovascular Effects.   No cardiovascular effects have been reported in humans after inhalation exposure to uranium. No effect on blood pressure or pulse rate was observed in a man accidentally exposed to powdered uranium tetrafluoride for 5 minutes (Zhao and Zhao 1990). Air concentration and mean particle size of the powder were not determined. Electrocardiograms and chest X-rays were normal shortly after the accident and over a 7.5-year follow-up period.

No cardiovascular effects were seen in rats exposed to 0.2 mg U/m^3 (0.13 nCi U/m^3) as uranium hexafluoride for 1 year (Stokinger et al. 1953) or in rats, mice, guinea pigs, and rabbits exposed to 4.8 mg U/m^3 (3.2 nCi U/m^3) triuranium octaoxide for 26 days (Dygert 1949c).

Gastrointestinal Effects.   Inhalation exposure to uranium has generally not resulted in gastrointestinal effects in humans although transient effects occurred after one accidental exposure (Zhao and Zhao 1990). On the sixth day after a male worker at a uranium-enrichment plant was accidentally exposed for about 5 minutes in a closed room by inhalation to a high concentration of uranium tetrafluoride (natural uranium) powder, the patient reported nausea and loss of appetite. Air concentration and mean particle size of the powder were not determined. On post-accident day 8, the clinical findings were loss of appetite, abdominal pain, diarrhea, tenesmus, and pus and blood in the stool. On post-accident day 9, all parameters returned to normal. The study gave no indication of particle size for assessing deposition in the upper lung and no indication of whether fecal uranium analysis was undertaken to determine if the noted effects may have

been mediated by the mucocilliary clearance of the uranium tetrafluoride from the lung and its subsequent swallowing to the gastrointestinal tract in accordance with the current ICRP lung model (ICRP 1994) or whether the signs were the result of another intestinal irritant. Gastrointestinal symptoms were not among the clinical signs reported for other workers accidentally exposed to uranium hexafluoride (Eisenbud and Quigley 1955; Moore and Kathren 1985; USNRC 1986).

Dogs, but not other species, appear susceptible to gastrointestinal effects after inhalation exposure to high concentrations of uranium compounds. Vomiting was observed during intermediate-duration exposure to 9.5 mg U/m^3 uranyl nitrate (Roberts 1949), 18 mg U/m^3 uranium tetrafluoride (Dygert 1949a), and to 9.2 mg U/m^3 uranyl fluoride (Rothstein 1949a), It is possible that irritation of the gastrointestinal tract occurred either from clearance of uranium particles from the lungs or ingestion of uranium during these whole-body exposures. Histopathological examination of rat gastrointestinal tissues revealed no changes after 1-year exposures to 0.2 mg U/m^3 uranium hexafluoride or uranium tetrachloride (Stockinger 1953).

Hematological Effects. Inhalation exposure to uranium compounds has generally had no effect, or only minor effects on hematological parameters in both humans and animals. In human studies, no hematological effects were found in a man accidentally exposed to powdered uranium tetrafluoride for 5 minutes (Zhao and Zhao 1990). Air concentration and mean particle size of the powder were not determined. Small but significant decreases in the hemoglobin concentration and the mean corpuscular hemoglobin concentration and significant increases in red blood cells counts and mean corpuscular volume were found in uranium miners who had worked for <5–20 years. All values measured were well within the normal range, such that values for individual miners could not be used as an estimate of exposure. No evidence of damage to red blood cell formation was found. The ambient concentration to which these workers had been exposed was not provided in the study (Vich and Kriklava 1970).

A study on the mortality among uranium mill workers found four deaths from lymphatic and hematopoietic tissue effects other than leukemia, while only one was statistically expected among these workers, who were occupationally exposed to uranium dust at airborne levels corresponding to a radioactivity concentration of 0.07 nCi/m^3 (0.1 mg/m^3). However, the authors of this study suggest that this excess may be due to irradiation of the lymph nodes by thorium-230 (^{230}Th) (Archer et al. 1973b). No changes in hematological parameters were observed in humans occupationally exposed to uranium dust at a level of 1.7 nCi/m^3 (63 Bq/m^3 or 2.5 mg/m^3) for 5 years (Eisenbud and Quigley 1955).

Some intermediate-duration animal studies observed a range of hematological changes. Rats exposed to dusts of ammonium diuranate containing 6.8 mg U/m^3 for 6 hours a day for 30 days showed a decrease of 1 million in red blood cell counts and a loss of 4 g of hemoglobin/100 mL of blood (Dygert 1949b). It was not stated whether exposure was for 30 consecutive days or on weekdays only. Rats exposed to airborne uranyl nitrate hexahydrate containing 9.5 mg U/m^3 for 8 hours a day, 5 days a week for 30 exposure days showed decreased numbers of erythrocytes and hemoglobin (measured at 24 hours postexposure and weekly thereafter) (Roberts 1949). Increased percentages of lymphoid cells and myeloblasts in bone marrow were reported at termination in rats exposed to airborne uranium peroxide containing 15.4 mg U/m^3 5 hours a day 5 days a week for 23 days (Dygert 1949d). A 4-week study in rats exposed to airborne uranium as uranium trioxide at a concentration corresponding to 16 mg U/m^3 6 hours a day 6 days a week reported similar findings (significant increases in myeloblasts and lymphoid cells of bone marrow) (Rothstein 1949c). Rabbits and rats exposed to airborne uranium at a level corresponding to a uranium concentration of 0.13 mg/m^3 as uranyl nitrate hexahydrate for 30 days exhibited altered blood function as indicated by decreased fibrinogen during the final week of exposure (Roberts 1949).

In contrast to the above findings, most other intermediate-duration animal inhalation studies with soluble and insoluble uranium compounds found no adverse effects on the blood. In intermediate-duration dosing studies lasting 23–40 days, inhalation exposure to various uranium compounds at the following concentrations produced no harmful effects on hematological parameters: 22 mg U/m^3 as high-grade carnotite uranium ore to rats; 2.8 mg U/m^3 as uranium dioxide or triuranium octaoxide to dogs; 22 mg U/m^3 as uranium dioxide or triuranium octaoxide to rabbits; 11 mg U/m^3 as uranium tetrachloride to rats; 2 mg U/m^3 as uranium tetrachloride to rabbits; 1 mg U/m^3 as uranium tetrachloride to dogs; 13.2 mg U/m^3 as uranium hexafluoride to rabbits and dogs; 0.1 mg U/m^3 as uranium hexafluoride to dogs; 14.5 mg U/m^3 as triuranium octaoxide to mice; 14.5 mg U/m^3 as uranium dioxide or triuranium octaoxide to rabbits; 14.5 mg U/m^3 as triuranium octaoxide to guinea pigs and rabbits; 15.4 mg U/m^3 as uranium peroxide to dogs, rabbits, and cats; or 4.8 mg/m^3 as triuranium octaoxide to rats, mice, guinea pigs, and rabbits (Dygert 1949c, 1949d; Pozzani 1949; Rothermel 1949; Spiegl 1949).

In other intermediate-duration exposure studies, inhalation exposures to uranium dioxide dusts containing 1 mg U/m^3 for 30 weeks and 2 mg U/m^3 for 26 weeks in rabbits and guinea pigs, respectively (Stokinger et al. 1953), 19.4 mg U/m^3 for 5 weeks in mice, and 9.2 mg U/m^3 for 5 weeks in dogs and rats had no adverse effects on hematological parameters (Rothstein 1949b). Similarly, exposures to 9.2 mg U/m^3 for

5 weeks to rats and dogs (Rothstein 1949a); 16 mg U/m^3 for 4 weeks to rats, rabbits, cats, and dogs
(Rothstein 1949c); and 15 mg U/m^3 as sodium diuranate to rats had no harmful effects on hematological
parameters (Rothstein 1949d).

In chronic-duration exposures, dogs exposed to an airborne uranium concentration corresponding to a
concentration of 0.2 mg U/m^3 as uranium hexafluoride for 1 year exhibited a lengthening in blood clotting
time with a decrease in blood fibrinogen levels (Stokinger et al. 1953). However, hamsters exposed to
airborne carnotite uranium ore dust containing 0.7 mg U/m^3 for 16–27 months exhibited no adverse
hematological effects (Cross et al. 1981b). Similarly, no changes in hematological parameters were
observed in rats, dogs, rabbits, and monkeys exposed to airborne uranium at concentrations ranging from
1 to 5.1 mg U/m^3 for 1–5 years (Leach et al. 1970, 1973; Rothstein 1949b; Stokinger et al. 1953).

Musculoskeletal Effects.   No studies were located regarding the chemical or radiation effects of
uranium on the musculoskeletal system in humans or animals following inhalation exposure for any
duration.

Hepatic Effects.   No hepatic effects were found in a man accidentally exposed to powdered uranium
tetrafluoride for 5 minutes (Zhao and Zhao 1990). Air concentration and mean particle size of the powder
were not determined. Serum hepatic enzyme levels and liver function tests were within normal limits
from the time of the incident through a 3-year follow-up period

Data from the available studies provide equivocal evidence that exposure of animals to uranium has
effects on the liver, although the etiology for this effect is not clear. Urinary catalase, a measure of
hepatic injury, was significantly increased in rabbits at an inhalation concentration of 0.13 mg U/m^3 8
hours a day, 5 days a week for 30 exposure days (Roberts 1949). A slight decrease in hepatic lactate
content was observed in rabbits following exposure to 15 mg U/m^3 as sodium diuranate dust (Rothstein
1949d). Rabbits exposed to an inhalation concentration of 16 mg U/m^3 as uranium trioxide dust for
4 weeks suffered moderate fatty livers in 63% of the animals that died (Rothstein 1949c). Focal necrosis
of the liver was observed in rats exposed to an inhalation concentration of 0.4 mg U/m^3 as uranium
tetrafluoride for 30 days (Dygert 1949a). In other studies, no changes were found in the liver
morphology, histology, or function in the following animals: rabbits exposed to 0.15 or 2 mg U/m^3 as
uranyl nitrate hexahydrate for 26 weeks; rats exposed to 14.5 mg U/m^3 as triuranium octaoxide dust for

26 days; rats exposed to 16 mg U/m^3 as uranium trioxide for 4 weeks; mice and guinea pigs exposed to 3 mg U/m^3 as high-grade uranium ore dust for 30 days; and rabbits exposed for 30 days to 22 mg U/m^3 as high-grade uranium ore dust (contains uranium dioxide, triuranium octaoxide, and other potentially toxic contaminants) (Dygert 1949c; Pozzani 1949; Rothstein 1949c; Stokinger et al. 1953).

In chronic-duration exposure studies with animals, an unspecified strain of dogs exposed to ambient air concentrations of 0.05–0.2 mg U/m^3 as uranium hexafluoride for 1 year exhibited increased and persistent bromosulfalein retention, indicative of impaired biliary function, at the 0.2 mg U/m^3 concentration level (Stokinger et al. 1953).

Renal Effects.   Uranium has been identified as a nephrotoxic metal, exerting its toxic effect by chemical action mostly in the proximal tubules in humans and animals. However, uranium is a less potent nephrotoxin than the classical nephrotoxic metals (cadmium, lead, mercury) (Goodman 1985). Many of the non-radioactive heavy metals such as lead, cadmium, arsenic, and mercury would produce very severe, perhaps fatal, injury at the levels of exposures reported for uranium in the literature (especially for miners and millers). The negative findings regarding renal injury among workers exposed to insoluble compounds are particularly significant in view of the high levels of exposure reported (Eisenbud and Quigley 1955). The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has considered that limits for natural (and depleted) uranium in drinking water (the most important source of human exposure) should be based on the chemical toxicity rather than on a hypothetical radiological toxicity in skeletal tissues, which has not been observed in either people or animals (UNSCEAR 1993; Wrenn et al. 1985). However, it has been suggested that the renal damage from exposure to high-LET alpha-emitting heavy metals, such as uranium, may be the complementary effect of both the chemical toxicity and the radiotoxicity of these metals (Wrenn et al. 1987).

Several epidemiologic studies have found no increased mortality in uranium workers due to renal disease (Archer et al. 1973a, 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Polednak and Frome 1981). Also, case studies showed that workers accidentally exposed to high levels of uranium did not suffer renal damage, even up to 38 years postexposure (Eisenbud and Quigley 1956; Kathren and Moore 1986), although the tests for renal damage used in these studies were not very sensitive. A recent comparison of kidney tissue obtained at autopsy from 7 uranium workers and 6 referents with no known exposure to uranium showed that the groups were indistinguishable by pathologists experienced in uranium-induced

renal pathology (Russell et al. 1996). Three of 7 workers and 4 of 6 referents were categorized as abnormal. Uranium levels in the workers kidney tissue (estimated by alpha particle emission) ranged from 0.4 µg/kg to 249 µg/kg. One study on the kidney function of uranium mill workers chronically exposed to insoluble uranium (uranium dioxide) revealed renal tubular dysfunction as manifested by mild proteinuria, aminoaciduria, and a concentration-related clearance of β_2-microglobulin relative to that of creatinine when compared to a referent group of cement workers. Air levels of uranium dioxide were not reported. The incidence and severity of these nephrotoxic signs correlated with the length of time that the uranium workers had spent in the area where insoluble uranium oxide yellowcake was dried and packaged (Saccomanno et al. 1982; Thun et al. 1985), which is typically the second dustiest area of the uranium mill following the ore crushing and grinding station. The data from this study are indicative of reduced reabsorption in the proximal renal tubules.

Delayed renal effects were observed after a male worker at a uranium enrichment plant was accidentally exposed to a high concentration of uranium tetrafluoride powder for about 5 minutes in a closed room. While renal parameters were normal during an initial 30-day observation period, the patient showed signs of nephrotoxicity beginning at post-accident day 68 as indicated by significantly elevated levels of urinary proteins, nonprotein nitrogen, amino acid nitrogen/creatinine, and decreased phenolsulfonpthalein excretion rate. These abnormalities persisted through day 1,065 but gradually returned to normal values (Zhao and Zhao 1990). The authors used uranium urinalysis data and a pharmacokinetic model (ICRP 1979) to estimate a kidney dose of 2.6 µg U/g kidney on post-accident day 1.

Renal effects were not observed in another accidental exposure (Fisher et al. 1990) in which 24 of 31 initially exposed workers were followed for 2 years. Estimated airborne concentrations were 20 mg uranium hexafluoride/m^3 for a 1-minute exposure and 120 mg uranium hexafluoride/m^3 for a 60-minute exposure (15.2 and 91 mg U/m^3, respectively) (USNRC 1986). Initial intakes of workers involved in the accident were estimated from uranium excretion data and ranged from 470–24,000 µg uranium. Maximum uranium concentrations in the kidney were estimated by a kinetic model to be 0.048–2.5 µg U/g tissue (Fisher et al. 1991).

The pathogenesis of the kidney damage in animals indicates that regeneration of the tubular epithelium occurs upon discontinuation of exposure to uranium (Bentley et al. 1985; Dygert 1949b; Maynard and Hodge 1949; Pozzani 1949; Rothermel 1949; Rothstein 1949b, 1949c; Spiegl 1949; Stokinger et al. 1953).

The magnitude of uranium intake that causes kidney damage depends on the type of uranium compound to which the animal has been exposed, appearing to depend on its solubility and oxidation state. For example, in dogs and monkeys, exposure to 5 mg U/m^3 as uranium dioxide (insoluble) dust for up to 5 years produced no damage to the kidneys, even 6.5 years after the exposure ceased (Leach et al. 1970, 1973). Similarly, rats and guinea pigs were exposed to #10 mg U/m^3 as uranium dioxide for 1 year without noticeable kidney pathology (Stokinger et al. 1953). Uranium dioxide is relatively insoluble in water and is retained in the lungs longer than the other more soluble uranium compounds (uranium tetrafluoride, uranyl fluoride, uranium tetrachloride, uranium peroxide, uranyl acetate, and uranyl nitrate hexahydrate), thereby causing higher toxicity to the lungs and lower toxicity to distal organs such as the kidney. In contrast, relatively soluble uranium compounds have been shown to cause renal tubular damage in dogs, guinea pigs, rabbits, and rats (Leach et al. 1984; Morrow et al. 1982; Roberts 1949; Stokinger et al. 1953). Apparently, the difference in effect is due to the extent of absorption of uranium deposited in the lungs and, thus, the fraction that eventually gets into the blood. Differences in species susceptibility have also been suggested to be an additional factor.

Renal effects can be produced in animals after acute-duration inhalation exposures to uranium. A 10-minute exposure to 637 mg U/m^3 as uranium hexafluoride produced severe degeneration of the cortical tubules 5–8 days later in rats (Spiegl, 1949). These same effects were observed in dogs 1–3 days after a 1-hour exposure to 250 mg U/m^3 as uranyl fluoride (Morrow et al. 1982). Proteinuria and glucosuria were also observed in rats after 2–10-minute exposures to uranium hexafluoride (Leach et al. 1984).

In intermediate-duration studies with guinea pigs, mice, rats, cats, rabbits, and dogs, inhalation exposures to a variety of uranium compounds were damaging to the kidneys. The effects were compound- and concentration-dependent and ranged from minimal microscopic lesions in tubular epithelium, increased urinary catalase, decreased diodrast (iodopyracet) clearance, and transient increased bromosulfalein retention (for low concentrations) to severe necrosis of the tubular epithelium (for high concentrations) in several species (Dygert 1949a, 1949b, 1949c; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949a, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). In one of these intermediate-duration inhalation exposure studies, mice were exposed to uranium tetrachloride dust at ambient air concentrations of 0.1, 2.1, or 11 mg U/m^3 for 3–7 hours a day 6 days a week for approximately 30 days. The exposure resulted in severe degeneration and necrosis of the renal-cortical tubular epithelium, and mortality, in the 11 mg U/m^3 group by the third day. At the end of the study, moderate tubular

degeneration was observed in the 2.1 mg U/m^3 group and minimal degeneration in the 0.1 mg U/m^3 group. (Rothermel 1949). In another intermediate-duration study, rats suffered renal injury (of inconsistent severity), which became apparent on or about the 7th day and pronounced by the 25th or 26th day, following inhalation exposure to uranyl nitrate hexahydrate at 0.13, 0.2, 0.9, 2.1, or 9.5 mg U/m^3 daily for 8 hours per day, 5 days a week for 30 days. At 0.9 mg U/m^3, the rats showed significant degenerative changes only in the renal tubules and no changes to the glomeruli. Rats exposed to 0.2 mg U/m^3 exhibited only slight damage to the tubular epithelium of the kidneys. At 0.13 mg U/m^3, slight renal tubular degeneration was observed in 1 of the 3 animals sacrificed after 28 days of exposure. Except for the group receiving no dietary supplement, no significant difference in blood CO_2 values was seen at 14 days of exposure to uranium. Thirty days after the start of exposure, all groups exhibited increased blood nonprotein nitrogen (NPN) levels over 14 day values (maximum 111 mg/mL blood for the unsupplemented diet group). No clinical signs of toxicity were observed at any concentration level (Roberts 1949).

Dogs (of both sexes) exposed to 0.13 mg U/m^3 as uranyl nitrate hexahydrate showed mild inner cortex changes after 10 days of exposure. The dogs were given full body exposures to aerosols with an AMAD assumed to be 1.5–2.1 μm; the average was 1.8 μm (Pozzani 1949). Severe nephritis masked any damage from uranium in one dog sacrificed after 10 days of exposure. The dogs showed a transient elevation in protein excretion between days 9 and 12 of exposure. Increased bromosulfalein retention was observed during the second and fourth weeks of exposure. No alterations to blood NPN or total blood CO_2 were observed. Chloride clearance values, which were initially elevated and then became depressed in one dog, returned to normal 37 days after the beginning of exposure. Catalase and protein excretion increased significantly but returned to normal at the end of exposure. No significant changes in diodrast clearance, inulin clearance, and blood NPN levels were observed. Dogs exposed to 0.9 mg U/m^3 exhibited mild inner cortex and medullary ray degeneration and necrosis with moderate epithelial regeneration. Two of the four showed a steady rise in NPN from the beginning of the experiment until they were sacrificed 12 days later, at which time NPN values were 252 and 356 mg%, respectively. Urinary protein in the dogs significantly increased between the 5th and 24th days. The dogs showed a decrease in inulin clearance during the third week of exposure, with a return toward normal values during the fifth week. There was decreased diodrast clearance throughout the observation period, indicating a severe derangement of the excretory capability for diodrast after 1 week (one dog showed a decrease of 69%). Diodrast clearances returned to normal by days 35–37. Two dogs showed a transient decrease in inulin clearance during the third week, lasting until the fifth week. All four dogs showed a drop in total

blood CO_2, attaining a minimum value between the first and seventh days. The minimum value was generally less than half that of controls, indicating severe acidosis. Glucose tolerance was significantly decreased. Large quantities of protein (400–800 mg%) and sugar were excreted. The greatest excretion occurred during the first 6 days of exposure and decreased thereafter. There was also a decrease in urinary creatinine excretion during the exposure. At the 2 mg U/m^3 exposure level, the dogs did not show highly elevated NPN and blood urea nitrogen (BUN) values during exposure. There were no increases in blood NPN or BUN. All dogs exposed to 9.5 mg U/m^3 had severe renal tubular damage. Four dogs showed renal injury followed by repair when they were sacrificed at the end of the exposure (Roberts 1949).

No treatment-related renal effects were seen in other studies when animals were exposed to uranium compounds by inhalation at concentrations as high as 10 mg U/m^3 (as uranium dioxide) in guinea pigs for 28 weeks, 2 mg U/m^3 (as uranyl nitrate hexahydrate) in guinea pigs for 26 weeks, and 16 mg U/m^3 (as uranyl nitrate hexahydrate) in rats for 4 weeks (Rothstein 1949c; Stokinger et al. 1953).

The nephrotoxic effects of uranium in animals may also include damage to the glomerulus as evidenced by histopathological signs in the kidneys of rats and rabbits exposed to 15.4 mg U/m^3 as uranium dioxide for 23 days (Dygert 1949d) and of dogs exposed to 15 mg U/m^3 as uranyl fluoride for 5 weeks (Rothstein 1949d) and to 16 mg U/m^3 as uranium trioxide for 4 weeks (Rothstein 1949c).

In chronic-duration inhalation studies with rats and dogs, uranium (as uranium tetrachloride, uranium tetrafluoride, uranyl nitrate hexahydrate, or uranium dioxide) exposures as low as 0.05 mg U/m^3 and as high as 10 mg U/m^3 for 1–5 years were damaging to the kidneys. Nephrotoxic effects found in these animals ranged from minimal microscopic lesions in tubular epithelium (for low concentrations) to acute tubular necrosis (for high concentrations) (Leach et al. 1970; Stokinger et al. 1953). In one of these chronic-duration studies, dogs were exposed to ambient air concentrations of 0.05 or 0.2 mg U/m^3 as uranium hexafluoride for 1 year for a total of 1,680 exposure hours. The UF_6 was rapidly hydrolyzed to HF gas and UO_2F_2 fumes, whose AMAD was 0.1 μm. After 10 days in the study, there was evidence of mild tubular injury, which was characterized by desquamation of the epithelium and active regeneration in the proximal convoluted tubule in the inner cortex of the kidneys in 86% of animals exposed to 0.2 mg U/m^3. From the 16th week to the end of the study, regeneration of the tubular epithelium was almost complete, with a few flattened atrophic tubules in the inner zone of the cortex. These mild nephrotoxic effects were also observed in 12% of the 0.05 mg U/m^3 exposed animals. Blood non-protein

nitrogen (NPN) levels were normal (elevated blood NPN levels indicate a decrease in renal filtration capacity, similarly to elevated blood urea nitrogen (BUN)). Observed changes in urinary protein were inconsistent and insignificant (Stokinger et al. 1953).

In another study, dogs of both sexes (9–12 M, 9–13 F) were exposed to concentrations of 0.04, 0.15, 0.25, or 2 mg U/m^3 as uranyl nitrate for 6 hours a day, 5.5 days a week for 1 year. The AMAD of the aerosols was given as 2–5 μm. At the termination of the study, histological and biochemical examinations revealed minimal microscopic lesions in the renal tubules and transient increases in blood NPN in the 0.25 mg U/m^3 concentration-level dogs. Transient increases in blood NPN were also observed at higher concentration levels. There were transient decreases in plasma CO_2, although liver function was normal. No significant weight loss was observed in the dogs (Stokinger et al. 1953).

No treatment-related renal effects were seen when Rhesus monkeys and dogs were exposed to uranium dioxide by inhalation at airborne concentrations as high as 5.1 mg U/m^3 for 1–5 years (Leach et al. 1973). Blood NPN levels were consistently elevated in Rhesus monkeys although no renal histopathology was evident (Leach et al. 1973).

Endocrine Effects.   A single study was found that reported on possible effects of uranium on the endocrine system. In this study, no histopathology was seen in the endocrine organs (adrenal, pancreas) in rats given 0.2 mg U/m^3 as uranium tetrachloride for 1 year (Stokinger et al. 1953).

Dermal Effects.   No dermal effects were found in a man accidentally exposed to powdered uranium tetrafluoride for 5 minutes (Zhao and Zhao 1990). Histopathologic examination of the skin was normal in rats exposed to 0.2 mg U/m^3 as uranium tetrachloride for 1 year (Stokinger et al. 1953).

Ocular Effects.   Chemical burns to the eyes were reported in humans after accidental exposure to uranium hexafluoride (Kathren and Moore 1986). Conjunctivitis and eye irritation have also been reported in animals after exposure to uranium hexafluoride (Spiegl 1949) and to uranium tetrachloride (Dygert 1949a). Ocular effects were due to direct contact of the eye with vapor or aerosols.

Body Weight Effects.   In general, inhalation of insoluble uranium compounds did not significantly affect body weight in animals. Decreased body weight was observed with the more water-soluble compounds. A 30% decrease in body weight was reported for rabbits exposed to 11 mg U/m^3 as uranium tetrachloride dust for 35–40 days. Mice and guinea pigs experienced unspecified weight loss and 13% weight loss, respectively, following exposure to 13 mg U/m^3 as uranium hexafluoride for 30 days. Rabbits suffered 12% weight loss following exposure to 0.2 mg U/m^3 as airborne uranium hexafluoride for 30 days (Spiegl 1949). Mild to severe weight loss was observed in several species during exposure to uranyl nitrate hexahydrate (Roberts 1949). Rabbits lost 22% of their body weight during a 30 day exposure to 0.9 mg U/m^3, dogs and cats lost approximately 25% of their body weight during a similar exposure to 9.5 mg U/m^3. Similar effects were observed with uranium tetrafluoride (Dygert 1949a). Rabbits, rat, cats, and dogs all experienced a greater than 20% weight loss during 30 days exposure to 18 mg U/m^3.

Several intermediate-duration animal inhalation studies with soluble and insoluble uranium compounds found no significant adverse effects on body weight. In short-term intermediate-duration dosing studies lasting from 23 to 40 days, exposure to concentrations at the following levels were without significant effects on body weight: 22 mg U/m^3 as high-grade or carnotite uranium ore to rats, 2.9 mg U/m^3 as uranium dioxide or triuranium octaoxide to dogs, 22 mg U/m^3 as uranium dioxide or triuranium octaoxide to rabbits, 11 mg U/m^3 as uranium tetrachloride to rats, 2.1 mg U/m^3 as uranium tetrachloride to rabbits, 1.1 mg U/m^3 as uranium tetrachloride to dogs, 13 mg U/m^3 as uranium hexafluoride to rabbits and dogs, 0.2 mg U/m^3 as uranium hexafluoride to dogs and guinea pigs, 14.5 mg U/m^3 as triuranium octaoxide to mice, and 4.8 mg U/m^3 as triuranium octaoxide to guinea pigs and rabbits (Dygert 1949c; Spiegl 1949); 15 mg U/m^3 as uranium peroxide to cats and rabbits (Dygert 1949d); 15 mg U/m^3 as carnotite ore (mostly uranium dioxide, triuranium octaoxide) to dogs or 22 mg U/m^3 as carnotite ore to rabbits for 30 days (Pozzani 1949); and 1 mg U/m^3 for 30 weeks to rabbits or 2 mg U/m^3 for 26 weeks to rabbits and guinea pigs (Stokinger et al. 1953). Exposures of rats to 13 mg U/m^3 or of rabbits to 0.1 mg U/m^3 as uranium hexafluoride for 30 days also were without harmful effects (Spiegl 1949).

No effects on body weight were observed after several intermediate-duration dosing studies that lasted 4–5 weeks. These studies researched exposures by the inhalation route as follows: 16 mg U/m^3 as uranium trioxide to rats, rabbits, dogs, and cats; 19 mg U/m^3 as uranium dioxide to mice; 16 mg U/m^3 as uranium dioxide to guinea pigs; 9.2 mg U/m^3 as uranyl fluoride to dogs and rabbits; 2.2 mg U/m^3 as uranyl fluoride to rats; 9.2 mg U/m^3 as uranium dioxide to dogs; 19.2 mg U/m^3 as uranium dioxide to rabbits; 15 mg U/m^3

as sodium diuranate to rats and dogs; and 12 mg U/m^3 as ammonium diuranate to rats for 30 days (8 hours a day, 5 days a week for 6 weeks) (Rothstein 1949a, 1949b, 1949c, 1949d; Stokinger et al. 1953). Hamsters exposed to 0.8 mg U/m^3 as carnotite uranium ore by inhalation for 16–27 months also exhibited no adverse body weight effects (Cross et al. 1981b). Similarly, no changes in body weight were observed in rats, dogs, rabbits, and monkeys exposed to airborne uranium dioxide at 0.1–5 mg U/m^3 for 1–5 years (Leach et al. 1970, 1973; Stokinger et al. 1953).

In chronic-duration studies, exposure to inhalation concentrations of 3 mg U/m^3 as uranium dioxide to monkeys for 5 years produced no significant body weight changes (Leach et al. 1970).

Other Systemic Effects.   Several general effects have been attributed to uranium inhalation exposure. In animal studies, dogs exposed to 13 mg U/m^3 as uranium hexafluoride for 30 days exhibited decreased water intake (Spiegl 1949). Reduced food intake was also observed in a 4-week study of rats and mice exposed to 16 mg U/m^3 as uranium trioxide (Rothstein 1949c) and in a 5-week study of rats and mice exposed to 15 mg U/m^3 as sodium diuranate for 6 hours per day, 5½ days per week (Rothstein 1949d).

2.2.1.3 Immunological and Lymphoreticular Effects

Although no studies were located that specifically tested immunological effects in humans following inhalation exposure to uranium, all epidemiologic studies of workers in uranium mines and fuel fabrication plants showed no increased incidence of death due to diseases of the immune system (Brown and Bloom 1987; Checkoway et al. 1988; Keane and Polednak 1983; Polednak and Frome 1981).

Human studies that assessed damage to cellular immune components following inhalation exposure to uranium found no clear evidence of an immunotoxic potential for uranium. No association was found between the uranium exposure and the development of abnormal leukocytes in workers employed for 12–18 years at a nuclear fuels production facility (Cragle et al. 1988). Increases in the number of fatal malignant disease of the lymphatic and hematopoietic tissue reported among uranium mill workers may have been caused by other carcinogens in the work environment such as ^{230}Th. The authors of this report estimated that the workers were exposed to 8–5,100 mg/m^3 (median 110 mg/m^3) uranium mill dust, which contains ^{230}Th as a natural component (Archer et al. 1973b).

2. HEALTH EFFECTS

In animal studies, rats exposed to dusts of ammonium diuranate containing 6.8 mg U/m^3 for 6 hours a day, 5 days per week for 30 days developed a rise in neutrophils, a decrease in lymphocytes, a moderate fall in the white blood cell count, and a rise in the number of eosinophils (Dygert 1949b). Rats exposed to airborne uranyl nitrate hexahydrate containing 9.5 mg U/m^3 8 hours a day, 5 days a week for 30 exposure days showed an initial increase and a subsequent decrease in the absolute number of lymphocytes and neutrophils (Roberts 1949). Focal necrosis of the spleen and edematous cecal lymph nodes were observed in some rats exposed for 30 days for 6 hours a day to 0.4 and 4 mg U/m^3 uranium tertrafluoride (Dygert 1949a). However, these effects were not observed at 18 mg U/m^3, so the significance of this finding is unclear.

No histopathological changes or accumulation of uranium were evident in the spleens of 110 dogs and 25 monkeys exposed to uranium dioxide dusts (5 mg U/m^3) for 6 hours a day, 5 days a week, 1–5 years and then monitored for up to 6.5 more years. Similar results were seen for rats similarly exposed for 1 year (Leach et al. 1970, 1973). Rats, rabbits, guinea pigs, and dogs exposed to dusts of various uranium compounds for 7–12 months showed no significant histological changes in the lymph nodes and marrow (Stokinger et al. 1953).

There is some evidence from animal studies that exposure to $90% enriched uranium may affect the immune system. Increased macrophage activity, associated with localized alpha tracks in all 5 lobes of the lungs, was seen in Fischer 344 rats exposed to 6,825.5 nCi/m^3 (252 kBq/m^3) through inhalation exposure to enriched uranium dioxide for 100 minutes. The increased activity was evident from days 1–7, 180, 360, 540, and 720 with increases in percent activity of 0.44, 2.15, 19.70, 6.54, and 37.84, respectively. The number and size of macrophage clusters in the lung increased with time postexposure. The radioactive material concentration of the mixture was estimated as 1.91 kBq/mg (51.6 nCi/mg) (Morris et al. 1992). The degree of enrichment was calculated based on this specific activity.

Albino HMT (Fischer 344) male rats were exposed to 92.8% enriched uranium dioxide with a concentration ranging from 2,274.2 nCi/m^3 (84.1 kBq/m^3) to 5,458 nCi/m^3 (202 kBq/m^3). Increases in the sizes and numbers of lung macrophages, with a significant increase in the size of lysosomal granules within the macrophages, were reported 8 days postexposure (Morris et al. 1989).

Dogs exposed to airborne uranium dioxide concentrations of 5.1 mg/m^3 for 1–5 years showed lymph node fibrosis in the lungs. Rhesus monkeys similarly exposed for 5 years showed fibrotic changes in the tracheobronchial lymph nodes. The investigators of these studies concluded that although these effects could not be extrapolated to humans because of the absence of squamous cell carcinomas in the lungs, the changes were suggestive of radiation injury (Leach et al. 1973). However, the morphological changes observed in these studies were similar to observations in humans and animals as a result of exposure to diverse inorganic dust (Dockery et al. 1993).

The highest NOAEL values and all reliable LOAEL values in each species and duration category for immunological effects from chemical exposures by the inhalation route to uranium are presented in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

Uranium has not been shown to cause damage to the nervous system of humans by metallotoxic or radiotoxic action following inhalation exposures for any duration. Although no studies were located that specifically tested neurological effects in animals following inhalation exposure to uranium, none of the available studies reported any neurological deficits, such as narcosis, ataxia, or cholinergic signs. Clinical signs in humans following acute exposure to enriched uranium included dizziness and anorexia in one man 6 days after being exposed for 5 minutes to uranium tetrafluoride by inhalation (Zhao and Zhao 1990), but did not include neurological effects in others similarly exposed to uranium hexafluoride (Kathren and Moore 1986; USNRC 1986). Some of the victims were evaluated for as long as 38 years after exposure (Kathren and Moore 1986). In longer-term exposures, epidemiologic studies found no increase in deaths from brain tumors or other neurological diseases that could be attributed to uranium in workers at uranium-processing plants (Brown and Bloom 1987; Carpenter et al. 1988; Cragle et al. 1988; Polednak and Frome 1981; Reyes et al. 1984). The autopsy reports also did not reveal any other structural pathology of the central nervous system. In a retrospective study, more deaths than expected were found from central and peripheral nervous system diseases (SMR=2.98) in employees in a nuclear fuels fabrication plant. However, the employees were also concurrently exposed to other radiological and chemical agents. The investigators of this study concluded that there was no etiology associated with uranium for the central nervous system and peripheral nervous system diseases (Hadjimichael et al. 1983).

In intermediate-duration animal studies, neurological signs were observed in dogs and cats following inhalation exposure to uranium. On the 13th day of a 30-day study, dogs exposed to 0.5, 3, 4, or 18 mg U/m^3 as uranium hexafluoride gas by inhalation exhibited muscular weakness followed by instability of gait indicative of neurological dysfunction at the highest concentration tested (Dygert 1949a). Anorexia observed in another 8 hours a day, 5 days a week, 30-day study with dogs exposed to an inhalation concentration of 9.5 mg U/m^3 as uranyl nitrate hexahydrate may also have had its origin in neurological dysfunction (Roberts 1949). Similarly, cats exposed to an inhalation concentration of 18 mg U/m^3 as uranium tetrafluoride exhibited unsteady gait on the 7th day in a 30-day study (Dygert 1949a). In 5 week studies (8 hours a day, 5 days a week), dogs and cats exposed to 0.15, 2.2, or 9.2 mg U/m^3 as uranyl fluoride suffered anorexia, severe muscle weakness, and lassitude at the highest concentration tested (Rothstein 1949a). These studies did not assess the potential implications of hydrofluoric acid and fluoride ion exposure.

The highest NOAEL values and all reliable LOAEL values in each species and duration category for neurological effects by the inhalation route to uranium are presented in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

It is unlikely that inhalation of uranium produces a significant effect on reproductive health. Studies of one human population group (miners) were located which identified a reproductive effect associated with the inhalation exposure of mine air, but the association with uranium compounds was unclear, and the other miner studies observed no reproductive effects. Also, no adverse animal studies were found.

Three studies of one mining population were located that equivocally associated reproductive effects in humans following inhalation exposure to uranium. The studies reported that male uranium miners were found to have more first-born female children than expected, suggesting that uranium's alpha radiation damaged the y-chromosomes of the miners (Muller et al. 1967; Waxweiler et al. 1981b; Wiese 1981). In addition, it is not certain if the effect described is from exposure to uranium because the workers were also exposed to ^{222}Rn, chlorine, hydrofluoric acid, lead sulfate, nickel, nitric acid and nitrogen oxides, silicon dioxide, and sulfuric acid (Dupree et al. 1987).

No animal studies were located that described reproductive effects following inhalation exposure to uranium for any duration of exposure.

2.2.1.6 Developmental Effects

No studies were located which reported effects of uranium on development in humans or animals following inhalation exposures for any duration. The Department of Defense has preliminarily evaluated developmental effects among service members who were actually or potentially exposed to depleted uranium.

2.2.1.7 Genotoxic Effects

No information was located regarding the toxicity of uranium to genetic material in humans or animals following inhalation exposures for any duration.

In human studies, chromosome aberrations have been found in cultured lymphocytes of uranium miners. Miners who had more atypical bronchial cell cytology had more chromosomal aberrations, and some of the aberrations increased with increasing exposure to radon and its decay products. The investigators of the study concluded that this is probably a valid health risk indicator for miner groups, but that it has only limited applicability to individual miners (Brandom et al. 1978). In a similar study with uranium miners in Czechoslovakia, no increased incidence of aberrant DNA or chromosomes attributable to exposure to uranium was found. An increased occurrence of molds (genus *Aspergillus* and *Penicillium*) that produce mycotoxins was observed, suggesting that the inhaled dust was contaminated with these genotoxic microorganisms (Sram et al. 1993). A cytogenic study of men occupationally exposed to uranium found higher levels of chromosome aberrations in the miners than in controls. The investigators of this study concluded that this increase may be attributable to smoking (Martin et al. 1991). In addition, because the miners were also concurrently exposed to chlorine, hydrofluoric acid, lead sulfate, nickel, nitric acid and nitrogen oxides, silicon dioxide, diesel smoke, and sulfuric acid in addition to ^{222}Rn, it is unlikely that the effects described in these studies were related in any way to exposure to uranium (Dupree et al. 1987). Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

The National Toxicology Program (NTP) has not evaluated uranium compounds in rodent cancer bioassays by any route for the potential to induce cancer in humans. However, because uranium emits predominantly high-LET alpha particles, current theories on gene mutation and apoptotic mechanisms of cancer promotion by high-LET alpha radiation suggest a concern for carcinogenesis from uranium's radioactivity (BEIR 1980, 1988, 1990; Otake and Schull 1984; Sanders 1986; UNSCEAR 1982, 1986, 1988) (see Appendix D for a review of the hazards associated with radionuclide exposure).

Although several studies of uranium miners found increased deaths from lung cancer, it is difficult to attribute these cancers to uranium exposure because the miners were also concurrently exposed to known cancer-inducing agents (principally tobacco smoke, radon and its decay products, silica and other dusts, and diesel engine exhaust fumes) and the studies attributed the cancers to exposure to these toxicants and not to uranium exposure (Archer et al. 1973a; Auerbach et al. 1978; Band et al. 1980; Gottlieb and Husen 1982; Kusiak et al. 1993; Lundin et al. 1969; Saccomanno et al. 1971, 1976, 1986; Samet et al. 1984; Whittemore and McMillan 1983). Short-lived radon daughters alone, to which these miners were concurrently exposed, have been shown to increase the risk of developing lung cancer (Saccomanno et al. 1986). In addition, smoking appeared to increase the risk of developing lung cancer from exposure to radon daughters (Band et al. 1980). The available case-control or clinical studies of uranium-processing nuclear plant workers also generally report equivocal findings of cancer induction without establishing any uranium causality (Cookfair et al. 1983; Polednak and Frome 1981).

A review of the morphology of the tumor types induced in the lungs of rats and humans by radiation identified bronchoalveolar adenoma and bronchoalveolar carcinoma, papillary adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, and hemangiosarcoma. All the tumor types originated from the alveolar parenchyma region of the lungs. Of these tumor types, squamous cell carcinomas are most often associated with radiation exposure. In irradiated rats, the squamous cell carcinomas are less well differentiated and decidedly more locally invasive. Although cystic squamous tumors do occur after irradiation, the wall of these tumors is less differentiated. The pathogenesis of the radiation-induced squamous tumors appeared to be different from that of chemically induced tumors. The one common feature of the two tumor types may be chronic injury to alveolar type II cells (Hahn 1989).

Squamous cell metaplasia was the predominant aberrant cell type found in many of these cases. Squamous cell metaplasia is found in the young and old and does not always represent a benign-to-malignant process. More frequently, a nonspecific bronchial epithelial reaction develops, and this reaction is readily reversible with the disappearance of the toxic, infectious, or inflammatory factors that caused it. Although, squamous cell metaplasia may develop into neoplasia, patients with neoplasia also shed a variety of metaplastic squamous cells. In a study of 120 uranium miners who died from primary cancer of the lungs, squamous cell metaplasia progressed over time and developed into neoplasia of the lungs in 15–20 years (Saccomanno et al. 1976, 1982). However, a study that reviewed efforts to test uranium miners concluded that radon-progeny exposure may not cause any cell type of lung tumor other than the so-called small-cell (oat cell) carcinoma. The incidence of oat cell cancer of the lungs has decreased over the last 20 years and currently accounts for slightly more than 22% of developing neoplasia in uranium miners (Saccomanno et al. 1982).

An excess of lung cancers has been found in underground uranium miners from the Grants, New Mexico, area. Of 3,055 miners who worked for at least one year prior to 1971, a total of 58 died of lung cancer by the middle of 1985. Of the 43 cancers which had been examined histopathologically, 27 (63%) were small-cell, 14 (33%) were epidermoid, 1 (2%) was adenocarcinoma, and 1 (2%) was large-cell. These mortality data could not be related to the total radon exposure; radon exposure data for the individual miners was complete since 1967, but only mine-average concentrations had been determined for the period prior to that time (Samet et al. 1986) The radon concentration in mine air is measured in working levels (WL), where 1 WL = 100 pCi/L Rn in equilibrium with its daughters, and the total exposure to radon is measured in WLM s where 1 WLM = 170 WL, or the equivalent of breathing air at a concentration of 1 WL for a period of 170 hours (the typical miner work month). A total of 8,487 miners employed between 1948 and 1980 at the Beaver Edge uranium mine in Saskatchewan, Canada, exhibited significant increase in lung cancer deaths when compared to Canadian male mortality rates (65 in exposed populations as opposed to 34.2 expected [$p < 0.05$]). A higher incidence of lung cancer was found in workers exposed to more radon than 5 WLM (46 observed as opposed to 15.8 expected) than those exposed to 0–4 WLM (19 observed as opposed to 18.7 expected). A significant relationship was found between radon exposure and increase of lung cancer (3.3% per WLM and 20.8% per WLM/10^6 person-years). The age at first exposure also had a significant effect on risk; those first exposed before the age of 30 were at lower risk than those first exposed at or after 30 years of age. The authors suggested that exposure to radon daughters was the major factor, and it may be a contributory factor to lung cancer in

nonsmokers in the general population (Howe et al. 1986). The frequency of squamous cell cancer increased, relative to other types, with increased levels and durations of smoking, but relative frequency was not affected by radiation exposure. The relative frequencies of small-cell cancer and adenocarcinoma from radiation exposure were less affected by smoking (Archer et al. 1973a; Land et al. 1993; Saccomanno et al. 1988).

Histological examination of lungs from seven underground male uranium miners (ages 52–73) who had cancer and who also had been routinely exposed to radon daughters and other potential carcinogens in the mine environment showed elevated concentrations of ^{238}U and ^{234}U.   Four of the seven lungs had squamous cell carcinoma, one had a carcinoma in the left upper lobe, one had carcinoma of the ascending colon, and one had carcinoma *in situ* in the lung. The average radiation dose from uranium was approximately 2 mrad/year (2×10^{-5} Gy/year) compared with more than the 360 mrad (3.6×10^{-3} Gy) dose to the typical U.S. resident from all sources of radiation. Five of the seven miners smoked at least half a pack of cigarettes per day (Wrenn et al. 1983).

A study of miners in northern Ontario with previous inhalation exposure to uranium dust at levels of 0–181 mg U/m^3 (0–121 nCi/m^3 [0–4,487 Bq/m^3]) and a diagnosis of lung cancer found a linear relationship between uranium dose and incidence of lung cancer, but no relationship to uranium exposure was suggested. The latency period was shorter for those employed for a short period of time. Oat cell, anaplastic, small-cell tumors were found more often than squamous, large-cell, poorly differentiated tumors in workers exposed for a short time (Chovil and Chir 1981; Sanders 1986). The frequency of squamous cell cancer in U.S. uranium miners increased, relative to other types, with increased levels and durations of smoking; but relative frequency was not affected by radiation (presumed to be mostly from radon daughters) exposure, which indicated a more likely smoking etiology. However, the relative frequencies of small-cell cancer and adenocarcinoma were less affected by smoking history than by increasing radiation dose. The miners in one of these studies were exposed to a cumulative radiation dose from radon daughters of 40–9,700 WLM (Archer et al. 1973a; Land et al. 1993; Saccomanno et al. 1971, 1982, 1988). A reanalysis study in which sputum samples from 98,181 uranium miners employed on the Colorado Plateau between 1960 and 1980 were collected and used in a cytological analysis for the early detection of cancer development found a significant relationship between exposure to radon decay products and positive cytological diagnosis. No evidence was found linking lung cancer with exposure to uranium. No synergism was seen between age, smoking, and mining exposure, although an additive

effect was seen. No increase in lung cancer was found in men exposed to radon for <300 WLM who also did not smoke (Moolgavker et al. 1993; Saccomanno et al. 1986; Whittemore and McMillan 1983).

A study of 16 Navajo men working as underground uranium miners, who developed lung cancer and were admitted to the hospital between February 1965 and May 1979, concluded that the lung cancers were attributable to radon and its decay products and not from uranium itself. The mean value of the cumulative radon exposure was 1,140 WLM. The authors noted that the minimal use of cigarettes among this group of uranium miners was a strong argument that cigarette smoking was not a major factor in the lung cancers of uranium miners (Gottlieb and Husen 1982). Evaluation of the incidence of bronchiogenic carcinoma in 3,699 Canadian uranium workers employed between 1942 and 1960 found a statistically significant association between inhalation exposure to mine dust and the development of lung cancer (6 of 1,825 surface workers and 16 of 1,874 underground workers). The authors of this study indicated that the workers employed underground for 5 years were generally older than the other groups, which may have contributed to the increase in lung cancer (Grace et al. 1980). In addition, the miners were exposed to greater amounts of airborne radon radioactivity, a known cancer inducer, than airborne uranium radioactivity. Therefore, the lung cancers may be more appropriately attributed to the radioactivity of airborne radon and its short-lived decay products.

A number of case-control studies of uranium-processing nuclear plant workers failed to provide an unequivocal link between the development of lung cancers by workers and uranium exposure because the workers were concurrently occupationally exposed to other radioactive sources, including thorium, tritium, fission products, iodine, activation products, and transuranic products such as americium, curium, californium, and plutonium (Cragle et al. 1988). In one of these case-control studies, a significant increase in the incidence of leukemia deaths was found among employees of a facility exposed to a mean cumulative gamma radiation dose (mostly external) equivalent of 920 mrem (9.2 mSv). In the same study, no increase in death from lymphopoietic and lung cancers was found among the 9,860 male employees of the nuclear fuels production facility who had been occupationally exposed to uranium and other radioactive sources for 90 days to 15 years (Cragle et al. 1988). Another case-control study of male workers who died from lung cancer also could not establish an association between workplace exposure to uranium and lung cancer. The plant operated between 1943 and 1947, separating and enriching uranium for use in atomic bombs. The men were exposed to external gamma radiation lung doses of 0.001–75 rads (0.00001–0.75 Gy) over a period of about 45 years. Although the study found an increase

in the relative risk for those men who were 45 years or older when first exposed, no clear association was established between the development of lung cancer and radiation or uranium exposure (Cookfair et al. 1983; Polednak et al. 1982). An earlier study conducted on the same cohort found no increase in deaths from other causes associated with radionuclides (e.g., bone cancer, leukemia, respiratory or urogenital diseases) (Polednak and Frome 1981). No statistically significant associations were shown between brain tumor deaths and exposure to low levels of uranium dust, plutonium, external radiation, or other occupational risk factors for workers at the Rocky Flats Nuclear Plant in Colorado. None of the workers had body burdens >1 nCi (37 Bq) (Reyes et al. 1984).

The available human studies that investigated the association between the development of bone sarcomas and exposure to uranium failed to produce evidence for the development of bone sarcomas or bone cancers of any type (Archer et al. 1973a; Chovil and Chir 1981; Cookfair et al. 1983; Cragle et al. 1988; Gottlieb and Husen 1982; Grace et al. 1980; Kusiak et al. 1993; Land et al. 1993; Polednak et al. 1982; Reyes et al. 1984; Saccomanno et al. 1971, 1976, 1988; Samet et al. 1986; Wrenn and Singh 1983).

Development of lymphatic malignancies (other than leukemia) has also been associated with inhalation exposure to materials associated with uranium. In a study of 2,002 uranium millers, 6 deaths from lymphatic malignancies occurred when 2.6 were expected. The latency period was 20 years (Waxweiler et al. 1983). Another study of uranium mill workers found a slight increase in deaths from tumors of the lymphatic and hematopoietic tissue (Archer et al. 1973b). The authors suggested that this finding might not be due to uranium itself, but rather due to irradiation of the lymph nodes by ^{230}Th, a decay product of ^{234}U and a member of the ^{238}U decay chain.

In intermediate-duration animal studies, golden Syrian hamsters exposed to carnotite uranium ore dust (AMAD=1.5–2.1 μm) at a concentration of 19 mg U/m^3 by inhalation for 16 months failed to shown signs of cancer development upon examination of selected tissues including lungs, trachea, liver, kidneys, spleen, heart, and any abnormal tissue. As compared to unexposed controls, the hamsters had significantly more necrotic liver foci and inflammatory lung responses (Cross et al. 1981b).

In the same study, the results of exposure of golden Syrian hamsters for 16–27 months to concentrations of radon progeny, uranium ore dust (0.5 nCi/m^3 [18.5 Bq/m^3]), or a combination of uranium and radon progeny provided evidence that, while prolonged exposure to uranium dust causes inflammation and

proliferative pulmonary changes, inhalation of radon progeny produced bronchiolar epithelial hyperplasia and changes in the alveolar epithelium in hamsters. The authors also concluded that exposure to radon progeny and development of squamous metaplasia and carcinoma were related. The animals had cumulative radon progeny exposures of more than 8,000 WLM. Pulmonary neoplasms occurred in the three radon-progeny-exposed hamsters and in one hamster exposed to a combination of uranium, radon, and radon progeny. Both the hamsters exposed to radon progeny and those exposed to a combination of uranium and radon progeny had a significantly greater incidence of adenomatous proliferative changes in the alveolar epithelium. Uranium ore-exposed hamsters had significantly more necrotic liver foci and inflammatory lung responses than animals from other exposure groups. Specifically, one pheochromo-cytoma (zero in controls), one melanoma (zero in controls), one hemangioendothelioma (one in controls), two reticulum cell sarcomas (three in controls), and one adrenal cell carcinoma (zero in controls) were seen in animals exposed to uranium dust alone. Two osteosarcomas (zero in controls) were reported in animals exposed to the mixture of uranium ore dust and radon progeny. Four reticulum cell sarcomas (three in controls) and one adrenal cell sarcoma (zero in controls) were also seen in these animals. In animals exposed to radon progeny alone, one undifferentiated sarcoma (zero in controls), three reticulum cell sarcomas (three in controls), and one myelogenous leukemia (one in controls) were observed (Cross et al. 1981b).

In chronic animal studies, analysis of Beagle dogs exposed to 3.4 nCi/m^3 (126 Bq/m^3 or 5 mg U/m^3) uranium dioxide found frank pulmonary neoplasms and atypical epithelial proliferation in 30–46% of the animals. The lung dose was estimated as 600–700 rads (6–7 Gy). Spontaneous tumors in dogs were infrequent, and the incidence found in this study was 50–100 times higher than the expected rate of spontaneous tumors. The authors of the study recommended against the extrapolation of these findings to humans because these glandular neoplasms do not occur frequently in humans (Leach et al. 1973).

Cancer effect levels (CELs) for chemical and radiation inhalation exposure to uranium are shown in Tables 2-1 and 2-2 and plotted in Figures 2-1 and 2-2.

2.2.2 Oral Exposure

The oral toxicity of uranium compounds has been evaluated in several animal species. The maximal dosage just failing to be lethal for rats in a 30-day feeding test was about 0.5% uranium compound in the diet for the 3 soluble compounds (uranyl nitrate hexahydrate, uranyl tetrafluoride, and uranium tetrachloride) and 20% uranium compound for the 3 insoluble uranium compounds (uranium dioxide, uranium trioxide, and triuranium octaoxide) tested. Some of these studies sweetened the feed to make it edible. No amount of insoluble uranium compounds acceptable to the rat was lethal. Dietary levels of 1–4% soluble uranium compound produced 50% mortality in 30 days. The marked difference in the toxicity of soluble and insoluble uranium compounds is attributable to the ease of absorption and, thus, the dose that reaches the target organs. In general, the water-soluble compounds are more toxic by the oral route because of the greater ease of absorption in the gastrointestinal tract (Domingo et al. 1987, 1989a, 1989b; Goel et al. 1980; Maynard and Hodge 1949; Paternain et al. 1989). In a summary of the oral toxicity in both rats and dogs, several uranium compounds were ordered by relative toxicity as follows: very toxic compounds included uranium tetrachloride, uranium peroxide, and uranyl fluoride; toxic compounds included uranium nitrate hexahydrate, uranyl acetate, ammonium diuranate, sodium diuranate, uranium trioxide, and high-grade uranium ore (carnotite); practically nontoxic compounds were uranium tetrafluoride, triuranium octaoxide, and uranium dioxide (Maynard and Hodge 1949).

2.2.2.1 Death

There are no reports of human deaths from oral exposure to uranium compounds. However, data from animal studies demonstrate that soluble uranium compounds, at very high intake levels, can be lethal to animals through the oral route for all durations of exposure. Uranium compounds at these concentrations are not palatable to animals and require sweetening.

Oral LD_{50} (lethal dose, 50% mortality rate) values of 114 and 136 mg U/kg have been estimated for male Sprague-Dawley rats and male Swiss-Webster mice, respectively, following single gavage administrations of uranyl acetate dihydrate (Domingo et al. 1987). Mortality occurred in pregnant Swiss mice exposed to 0.028, 0.28, 2.8, 28 mg U/kg/day uranium as uranyl acetate dihydrate by gavage in water from day 13 of gestation through postnatal day 21. Two dams in the 2.8 and three in the 28 mg U/kg/day groups died before delivery (Domingo et al. 1989b). Deaths were also reported in mice during the first 10

days of feeding studies with uranyl nitrate (8 of 25 at 925 mg U/kg/day) and with uranyl fluoride (2 of 25 at 452 mg/kg/day) (Tannenbaum and Silverstone 1951)

In 30-day oral studies, oral LD_{50} values for both sexes of rats of an unspecified strain given uranyl fluoride or uranyl nitrate hexahydrate have been estimated as 540 and 1,579 mg U/kg/day, respectively. Oral LD_{50} values were 658 and 1,096 mg U/kg/day as uranium tetrachloride for male and female rats, respectively, in a similar 30-day study (Maynard and Hodge 1949). Another 30-day study, in which male and female rats of an unspecified strain were exposed to oral uranium peroxide doses, oral LD_{50} values were estimated as 827 and 1,103 mg U/kg/day, respectively (Maynard and Hodge 1949). In other intermediate-duration feeding studies with rats, 16% mortality was reported in the animals following dietary administration of 664 mg U/kg/day for 30 days. Most of the animals died from complications of chemically induced kidney damage (Maynard et al. 1953).

Two-year feeding studies with uranyl fluoride, uranyl nitrate hexahydrate, uranium tetrafluoride, and uranium dioxide showed that chronic intake of large amounts of uranium can lead to a decrease in lifespan. The largest daily intake that did not affect longevity in the rat was 81 mg U/kg/day as uranyl fluoride. For the other uranium compounds studied, the maximum daily intakes that did not affect longevity were 1,130 mg U/kg/day as uranyl nitrate, 1,390 mg U/kg/day as uranium tetrafluoride, and 1,630 mg U/kg/day as uranium dioxide. About 18% of the experimental rats survived for the entire 2-year duration of the study, while about 38% of the control animals survived (Maynard and Hodge 1949). Most of the deaths in the available animal studies resulted from chemically induced renal damage.

The LD_{50} values for each species and other LOAEL values for mortality from exposure to uranium by the oral route are presented in Table 2-3 and plotted in Figure 2-3.

2.2.2.2 Systemic Effects

No human studies were located regarding respiratory, endocrine, dermal, ocular, body weight, or other systemic effects in humans following acute-, intermediate-, or chronic-duration oral exposure to uranium compounds.

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	

ACUTE EXPOSURE

Death

1	Rat (Sprague-Dawley)	once (GW)				114 M (LD$_{50}$)	Domingo et al. 1987 UO2(C2H5O)2* 2H2O
2	Rat (NS)	once (F)				664 (16% mortality)	Maynard et al. 1953 UO2(NO3)2*6H2O
3	Mouse (Swiss-Webster)	once (GW)				136 M (LD$_{50}$)	Domingo et al. 1987 UO2(C2H5O)2* 2H2O

Systemic

4	Human	once (W)	Gastro		14.3 M (nausea, vomiting, diarrhea)		Butterworth 1955 UO2(NO3)2*6H2O
5	Human	once (IN)	Cardio			131 M (myocarditis)	Pavlakis et al. 1996 UO2(C2H3O2)2*2H2O
			Hemato			131 M (anemia)	
			Musc/skel			131 M (rhabdomyolosis, paralytic ileus)	
			Hepatic		131 M (increased serum ALT, AST, GGT)		
			Renal			131 M (anuria, kidney failure, renal tubule acidosis persisting over 6 months after exposure)	

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
6	Rat (Sprague-Dawley)	once (GW)	Resp	118 M			Domingo et al. 1987 UO2(C2H5O)2* 2H2O
			Hepatic			5.6 M (microhemorrhagic foci)	
			Renal		5.6 M (slight renal dysfunction; minimal focal microscopic lesions in tubular epithelium)		
			Bd Wt		5.6 M (significant weight loss)		
Neurological							
7	Rat (Sprague-Dawley)	once (GW)				11 M (piloerection, tremors, hypothermia, pupillary size decrease, exophthalmos)	Domingo et al. 1987 UO2(C2H3O2)2*2H2O
Reproductive							
8	Rat (NS)	once (F)				664 (reduced litter size)	Maynard et al. 1953 UO2(NO3)2*6H2O
9	Mouse (Swiss-Webster)	Gd 6-15 (GW)			3 F (maternal reduced weight gain and food consumption; increased relative liver weight)		Domingo et al. 1989a UO2(C2H3O2)2*2H2O
Developmental							
10	Mouse (Swiss-Webster)	Gd 6-15 (GW)				3 (underdeveloped renal papillae; cleft palate)	Domingo et al. 1989a UO2(C2H3O2)2*2H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE							
Death							
11	Rat (NS)	30 d (F)				541 (LD$_{50}$)	Maynard and Hodge 1949 UO2F2
12	Rat (NS)	30 d (F)				658 M (LD$_{50}$) 1096 F (LD$_{50}$)	Maynard and Hodge 1949 UCI4
13	Rat (NS)	30 d (F)				827 M (LD$_{50}$) 1103 F (LD$_{50}$)	Maynard and Hodge 1949 UO4
14	Rat (NS)	30 d (F)				7858 M (100% mortality)	Maynard and Hodge 1949 UO2(C2H3O2)2*2H2O
15	Rat (NS)	30 d (F)				664 (increased mortality)	Maynard et al. 1953 UO2(NO3)2*6H2O
16	Mouse (Swiss-Webster)	30 d 1x/d (G)				2.8 F (10% mortality)	Domingo et al. 1989b UO2(C2H3O2)2*2H2O
17	Mouse (Swiss)	38-60 d 1x/d (GW)				5.6 (significant increase in offspring mortality)	Paternain et al. 1989 UO2(C2H5O)2* 2H2O
18	Mouse (dba)	48 wk *ad lib* (F)				925 F (24% mortality)	Tannenbaum and Silverstone 1951 UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
19	Mouse (dba)	48 wk ad lib (F)				452 F (8% mortality)	Tannenbaum and Silverstone 1951 UO2F2
20	Dog (Beagle)	30 d 6 d/wk (F)				15.4 (lethal dose)	Maynard and Hodge 1949 UO2F2
21	Dog (Beagle)	30 d 6 d/wk (F)				63 (lethal dose)	Maynard and Hodge 1949 UCl4
22	Dog (Beagle)	30 d 6 d/wk (F)				386.4 (lethal dose)	Maynard and Hodge 1949 UO4
23	Dog (Beagle)	30 d 6 d/wk (F)				441 (lethal dose)	Maynard and Hodge 1949 UO2
24	Dog (Beagle)	30 d 6 d/wk (F)				5653 (lethal dose)	Maynard and Hodge 1949 U3O8
25	Dog (Beagle)	30 d 6 d/wk (F)				416 (lethal dose)	Maynard and Hodge 1949 UO3
26	Dog (Beagle)	30 d 6 d/wk (F)				237 (lethal dose)	Maynard and Hodge 1949 UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
27	Dog (Beagle)	30 d 6 d/wk (F)				188 (lethal dose)	Maynard and Hodge 1949 Na2U2O7
28	Dog (NS)	138 d (F)				95 (lethal dose)	Maynard and Hodge 1949 UO2(NO3)2*6H2O
29	Dog (Beagle)	30 d 6 d/wk (F)				7580 (lethal dose)	Maynard and Hodge 1949 UF4
30	Dog (Beagle)	30 d 6 d/wk (F)				191 (lethal dose)	Maynard and Hodge 1949 (NH4)2U2O7
31	Rabbit (NS)	30 d (F)				14.2 (67% mortality)	Maynard and Hodge 1949 UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Systemic							
32	Rat (Sprague-Dawley)	28 d (W)	Resp	35.3 M 40.0 F			Gilman et al. 1998a UO2(NO3)2*6H2O
			Cardio	35.3 M 40.0 F			
			Gastro	35.3 M 40.0 F			
			Hemato	35.3 M 40.0 F			
			Musc/skel	35.3 M 40.0 F			
			Hepatic	35.3 M 40.0 F			
			Renal	35.3 M	40.0 F (39% increase in serum uric acid)		
			Endocr	35.3 M 40.0 F			
			Bd Wt	35.3 M 40.0 F			
			Other	35.3 M 40.0 F			

Table 2-3. Levels of Significant Exposure to Uranium – Chemical Toxicity – Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
33	Rat (Sprague-Dawley)	91 d (W)	Resp	36.73 M 53.56 F			Gilman et al. 1998a UO2(NO3)2*6H2O
			Cardio	36.73 M 53.56 F			
			Gastro	36.73 M 53.56 F			
			Hemato	36.73 M 53.56 F			
			Musc/skel	36.73 M 53.56 F			
			Hepatic		0.06 M (anisokaryosis, 0.09 F vesiculation, increased portal density, perivenous vacuolation and homogeneity)		
			Renal		0.06 M (tubular dilation, apical 0.09 F nuclear displacement, vesiculation, cytoplasmic vacuolation, glomerular capsular sclerosis, interstitial reticulin sclerosis and lymphoid cuffing)		
			Endocr	0.06 M 0.42 F	0.31 M (multifocal reduction of 2.01 F follicular size, incr. epithelial height in thyroid, decr. amount and density of colloid in males only)		
			Bd Wt	36.73 M 53.56 F			
			Other	36.73 M 53.56 F			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
34	Rat (NS)	30 d (F)	Resp	6637			Maynard and Hodge 1949 UO2(NO3)2*6H2O
			Cardio	6637			
			Gastro	6637			
			Hemato	6637			
			Hepatic	6637			
			Renal	3.3	16.6 (minimal microscopic lesions in tubular epithelium)		
			Bd Wt	331		664 (27% reduction in body weight)	
35	Rat (NS)	30 d (F)	Resp	8768			Maynard and Hodge 1949 UCl4
			Cardio	8768			
			Gastro	8768			
			Hemato	8768			
			Hepatic	8768			
			Renal	88	438 (mild to moderate renal changes)		
			Bd Wt	658	877 M (18% reduction in body weight gain)		

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
36	Rat (NS)	30 d (F)	Resp	11033			Maynard and Hodge 1949 UO4
			Cardio	11033			
			Gastro	11033			
			Hemato	11033			
			Hepatic	11033			
			Renal	55	138 (minimal microscopic lesions in tubular epithelium)		
			Bd Wt		55 (unspecified decreased body weight gain)		
37	Rat (NS)	30 d (F)	Resp	10818			Maynard and Hodge 1949 UO2F2
			Cardio	10818			
			Gastro	10818			
			Hemato	10818			
			Hepatic	10818			
			Renal	5.4	27 (minimal microscopic lesions in tubular epithelium)		
			Bd Wt	541	1082 (35% decreased body weight gain)		

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	Serious (mg/kg/day)	Reference Chemical Form
38	Rat (NS)	30 d (F)	Resp	12342			Maynard and Hodge 1949 UO2
			Cardio	12342			
			Gastro	12342			
			Hemato	12342			
			Hepatic	12342			
			Renal	12342			
			Bd Wt	12342			
39	Rat (NS)	30 d (F)	Resp	7858 M			Maynard and Hodge 1949 UO2(C2H3O2)2*2H2O
			Cardio	7858 M			
			Gastro	7858 M			
			Hemato	7858 M			
			Hepatic	7858 M			
			Renal	786 M	7858 M (minimal microscopic lesions in tubular epithelium)		
			Bd Wt	196 M	786 M (reduced growth)		
40	Rat (NS)	30 d (F)	Resp	11650 M			Maynard and Hodge 1949 UO3
			Cardio	11650 M			
			Gastro	11650 M			
			Hemato	11650 M			
			Hepatic	11650 M			
			Renal	11650 M			
			Bd Wt	1165 M	11650 M (14% reduced growth)		

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
41	Rat (NS)	30 d (F)	Bd Wt			6637 (retarded growth)	Maynard et al. 1953 UO2(NO3)2*6H2O
42	Rat (Sprague-Dawley)	4 wk (W)	Hemato	4.5 M	9 M (5.3 % increased hematocrit, 9% increased mean corpuscular hemoglobin concentration, 7% increased erythrocytes)		Ortega et al. 1989a UO2(C2H3O2)2*2H2O
			Hepatic	2.2 M	4.5 M (28% increased blood glucose; 34% increased SGOT, 32% increased SGPT)		
			Renal		1.1 M (6% increased total plasma proteins)		
43	Mouse (dba)	48 wk ad lib (F)	Bd Wt	462 F			Tannenbaum and Silverstone 1951 UO2(NO3)2*6H2O
			Other	462 F			
44	Mouse (C3H)	18 wk ad lib (F)	Bd Wt	925 F			Tannenbaum and Silverstone 1951 UO2(NO3)2*6H2O
			Other	925 F			
45	Mouse (C3H)	48 wk ad lib (F)	Renal		452 M (nodular development on kidney surface)		Tannenbaum and Silverstone 1951 UO2F2
46	Mouse (dba)	48 wk ad lib (F)	Renal		452 M (nodular development on kidney surface)		Tannenbaum and Silverstone 1951 UO2F2

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
47	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	7.7	15.4	(minimal hemorrhagic lesions)			Maynard and Hodge 1949 UO2F2
			Hepatic	7.7	15.4	(fatty infiltration)			
			Renal	7.7			15.4	(moderate degeneration or tubular epithelium)	
48	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	15.4			386.4	(hemorrhage)	Maynard and Hodge 1949 UO4
			Hepatic	15.4	386.4	(mild degeneration)			
			Renal		15.4	(minimal microscopic lesions in tubular epithelium)			
49	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	5653					Maynard and Hodge 1949 U3O8
			Hepatic	2827	5653	(fatty infiltration)			
			Renal		5653	(proteinuria; glucosuria; minimal microscopic lesions in tubular epithelium)			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		Serious (mg/kg/day)		Reference Chemical Form
50	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	7580	15160	(mild hemorrhage)			Maynard and Hodge 1949 UF4
			Hepatic	7580	15160	(degenerative fatty changes)			
			Renal		3790	(83% increase in blood urea nitrogen; proteinuria, glucosuria; minimal microscopic lesions in tubular epithelium)			
51	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	17.6	441	(slight hemorrhagic lesions)			Maynard and Hodge 1949 UO2
			Hepatic	17.6	441	(slight degenerative changes)			
			Renal	17.6	441	(proteinuria, glucosuria; minimal microscopic lesions in tubular epithelium)			
52	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	83			416	(hemorrhage)	Maynard and Hodge 1949 UO3
			Hepatic	83	416	(slight fatty infiltration)			
			Renal				83	(severe degeneration changes in tubular epithelium)	
53	Dog (Beagle)	138 d (F)	Renal	47	95	(elevated NPN and BUN, proteinuria, glucosuria)			Maynard and Hodge 1949 UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
54	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	191					Maynard and Hodge 1949 (NH4)2U2O7
			Hepatic	191					
			Renal		38	(proteinuria, glucosuria; minimal microscopic lesions in tubular epithelium)			
55	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	12			63	(mild hemorrhage)	Maynard and Hodge 1949 UCl4
			Hepatic	63	313	(minimal hepatic lesions)			
			Renal	63			313	(necrosis)	
56	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	188					Maynard and Hodge 1949 Na2U2O7
			Hepatic	37	188	(fatty infiltration)			
			Renal		37	(mild degenerative changes)			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
57	Rabbit (New Zealand)	91 d (W)	Resp	28.70 M 43.02 F			Gilman et al. 1998b UO2(NO3)2*6H2O
			Cardio	28.70 M 43.02 F			
			Gastro	28.70 M 43.02 F			
			Hemato	28.70 M 43.02 F			
			Musc/skel	28.70 M 43.02 F			
			Hepatic	28.70 M 43.02 F			
			Renal		0.05[b] M (anisokaryosis, nuclear 0.49 F vesiculation)	0.88 M (interstitial collagen and/or 43.02 F reticulin sclerosis)	
			Endocr	28.70 M 43.02 F			
			Bd Wt	28.70 M 43.02 F			
			Other	28.70 M 43.02 F			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
58	Rabbit (New Zealand)	91 d (W)	Resp	40.98 M			Gilman et al. 1998c UO2(NO3)2*6H2O
			Cardio	40.98 M			
			Gastro	40.98 M			
			Hemato	40.98 M			
			Musc/skel	40.98 M			
			Hepatic		1.36 M (variation in nuclear size, nuclear pyknosis, extensive cytoplasmic vacuolization)		
			Renal		1.36 M (tubular dilation)	40.38 M (glycosuria, proteinuria, anisokaryosis, nuclear vesiculation, interstitial collagen and/or reticulin sclerosis)	
			Endocr	40.98 M			
			Bd Wt	40.98 M			
			Other	40.98 M			
59	Rabbit (NS)	30 d (F)	Renal		2.8 (slight to moderate renal tubular degeneration)		Maynard and Hodge 1949 UO2(NO3)2*6H2O
			Bd Wt	2.8		14.2 (20% decreased body weight)	
60	Rabbit (New Zealand)	91 d (W)	Renal		0.93 M (increased glomerular basement membrane thickness)		McDonald-Taylor et al. 1992 UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
61	Rabbit (New Zealand)	91 d (W)	Renal		0.93 M (tubular debris, interstitial fibrosis, splitting and thickening of basal lamina, increased size of lysosomes and mitochondria)		McDonald-Taylor et al. 1997 UO2(NO3)2*6H2O
	Immunological/Lymphoreticular						
62	Rat (Sprague-Dawley)	28 d (W)		35.3 M 40.0 F			Gilman et al. 1998a UO2(NO3)2*6H2O
63	Rat (Sprague-Dawley)	91 d (W)		7.54 M 9.98 F	36.73 M (sinus hyperplasia in 53.56 F spleen)		Gilman et al. 1998a UO2(NO3)2*6H2O
64	Rabbit (New Zealand)	91 d (W)		28.70 M 43.02 F			Gilman et al. 1998b UO2(NO3)2*6H2O
	Neurological						
65	Rat (Sprague-Dawley)	28 d (W)		35.3 M 40.0 F			Gilman et al. 1998a UO2(NO3)2*6H2O
66	Rat (Sprague-Dawley)	91 d (W)		36.73 M 53.56 F			Gilman et al. 1998a UO2(NO3)2*6H2O
67	Rabbit (New Zealand)	91 d (W)		28.70 M 43.02 F			Gilman et al. 1998b UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Reproductive							
68	Rat (Sprague-Dawley)	28 d (W)		35.3 M 40.0 F			Gilman et al. 1998a UO2(NO3)2*6H2O
69	Rat (Sprague-Dawley)	91 d (W)		36.73 M 53.56 F			Gilman et al. 1998a UO2(NO3)2*6H2O
70	Mouse (Swiss-Webster)	64 d (W)				11.2 M (significantly reduced sperm counts)	Llobet et al. 1991 UO2(C2H3O2)2*2H2O
71	Mouse (Swiss-Webster)	4-8 wk (GW)		14			Paternain et al. 1989 UO2(C2H3O2)2*2H2O
72	Rabbit (New Zealand)	91 d (W)		28.70 M 43.02 F			Gilman et al. 1998b UO2(NO3)2*6H2O
Developmental							
73	Mouse (Swiss-Webster)	30 d 1 x/d (G)				28 (decrease in litter size on postnatal day 21; decreased day 21 viability index)	Domingo et al. 1989b UO2(C2H3O2)2*2H2O
74	Mouse (Swiss-Webster)	4-8 wk (GW)		6		14 (embryolethality)	Paternain et al. 1989 UO2(C2H3O2)2*2H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	

CHRONIC EXPOSURE

Death

75	Rat (NS)	2 yr (F)				308 (100% mortality)	Maynard and Hodge 1949; Maynard et al. 1953 UO2
76	Rat (NS)	2 yr (F)				135.2 M (6-12% mortality)	Maynard and Hodge 1949; Maynard et al. 1953 UO2F2
						270 F (57% mortality)	

Systemic

77	Rat (NS)	2 yr (F)	Hemato	16.6	33 (mild anemia; increased leucocyte count)		Maynard and Hodge 1949; Maynard et al. 1953 UO2(NO3)2*6H2O
			Renal	16.6	33 (minimal microscopic lesions in tubular epithelium)		
78	Rat (NS)	2 yr (F)	Bd Wt	135.2 M		270 M (30% decrease in body weight)	Maynard and Hodge 1949; Maynard et al. 1953 UO2F2
				135.2 F		270 F (29% decrease in body weight)	
79	Rat (NS)	2 yr (F)	Hemato	12341			Maynard and Hodge 1949; Maynard et al. 1953 UO2
			Renal	12341			
			Bd Wt	12341			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
80	Rat (NS)	2 yr (F)	Hemato	10611			Maynard and Hodge 1949; Maynard et al. 1953 UF4
			Renal	1061	10611 (mild renal tubular degeneration)		
			Bd Wt	10611			
81	Dog (NS)	1 yr (F)	Resp	95			Maynard and Hodge 1949 UO2(NO3)2*6H2O
			Renal	47	95 (elevated NPN, BUN; glucosuria, proteinuria)		
			Bd Wt	95			
82	Dog (Beagle)	1 yr (F)	Hemato	31			Maynard and Hodge 1949; Maynard et al. 1953 UCL4
			Renal	6.3	31 (mild glucosuria, proteinuria)		
83	Dog (NS)	1 yr (F)	Renal	8			Maynard and Hodge 1949; Maynard et al. 1953 UO2F2
			Bd Wt	8			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

| Key to[a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference Chemical Form |
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Reproductive						
84	Rat (NS)	2 yr (F)				331 M (testicular degeneration)	Maynard et al. 1953 UO2(NO3)2*6H2O

[a]The number corresponds to entries in Figure 2-3.

[b] Used to derive an intermediate-duration oral exposure minimum risk level (MRL) of 0.002 mg/kg/day; adjusted by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for variability among humans)

ad lib = ad libitum; Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; LD$_{50}$ = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; NPN = nonprotein nitrogen; NS = not specified; Resp = respiratory; (W) = water; wk = week(s); x = times; yr = year(s)

Figure 2-3. Levels of Significant Exposure to Uranium - Oral

Chemical Toxicity - Acute (≤ 14 days)

Figure 2-3. Levels of Significant Exposure to Uranium - Oral (cont.)

Chemical Toxicity - Intermediate (15-364 days)

Figure 2-3. Levels of Significant Exposure to Uranium - Oral (cont.)

Chemical Toxicity - Intermediate (15-364 days)

Figure 2-3. Levels of Significant Exposure to Uranium - Oral (cont.)

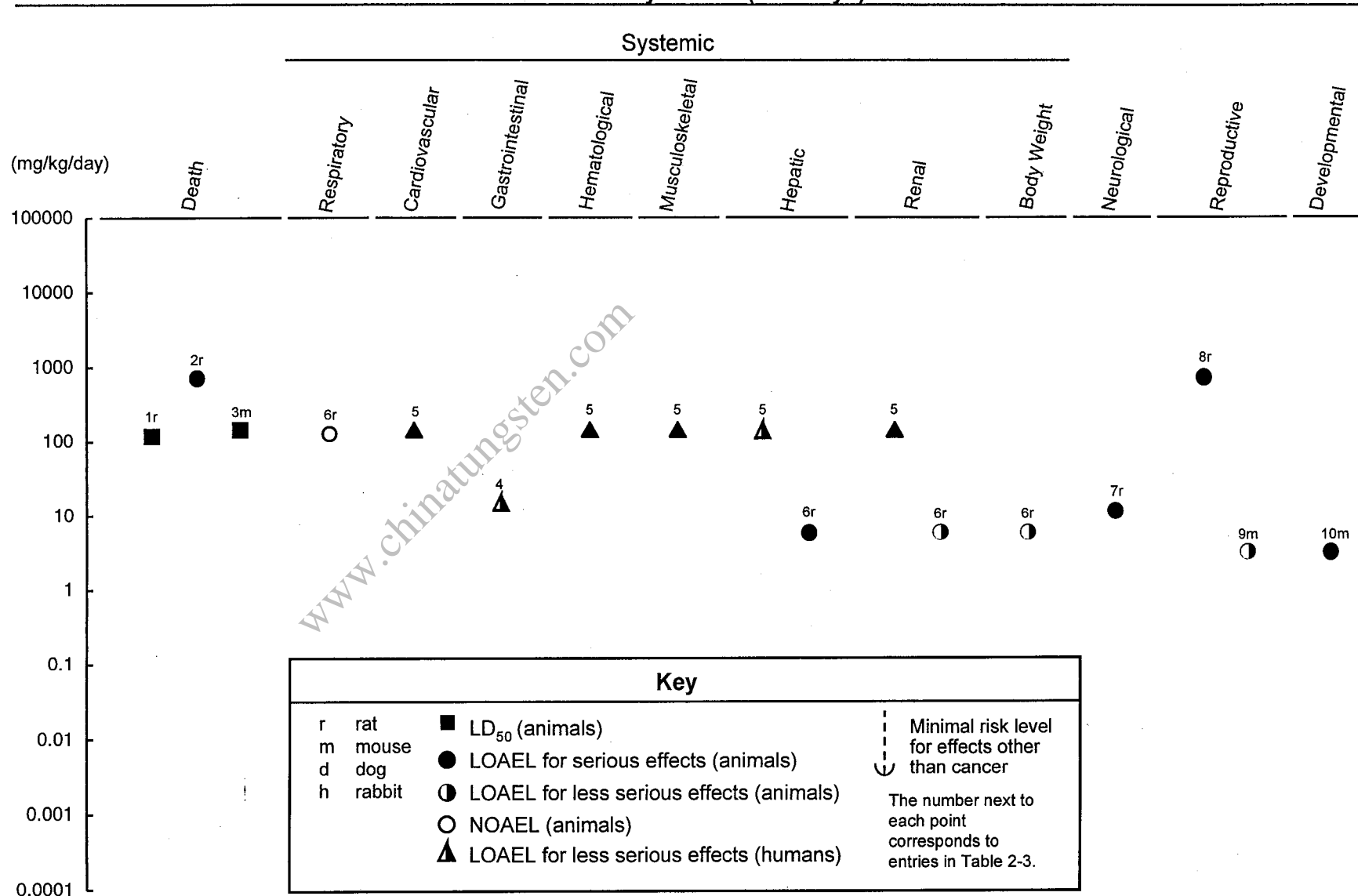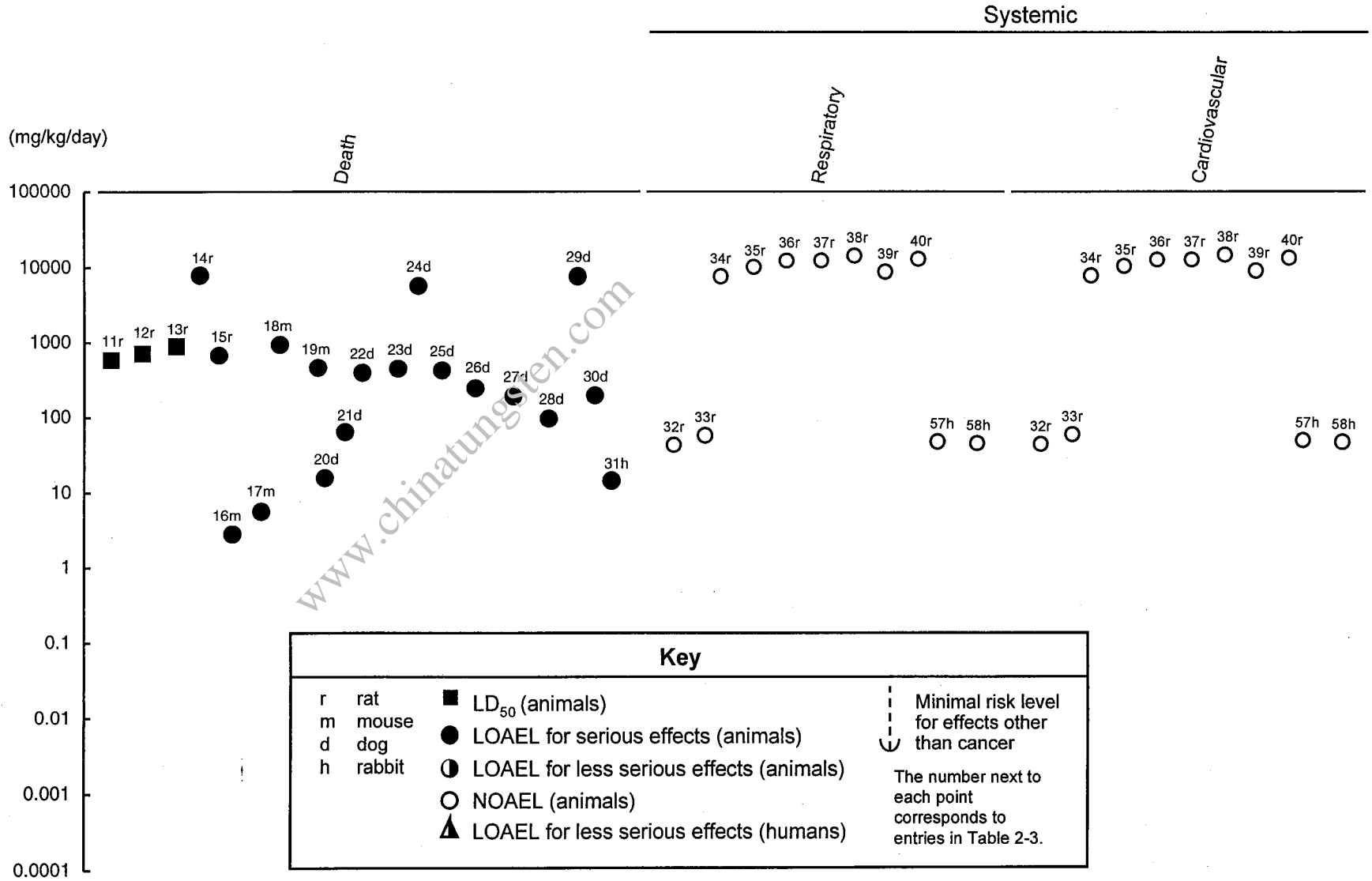## Chemical Toxicity - Intermediate (15-364 days)
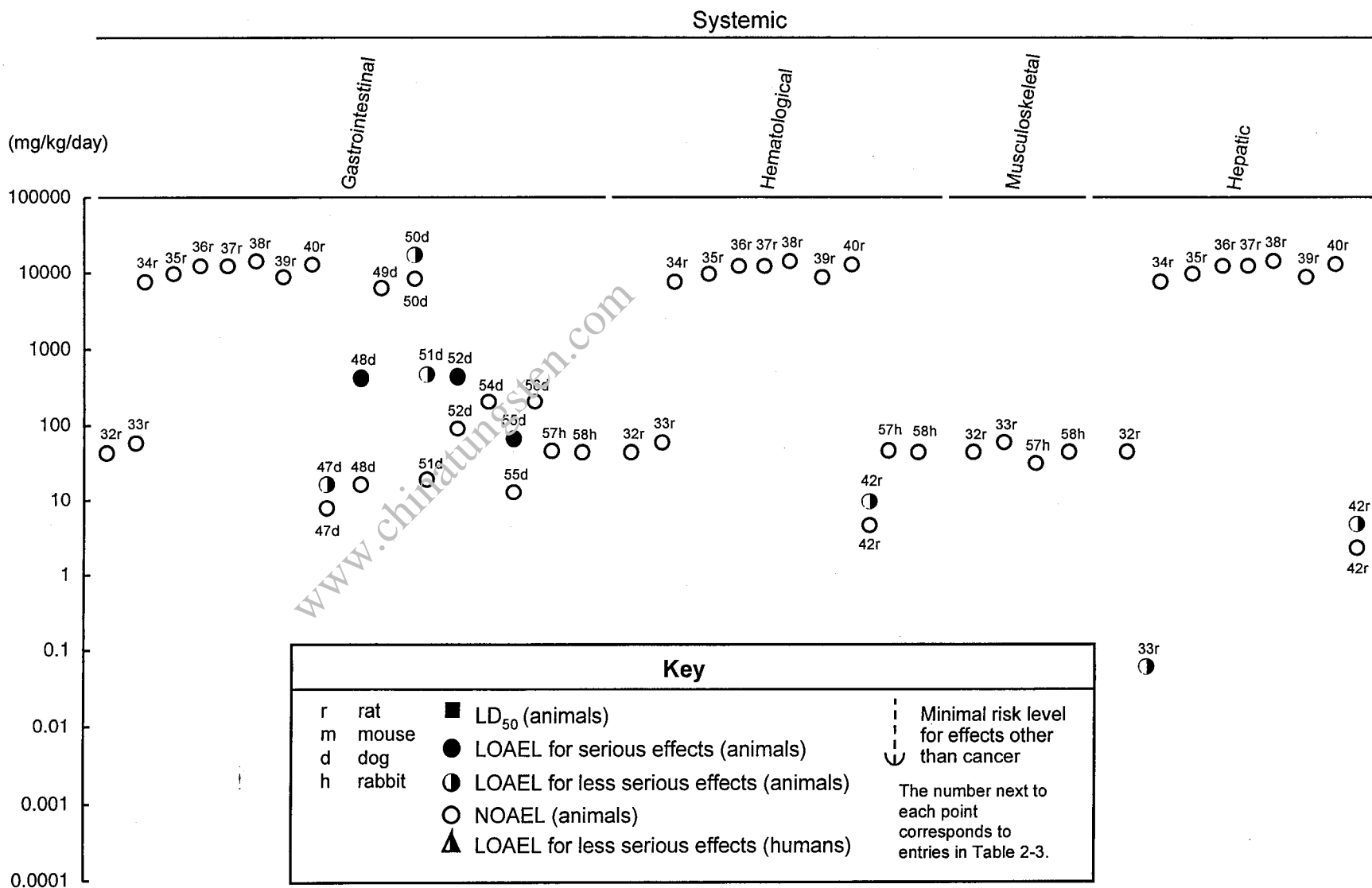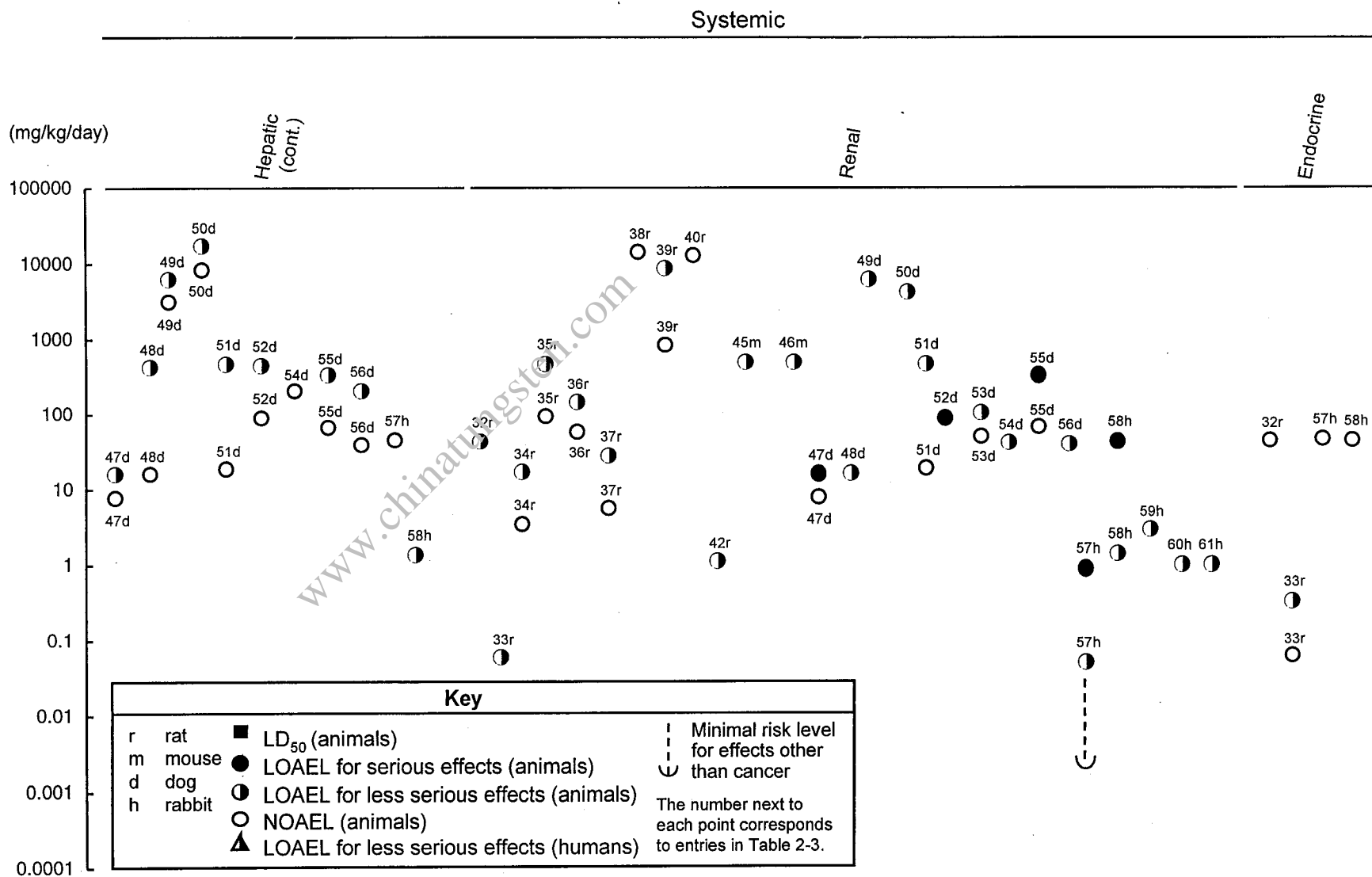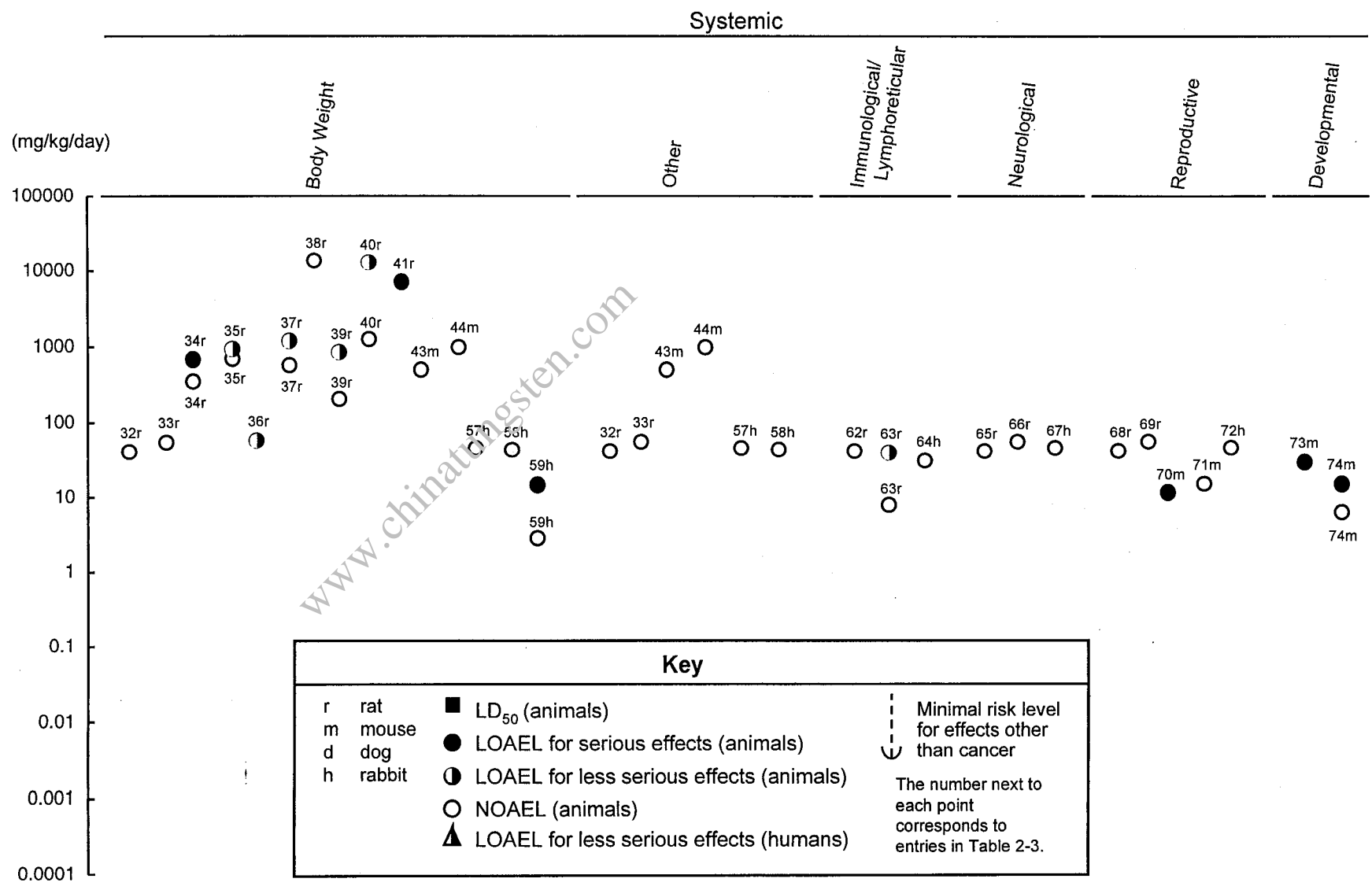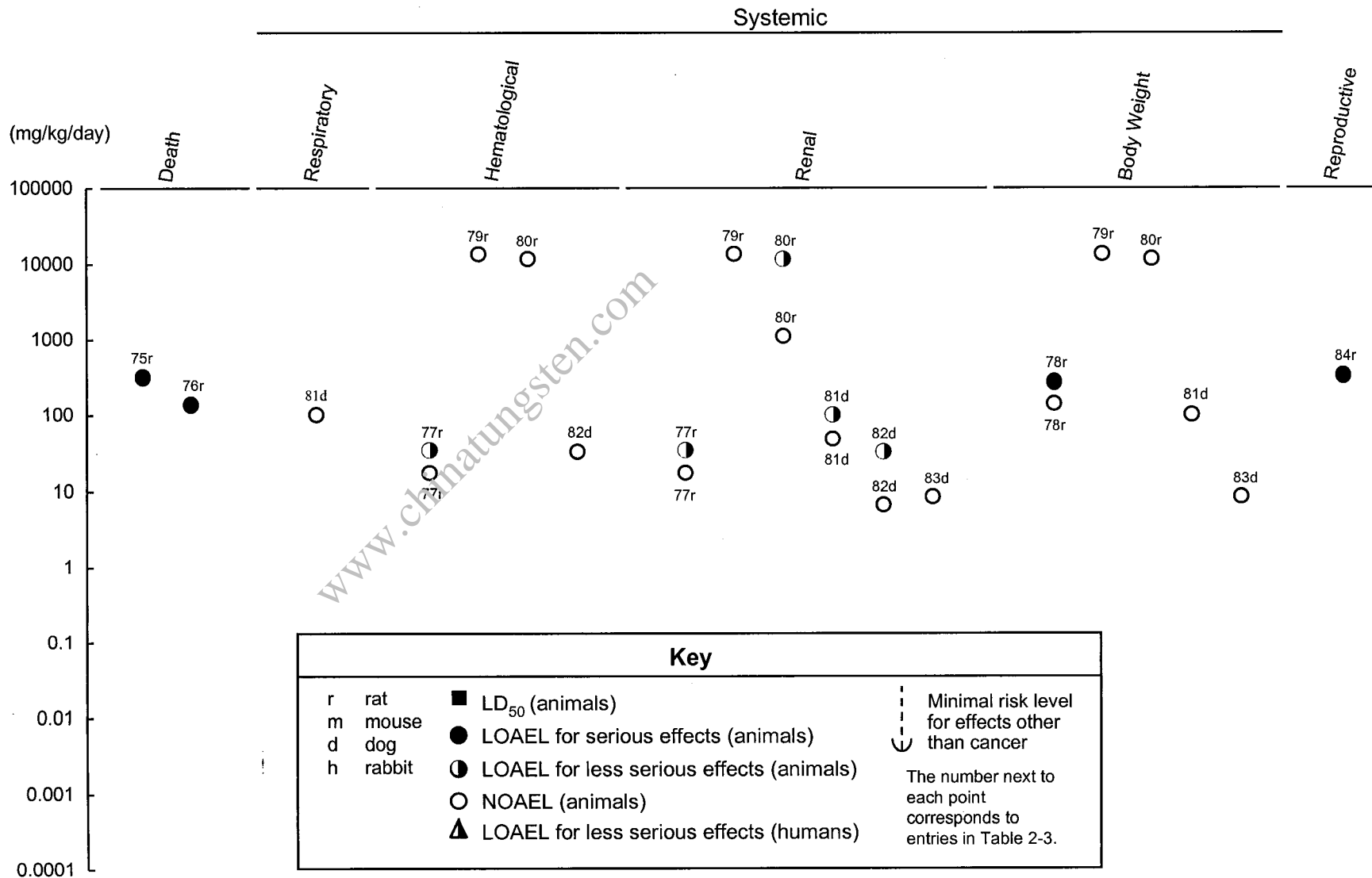
Figure 2-3. Levels of Significant Exposure to Uranium - Oral (cont.)

Chemical Toxicity - Intermediate (15-364 days)

Figure 2-3. Levels of Significant Exposure to Uranium - Oral (cont.)

Chemical Toxicity - Chronic (≥365 days)

Animal data are lacking regarding musculoskeletal, metabolic, dermal, or ocular effects following oral exposure to uranium and its compounds for all durations. Similarly, no animal studies were located on the hematological effects of uranium in animals following acute-duration oral exposure or on the cardio-vascular, endocrine, or other systemic effects following acute- or chronic-duration oral exposure. Data exist for the respiratory, renal, and body weight effects following oral exposure of animals to uranium for all durations. However, the existing data on the hematological, cardiovascular, hepatic, and other systemic effects of uranium in animals are limited to acute- or chronic-duration inhalation exposure; data on the gastrointestinal effects are limited to acute-duration exposure.

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

Respiratory Effects.   Respiratory effects from oral exposure to uranium are unlikely. In an acute-duration animal study, no adverse effects on the respiratory system were reported in rats given single oral doses of 118 mg uranium per kilogram body weight per day (U/kg/day) as uranyl acetate dihydrate (Domingo et al. 1987).

In intermediate-duration exposures, Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in the drinking water (males: up to 35.3 mg/kg/day; females: up to 40.0 mg/kg/day) for 28 days and then sacrificed. No treatment-related histopathological changes were found, and no changes in lung weights were noted (Gilman et al. 1998a).   In several 30-day dietary studies, no adverse effects on the respiratory system were reported in rats exposed to 6,637 mg U/kg/day as uranyl nitrate hexahydrate, 8,769 mg U/kg/day as uranium tetrachloride, 11,033 mg U/kg/day as uranium peroxide, 10,611 mg U/kg/day as uranium tetrafluoride, 10,818 mg U/kg/day as uranyl fluoride, 12,342 mg U/kg/day as uranium dioxide, 8.167 mg U/kg/day as uranyl acetate dihydrate, or 11,650 mg U/kg/day as uranium trioxide (Maynard and Hodge 1949; Maynard et al. 1953; Stokinger et al. 1953). Lengthening the duration of exposure to uranium failed to produce detectable lesions in lungs of laboratory animals. Sprague-Dawley rats (15/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg/kg/day; females: up to 53.56 mg/kg/day) for 91 days and were sacrificed. No treatment-related histopathological changes were found in the lungs, and no changes in lung weights were noted (Gilman et al. 1998a). In addition, New Zealand rabbits were exposed to uranium as uranyl nitrate in the

drinking water (males: up to 28.70 mg/kg/day; females: up to 43.02 mg/kg/day) for 91 days. No treatment-related histopathological changes were found, and no changes in lung weights were noted (Gilman et al. 1998b). Male New Zealand rabbits were also exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg/kg/day) for 91 days, again with no histopathological or organ weight changes found (Gilman et al. 1998c).

In chronic-duration feeding studies, no adverse effects on the respiratory system were reported in 1-year studies of dogs given oral doses of 31 mg U/kg/day as uranium tetrachloride, 3,790 mg U/kg/day as uranium hexachloride, 8 mg U/kg/day as uranyl fluoride, or 4,407 mg U/kg/day as uranium dioxide (Maynard and Hodge 1949; Maynard et al. 1953). In 2-year studies, the respiratory system was unaffected in dogs and rats given 2 mg U/kg/day as uranyl nitrate hexahydrate and in rats given 12,141 mg U/kg/day as uranium dioxide, 664 mg U/kg/day as uranyl nitrate hexahydrate, 10,611 mg U/kg/day as uranium tetrafluoride, or 405 mg U/kg/day as uranyl fluoride (Maynard and Hodge 1949; Maynard et al. 1953; Stokinger et al. 1953).

Cardiovascular Effects.   Cardiovascular effects following intake of uranium are unlikely. One case report documented a cardiovascular effect that was possibly related to uranium exposure in a male admitted to the hospital following deliberate ingestion of 15 g of uranyl acetate, along with an unknown quantity of benzodiazepine, in a failed suicide attempt. While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man. Initial blood chemistry was unremarkable, and decreased cardiac output was consistent with ingestion of benzodiazepam. The patient was reported to have suffered from myocarditis resulting from the uranium ingestion, resolving 6 months after the ingestion (Pavlakis et al. 1996).

The available studies in animals have found no adverse cardiovascular effects following oral exposures for up to 30 days to uranium compounds. In one study, Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 35.3 mg/kg/day; females: up to 40.0 mg/kg/day) for 28 days and sacrificed. No cardiac histopathological changes were found, and no changes in heart weights were noted (Gilman et al. 1998a). No changes in the heart or blood vessels were observed in rats following oral exposure to doses as high as 9,393 mg U/kg/day as uranyl nitrate hexahydrate, 8,769 mg U/kg/day as uranium tetrachloride, 11,033 mg U/kg/day as uranium peroxide, 10,611 mg U/kg/day as uranium tetrafluoride, 10,819 mg U/kg/day as uranyl fluoride,

12,342 mg U/kg/day as uranium dioxide, 11,650 mg U/kg/day as uranium trioxide, or 7,859 mg U/kg/day as uranyl acetate dihydrate (Maynard and Hodge 1949). Sprague-Dawley rats (15/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg/kg/day; females: up to 53.56 mg/kg/day) for 91 days and sacrificed. No uranium-related histopathological changes were found in the heart, and no changes in heart weights were noted (Gilman et al. 1998a). In addition, New Zealand rabbits were exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg/kg/day; females: up to 43.02 mg/kg/day) for 91 days. No treatment-related cardiac histopathological changes were noted, and no changes in heart weights were detected (Gilman et al. 1998b). Male New Zealand rabbits also were exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg/kg/day) for 91 days, with no histopathological or organ weight changes (Gilman et al. 1998c).

Gastrointestinal Effects.   A volunteer given a single dose of 1 g uranyl nitrate (14.3 mg/kg) and observed for clinical signs and symptoms within 24 hours after intake suffered acute nausea, vomiting, and diarrhea within a few hours of administration. All clinical signs returned to normal within 24 hours after administration of the oral uranyl nitrate dose (Butterworth 1955). Paralytic ileus was reported in a male after the deliberate ingestion of 15 g uranyl acetate (Pavlakis et al. 1996). While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man.   No other reports of gastrointestinal effects after acute-duration exposure to uranium in either humans or laboratory animals were available.

Studies of intermediate-duration exposure to uranium compounds were available for laboratory animals. In one study, Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in the drinking water (males: up to 35.3 mg/kg/day; females: up to 40.0 mg/kg/day) for 28 days and sacrificed. No treatment-related histopathological changes were found, and no changes in organ weights were noted (Gilman et al. 1998a). In a study of longer duration, Sprague-Dawley rats (15/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg/kg/day; females: up to 53.56 mg/kg/day) for 91 days and then sacrificed. No treatment-related histopathological changes were found in the gastrointestinal tract, and no changes in stomach and intestinal weights were noted (Gilman et al. 1998a). In addition, New Zealand rabbits were exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg/kg/day; females: 0 up to 43.02 mg/kg/day) for 91 days. No treatment-related histopathological changes were found, and no changes in organ weights (i.e., colon, duodenum, stomach [gastric cardia, fundus, and pylorus]) were noted (Gilman et al. 1998b). Male New Zealand

rabbits were exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg/kg/day) for 91 days, with no histopathological or organ weight changes found (Gilman et al. 1998c).

Hematological Effects.   In one case report, a male (no age or weight given), was admitted to hospital following the deliberate ingestion of 15 g of uranyl acetate, along with an unknown quantity of benzodiazepine, in a failed suicide attempt. While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man. Initial blood chemistry was unremarkable; however, an anemia developed and continued to progress over the next 8 weeks, along with persistent renal dysfunction (Pavlakis et al. 1996). While the authors attributed the renal dysfunction to uranium ingestion, the etiology of the anemia was unknown. The patient also suffered from peptic ulcer disease which may have been related to the anemia.

The majority of animal studies show no effect of uranium on hematological parameters after oral exposure. Exposure to uranium as uranyl nitrate in drinking water had no hematological effects in Sprague-Dawley rats after 28 days (up to 40 mg U/kg/day) or 91 days (up to 53 mg U/kg/day) (Gilman et al. 1998a), or in New Zealand rabbits after 91 days (up to 43 mg U/kg/day) (Gilman et al. 1998b, 1998c). Exposure to a variety of uranium compounds in feed had no effect on hematological parameters in intermediate- and chronic-duration studies (Maynard and Hodge 1949). One study reported a significant increase in the hematocrit and hemoglobin values, the mean corpuscular hemoglobin concentration, and the number of erythrocytes at 9 mg U/kg/day as uranyl acetate in drinking water for 4 weeks, but not at 4.5 mg U/kg/day and lower doses (Ortega et al. 1989a).

In a chronic-exposure feeding study, mild anemia and an increased leucocyte count were observed in rats given uranyl nitrate hexahydrate doses corresponding to 33 mg U/kg/day for 2 years (Maynard and Hodge 1949; Maynard et al. 1953).

Musculoskeletal Effects.   In one human case report, a human male (no age or weight given), was admitted to hospital following the deliberate ingestion of 15 g of uranyl acetate, along with an unknown quantity of benzodiazepine, in a failed suicide attempt. While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man. The patient suffered from increasing rhabdomyolysis (biochemically characterized by increased creatine kinase). At 6 months following the

initial toxic insult, the rhabdomyolysis had resolved, and the subject showed no residual signs of muscle toxicity (Pavlakis et al. 1996). The etiology of this effect is unknown.

In the available animal studies, the existing data provide evidence that uranium exposure does not cause detectable damage to the musculoskeletal system. Histopathological examination of muscle after exposure to uranium in drinking water as uranyl nitrate showed no effects in Sprague-Dawley rats after 28 days (up to 40 mg U/kg/day) or 91 days (up to 53 mg U/kg/day) (Gilman et al. 1998a), or in New Zealand rabbits after 91 days (up to 43 mg U/kg/day) (Gilman et al. 1998b, 1998c).

Hepatic Effects.   Few human data are available on the hepatic effects of uranium. In one case report, a human male (no age or weight given), was admitted to hospital following the deliberate ingestion of 15 g of uranyl acetate, along with an unknown quantity of benzodiazepine, in a failed suicide attempt. While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man. The patient suffered from increasing liver dysfunction, characterized by increased serum levels of ALT, AST, and GGK. Six months following the initial toxic insult, the patient had no residual signs of hepatic toxicity (Pavlakis et al. 1996). The etiology of this effect is unknown, although histological signs of hepatic toxicity have been observed in animals after oral exposure to uranium.

In the available animal studies, the existing data provide evidence that uranium exposure can damage the liver, although the etiology for this effect is not certain. In an acute-duration study in which Sprague-Dawley rats were given single gavage doses of 5.6 or 118 U/kg as uranyl acetate dihydrate, microhemorrhagic foci in the liver were observed at both doses tested (Domingo et al. 1987).

Ingested uranium doses were also hepatotoxic to dogs in studies of intermediate-duration exposure. When uranyl fluoride was tested at 7.7, 15.4, 77.3, 386.7, or 3,864 mg U/kg/day for 30 days, fatty infiltration was seen in dogs at the 15.4 mg U/kg/day dose level (Maynard and Hodge 1949). In other tests, uranium tetrachloride induced minimal hepatic lesions at a dose level of 313 mg U/kg/day; uranium peroxide induced mild degeneration at a dose level of 386 mg U/kg/day; uranium dioxide induced mild degeneration at a dose level of 441 mg U/kg/day; uranium trioxide induced slight fatty infiltration at a dose level of 416 mg U/kg/day; triuranium octaoxide induced mild fatty changes at a dose level of 5,653 mg U/kg/day; sodium diuranate induced mild degeneration at a dose level of 37.5 mg U/kg/day;

uranium tetrafluoride caused degenerative fatty changes at a dose level of 15,159 mg U/kg/day; and uranyl nitrate hexahydrate induced minimal hepatic degeneration at a dose level of 237 mg U/kg/day (Maynard and Hodge 1949).

Hepatic toxicity was also found several other studies. In one study, Sprague-Dawley rats (15/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg/kg/day; females: up to 53.56 mg/kg/day) for 91 days and then sacrificed. Hepatic lesions, which included anisokaryosis, vesiculation, increased portal density, perivenous vacuolation, and homogeneity, were observed in the liver at all doses (Gilman et al. 1998a), although the dose ranging portion of this study found no effects at essentially the same doses as those discussed below (Gilman et al. 1998c). However, in New Zealand rabbits exposed to uranium as uranyl nitrate in the drinking water (males: 0, 0.05, 0.20, 0.88, 4.82, and 28.70 mg/kg/day; females: 0, 0.49, 1.32, and 43.02 mg/kg/day) for 91 days, no treatment-related histopathological changes were found, and no changes in liver weights were noted (Gilman et al. 1998b). In contrast, another study by the same investigator in male New Zealand rabbits exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg/kg/day) for 91 days found irregular accentuation of zonation in the liver, accompanied by increased variation in hepatocellular nuclear size, nuclear pyknosis, and extensive cytoplasmic vacuolization. These changes were found to be treatment-related but not dose-related (Gilman et al. 1998c).

In other intermediate-duration studies, no effects were seen on the liver of dogs given oral doses of 9,393 mg U/kg/day as uranyl nitrate hexahydrate or 191 mg U/kg/day as ammonium diuranate for 30 days (Maynard and Hodge 1949). Similarly, no effects were seen on the liver of rats given oral doses of 8,769 mg U/kg/day as uranium tetrachloride, 11,033 mg U/kg/day as triuranium peroxide, 10,818 mg U/kg/day as uranyl fluoride, 12,342 mg U/kg/day as uranium dioxide, 11,650 mg U/kg/day as triuranium trioxide, or 7,859 mg U/kg/day as uranium acetate dihydrate for 30 days (Maynard and Hodge 1949). Sprague-Dawley rats (10/sex/dose, 60 g) were exposed to uranium as uranyl nitrate in drinking water (males: up to 35.3 mg/kg/day; females: up to 40.0 mg/kg/day) for 28 days and then sacrificed. No treatment-related histopathological changes were found, and no changes in liver weights were noted (Gilman et al. 1998a).

Renal Effects.   Uranium has been identified as a nephrotoxic metal, exerting its toxic effect by chemical action mostly in the renal proximal tubules of humans and animals. In this regard, uranium is a less potent nephrotoxin than the classical nephrotoxic metals (cadmium, lead, mercury) (Goodman 1985).

Few human data are available that adequately describe the dose-response toxicity of uranium after an oral exposure. In one human case report study, a male (no age or weight given), was admitted to hospital following the deliberate ingestion of 15 g of uranyl acetate, along with an unknown quantity of benzo-diazepine, in failed a suicide attempt. While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man. Initial blood chemistry was normal; however, 16 hours after admission, his blood urea levels had doubled and creatinine levels had increased 3.5-fold, which suggested renal damage. A diagnosis of acute nephrotoxicity from heavy metal exposure was made, and chelation therapy with Ca-EDTA, sodium bicarbonate, and mannitol was initiated. His plasma uranium on the day following commencement of chelation therapy was 3.24 µmol/L, decreasing to 1.18 µmol/L after 5 days of chelation and dialysis. Chelation therapy was then stopped; however, dialysis continued for 2 weeks at which point kidney function recovered sufficiently to allow withdrawal of dialysis therapy. The patient's anemia persisted over the next 8 weeks, along with persistent renal dysfunction. Additional chelation therapy was initiated with both Ca EDTA and Ca DTPA (diethylenetriamine pentaacetic acid) without success. At 6 months following the initial toxic insult, the patient still suffered from an incomplete Fanconi syndrome (renal tubular acidosis) requiring supplemental sodium bicarbonate therapy on a daily basis (Pavlakis et al. 1996). The authors suggested that pre-existing peptic ulcer disease in this patient may have exacerbated toxicity by increased absorption of uranium through the damaged stomach mucosal layer.

Although there is little additional information about renal effects in humans following oral exposure to uranium compounds, there is sufficient information in animals with high exposures to both soluble and insoluble uranium to permit the conclusion that uranium has a low order of metallotoxicity in mammals. Many of the nonradioactive heavy metals such as lead, arsenic, and mercury would produce severe, perhaps fatal, injury at the levels of exposure reported for uranium in the literature. The negative findings regarding renal injury among workers exposed over long time periods to insoluble compounds are particularly significant in view of the high levels of exposure reported (Eisenbud and Quigley 1955). The pathogenesis of the kidney damage in animals indicates that regeneration of the tubular epithelium occurs in survivors upon discontinuation of exposure to uranium (Bentley et al. 1985; Dygert 1949b; Maynard and Hodge 1949; Pozzani 1949; Rothermel 1949; Rothstein 1949c; Spiegl 1949; Stokinger et al. 1953).

Male Sprague-Dawley rats exposed to a single gavage dose of 5.6 mg U/kg suffered slight renal dysfunction and minimal microscopic lesions in the tubular epithelium (Domingo et al. 1987).

An intermediate-duration oral study in which dogs were given doses of 37.5 or 187 mg U/kg/day as sodium diuranate in the diet for 30 days found elevated peak NPN and BUN but not in a dose-dependent manner. Blood sugar was also slightly elevated. Necropsy findings revealed mild degeneration and necrosis in the kidneys at the higher dose level but only minimal degeneration and necrosis at 37.5 mg U/kg/day (Maynard and Hodge 1949). In other animal studies, exposure to uranium (uranyl fluoride, triuranium octaoxide, uranyl nitrate hexahydrate, uranium tetrachloride, uranium peroxide, ammonium diuranate) at oral doses as low as 0.05 mg U/kg/day and as high as 7,859 mg U/kg/day for 30 days were damaging to the kidneys. Nephrotoxic effects found in these animals ranged from minimal microscopic lesions in the tubular epithelium (for low doses) to extensive necrosis in the tubular epithelium (for high doses of soluble compounds) (Maynard and Hodge 1949). No effects on the kidneys were found in rats similarly exposed to 12,342 mg U/kg/day as uranium dioxide or 11,650 mg U/kg/day as uranium trioxide for 30 days (Maynard and Hodge 1949); perhaps, this finding was due to the low gastrointestinal absorption of the insoluble salt.

In intermediate-duration studies, dogs orally exposed to up to 95 mg U/kg/day as uranyl nitrate hexahydrate for 138 days suffered elevated NPN, BUN, glucosuria, and proteinuria at doses of 95 mg U/kg/day and higher, no effect was seen at 47 mg U/kg/day (Maynard and Hodge 1949). Exposure of mice to 452 mg U/kg/day as uranyl fluoride for 48 weeks resulted in the kidneys being tan-gray in color with nodules on the surface (Tannenbaum and Silverstone 1951). However, the kidneys appeared to be normal upon microscopic examination. In other studies, Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: 0.05, 0.27, 1.34, 6.65, 35.3 mg U/kg/day; females: 0.07, 0.33, 1.65, 7.82, 40.0 mg U/kg/day) for 28 days and then sacrificed. No treatment-related histopathological changes were found, and no changes in organ weights were noted. The only effect observed was a significant increase in serum uric acid in females at 40 mg U/kg/day (1.64 vs. 1.18 mg/dL in controls). This 28-day dose range finding study found few adverse effects at even the highest dose, but was followed by a 91-day study of the same regimen, with significantly different results. In that study, Sprague-Dawley rats (15/sex/dose) exposed to uranium as uranyl nitrate in drinking water (males: <0.0001, 0.06, 0.31, 1.52, 7.54, 36.73 mg U/kg/day; females: <0.0001, 0.09, 0.42, 2.01, 9.98, 53.56 mg U/kg/day) for 91 days were found to have renal lesions of the tubules (apical nuclear displacement and vesiculation, cytoplasmic vacuolation, and dilation), glomeruli (capsular sclerosis), and interstitium (reticulin sclerosis and lymphoid cuffing) observed in the lowest exposure groups. No explanation for the differences was provided (Gilman et al. 1998a).

Two studies by MacDonald-Taylor et al. (1992, 1997) produced similar renal lesions in rabbits. In these studies, weanling New Zealand male rabbits were exposed to uranium for 91 days via drinking water containing 0, 24, or 600 mg/L uranyl nitrate   Doses were not calculated from water intake. Calculations using default reference values for this species result in doses of 0, 0.93, and 23 mg U/kg/day (EPA 1998). Each treatment group was divided into 3 subgroups: immediate sacrifice and either 45-day or 91-day recovery period. At the end of the recovery periods, rabbits were sacrificed and renal sections prepared for electron microscopy. Thickness of the glomerular basement membrane (GBM) was measured from electron micrographs. Measurements were taken at approximately 35 μm increments; 600–900 measurements were made for each treatment group and recovery period. Uranyl nitrate exposure resulted in thickening of the membrane in the rabbits. Control thickness was approximately 80 μm; the thickness was 96.3 μm immediately after exposure at the low dose and increased to 103 μm after a 91-day recovery. Initial thickness after 91 days exposure in the high-dose group was 109 μm and had increased to 117 μm after a 91-day recovery period. Similarly, New Zealand rabbits were exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg U/kg/day; females: up to 43.02 mg U/kg/day) for 91 days (Gilman et al. 1998b). Dose-dependent differences consisted of histopathological changes limited primarily to kidney and were more pronounced in male rabbits. In the males, a significant increased incidence of anisokaryosis and nuclear vesiculation was observed in all treated groups. Nuclear pyknosis and hyperchromicity were observed in all treated groups except in the 0.05 mg U/kg/day treatment group. Tubular dilation, atrophy, protein casts, and collagen sclerosis were observed at 4.82 and 28.70 mg U/kg/day. Reticulin sclerosis was observed at 0.88, 4.82, and 28.70 mg U/kg/day. Anisokaryosis and nuclear vesiculation were observed in all treated female groups. Tubular dilation and atrophy were also observed. Collagen sclerosis was observed at 43.02 mg U/kg/day, reticulin sclerosis was observed at 0.49 and 43.02 mg U/kg/day. Females drank 65% more water than the males; however, the females appeared to be less affected by the exposure regimen. These exposed females did develop significant tubular nuclear pathology in the lowest exposure group, but not to the degree of the exposed males (Gilman et al. 1998b). The LOAEL of 0.5 mg U/kg/day from this study was used to develop an intermediate-duration MRL of 2.0x10^{-3} mg/kg/day for oral exposure to uranium and is shown in Table 2-3 and plotted in Figure 2-3.

In another study, male New Zealand rabbits were exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg U/kg/day) for 91 days, and were then allowed to recover for several weeks after dosing ceased (Gilman et al. 1998c). No differences in urinary parameters were noted in any of the groups exposed to the 1.36 mg U/kg/day dose. Kidney weight as a percentage of body weight was

significantly increased in the 40.98 mg U/kg/day group (compared to controls) immediately after exposure, but was not significantly increased after 45 days of exposure. In rabbits exposed to the 40.98 mg U/kg/day dose, urinary output was decreased at week 1, with increased excretion of glucose, protein and leucine aminopeptidase activity. Similar results were observed at week 4 after dosing began. Seven days after the start of the recovery period, urinary volume was increased and glucose secretion remained elevated. Protein and leucine aminopeptidase activity excretion returned to normal. At 3, 5, and 13 weeks post-exposure, urinary parameters were normal. Groups exposed to 40.98 mg U/kg/day had increases in percentage and total lymphocyte counts after the 91-day recovery period but not at the end of exposure. Focal dilation of renal proximal tubules was observed in both treated groups accompanied by cytoplasmic vacuolation. Nuclear changes included apical displacement and irregular placement with vesiculation, anisokaryosis, and pyknosis. Tubular basement membranes were normal early in injury but thickened focally during recovery. Changes induced by exposure at 40.98 mg U/kg/day persisted for up to 45 days and in some cases for 91 days (Gilman et al. 1998c).

Endocrine Effects.   No endocrine effects after oral intake of uranium have been reported in humans. Few endocrine effects have been reported after uranium exposure in laboratory animals. In animal studies, a dose of 0.07 mg U/kg/day as uranyl nitrate hexahydrate for 16 weeks in drinking water resulted in degenerative changes in the thyroid epithelium and altered thyroid function in Wistar rats (Malenchenko et al. 1978). Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 35.3 mg U/kg/day; females: up to 40.0 mg U/kg/day) for 28 days and then sacrificed. No treatment-related histopathological changes were found in any of the endocrine organs studied (adrenal, pancreas, parathyroid, pituitary, thymus, thyroid), and no treatment-related changes in these organ weights were noted (Gilman et al. 1998a). In addition, New Zealand rabbits were exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg U/kg/day; females: up to 43.02 mg U/kg/day) for 91 days. No treatment-related histopathological changes were found, and no weight changes in the adrenal, pancreas, parathyroid and pituitary glands were noted (Gilman et al. 1998b). Male New Zealand rabbits exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg U/kg/day) for 91 days also failed to show any treatment-related histopathological or organ weight changes (Gilman et al. 1998c). In another study, Sprague-Dawley rats (15/sex/dose) were exposed to uranium as uranyl nitrate in the drinking water (males: up to 36.73 mg U/kg/day; females: up to 53.56 mg U/kg/day) for 91 days. Thyroid lesions were observed in both sexes (multifocal reduction of follicular

size, increased epithelial height in males at 0.31 mg U/kg/day and females at 2.01 mg U/kg/day). A decreased amount and density of colloid in the thyroid was observed in males only.

Body Weight Effects.   No body weight effects after oral intake of uranium have been reported in humans.

Oral exposure to uranium compounds has caused body weight effects in animals, but these effects are not necessarily the result of systemic toxicity. The initial loss of body weight observed in animals exposed to high doses of uranium in the diet in acute-, intermediate-, and chronic-duration studies is usually accompanied by decreased food consumption in these animals. The decreased food consumption could be due to the aversive taste of uranium compounds in food. Subsequent acclimatization of the animals to the taste would normalize food intake and, consequently, reverse the initial loss of body weight. Thus, the changes in body weight seen in such studies may be due more to reduction in food consumption due to distaste than to uranium-specific chemical or radiological toxicity. More recent studies in which sugar was added to the drinking water of animals to remove the aversive effect of uranium (Ortega et al. 1989a) support this hypothesis.

Rats given single oral doses of 664 mg U/kg as uranyl nitrate hexahydrate or 55 mg U/kg as uranium peroxide (Maynard et al. 1953), 7,859 mg U/kg as uranium acetate dihydrate for 30 days (Maynard and Hodge 1949), or 664 mg U/kg as uranyl nitrate hexahydrate for 30 days in the feed suffered unspecified decreases in body weight gain (Maynard et al. 1953). Similarly, body weight losses of 18, 35, 27, 20, and 29%, respectively, were observed in rats given oral doses of 886 mg U/kg/day as uranium tetrachloride, 1,081 mg U/kg/day as uranyl fluoride, or 664 mg U/kg/day as uranyl nitrate hexahydrate for 30 days (Maynard and Hodge 1949); rabbits given oral doses of 14.2 mg U/kg/day as uranyl nitrate hexahydrate for 30 days (Maynard and Hodge 1949); and rats given oral doses of 270 mg U/kg/day as uranyl fluoride for 2 years (Maynard and Hodge 1949; Maynard et al. 1953).

No harmful effects on body weight were seen in rats given 12,342 mg U/kg as uranium dioxide or 11,650 mg U/kg as uranium trioxide for 30 days (Maynard and Hodge 1949), mice given 1,100 mg U/kg as uranyl nitrate hexahydrate for 18 weeks or 462 mg U/kg as uranyl nitrate hexahydrate for 48 weeks (Tannenbaum and Silverstone 1951), or in Sprague-Dawley rats exposed to uranium as uranyl nitrate in drinking water at doses up to 35.3 mg U/kg/day (males) and 40 mg U/kg/day (females) for 28 days or up

to 36.73 mg U/kg/day (males) and 53.56 mg U/kg/day (females) for 91 days (Gilman et al. 1998a). No alterations in body weights were observed in rats given 12,341 mg U/kg as uranium dioxide or 10,611 mg U/kg as uranium hexafluoride for 2 years, or dogs given 8 mg U/kg as uranyl fluoride or 95 mg U/kg as uranyl nitrate hexahydrate for 1 year (Maynard and Hodge 1949; Maynard et al. 1953). In animal studies, reduced food intake was observed following a single oral dose of 5.6 mg U/kg as uranyl nitrate hexahydrate to rats (Domingo et al. 1987) and in a 48-week study in rats and mice at 1,100 mg U/kg/day as uranyl nitrate hexahydrate (Tannenbaum and Silverstone 1951). It has been suggested that this reduced food intake is a result of loss of appetite due to the unpalatability of the uranium compounds in the animals' food (Dygert 1949e).

2.2.2.3 Immunological and Lymphoreticular Effects

No information was located regarding the effects of uranium on the immune system in humans following oral exposure for any duration.

In laboratory animals, oral exposure of rats, mice, and rabbits to uranium had no significant effect on immune system function. In one study Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 35.3 mg U/kg/day; females: up to 40.0 mg U/kg/day) for 28 days and then sacrificed. No treatment-related effects were noted in the immunological/lymphoreticular tissues examined (bone marrow, mesenteric and mediastinal lymph nodes, spleen, and thymus) (Gilman et al. 1998a). In addition, New Zealand rabbits were exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg U/kg/day; females: up to 43.02 mg U/kg/day) for 91 days. No histopathological changes were found, and no changes in the bone marrow, mesenteric and mediastinal lymph nodes, or thymus were noted (Gilman et al. 1998b). Rats exposed to oral doses of 0.07 mg U/kg as uranyl nitrate hexahydrate for 4 weeks showed an increase in spleen weight but the body weights of both the control and test animals were not provided, making it impossible to determine whether the net change in spleen weight had any toxicological significance (Malenchenko et al. 1978). Sprague-Dawley rats exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg U/kg/day; females: up to 53.56 mg U/kg/day) for 91 days showed sinus hyperplasia of the spleen in both sexes at the highest dose (males: 36.73; females: 53.56 mg U/kg/day). No lesions were observed in bone marrow, mesenteric and medistinal lymph nodes, or in the thymus (Gilman et al. 1998a). In other studies with mice and rats, no histological changes in the spleen, lymph nodes, or bone marrow were seen

in the animals following administration of up to 5,000 mg U/kg of various uranium compounds (uranyl nitrate hexahydrate, uranyl fluoride, uranium dioxide, uranium peroxide, uranium tetrafluoride, uranium tetrachloride, triuranium octaoxide, or uranium trioxide) in the diet for 48 weeks or 2 years. No consistent hematological changes were found in hematocrit, hemoglobin, or white blood cell counts (Maynard et al. 1953; Tannenbaum and Silverstone 1951). No other specific immunological tests were performed.

2.2.2.4 Neurological Effects

No studies were located for humans regarding neurological effects following oral exposure to uranium compounds.

No evidence of histological effects in nervous tissue have been reported after oral exposure to uranium compounds in animal studies, although one study reported clinical signs of neurotoxicity. Piloerection, tremors, hypothermia, pupillary size decreases and exophthalmos were seen at all dose levels in a study with Sprague-Dawley rats given single gavage doses of 11, 22, 45, 90, 179, 358, or 717 mg U/kg as uranyl acetate dihydrate. The signs became more severe as the number of days post-treatment increased (Domingo et al. 1987). In another study, Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 35.3 mg U/kg/day; females: up to 40.0 mg U/kg/day) for 28 days and then sacrificed. No treatment-related effects were noted in the three sections of brain examined histopathologically (Gilman et al. 1998a). No treatment-related effects on the brains of Sprague-Dawley rats (15/sex/dose) exposed to uranium as uranyl nitrate in the drinking water (males: up to 36.73 mg U/kg/day; females: up to 53.56 mg U/kg/day) for 91 days were found (Gilman et al. 1998a). Additionally, New Zealand rabbits exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg U/kg/day; females: up to 43.02 mg U/kg/day) for 91 days showed no brain histopathological changes.

The LOAEL value for this study is presented in Table 2-3 and plotted in Figure 2-3.

2.2.2.5 Reproductive Effects

No human studies were located regarding reproductive effects following oral exposure to uranium compounds. Limited animal studies have shown some effects on reproductive function but generally no evidence of histopathological damage to reproductive tissues. No reproductive effects or changes in

reproductive organ weights were found in the epididymis, testes, ovary, or uterus of Sprague-Dawley rats (10/sex/dose) exposed to uranium as uranyl nitrate in the drinking water (males: up to 35.3 mg U/kg/day; females: up to 40.0 mg U/kg/day) for 28 days (Gilman et al. 1998a). No reproductive effects or changes in reproductive organ weights were found in the epididymis, testes, ovary, or uterus of Sprague-Dawley rats (15/sex/dose) exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg U/kg/day; females: up to 53.56 mg U/kg/day) for 91 days (Gilman et al. 1998a). New Zealand rabbits exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg U/kg/day; females: up to 43.02 mg U/kg/day) for 91 days showed no histopathological or organ weight changes in the epididymis, ovary, testes, or uterus (Gilman et al. 1998b). No effects on fertility were found in mice given oral gavage doses of 14 mg U/kg/day as uranyl acetate dihydrate in a 4- to 8-week study (Paternain et al. 1989). In a 64-day study with Swiss-Webster mice, no significant differences in the total implantations, early and late resorptions, or the number of live and dead fetuses were observed in females mated with male mice treated with drinking water doses of 45 mg U/kg/day as uranyl acetate dihydrate, as compared to untreated controls; but a reduced sperm count was observed in the 11.2 mg U/kg/day group (Llobet et al. 1991). However, in another study, offspring of male Swiss mice exposed to 2.8, 5.6, or 14 mg U/kg/day intragastrically as uranyl acetate dihydrate for 38–60 days before mating with female mice that had received the same doses orally for 14 days prior to mating exhibited reproductive abnormalities manifested as reduced implantations and increased fetal resorptions. The average number of total implantations was only different in the 2.8 mg U/kg/day group (Paternain et al. 1989). Maternal toxicity (reduced weight gain and food consumption, increased relative liver weight) was seen at all doses in 20 pregnant Swiss mice given uranyl acetate dihydrate (3, 6, 14, or 28 mg U/kg/day) by gavage on gestation days (Gds) 6–15 and sacrificed on Gd 18 to assess potential maternal and fetal toxicity (Domingo et al. 1989a).

In chronic-duration studies, male rats given high oral doses (331 mg U/kg/day) of uranyl nitrate hexahydrate in the diet for 2 years developed testicular degeneration; female rats given oral doses of 664 mg U/kg/day as uranyl nitrate hexahydrate for 2 years had reduced litter sizes (Maynard et al. 1953). Since incidence and dose-response data were not provided in this report, its significance is unclear.

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

2.2.2.6 Developmental Effects

No studies were located that reported developmental effects in humans following oral exposure to
uranium for any duration. Animal studies indicate that oral exposure to uranium can cause developmental
effects, but only at relatively high doses.

In animal studies, pregnant Swiss mice were exposed to uranium as uranyl acetate dihydrate by gavage in
water at a dose of 0.028, 0.28, 2.8, 28 mg U/kg/day from day 13 of gestation through postnatal day 21.
Treatment had no significant effects on mean litter size at birth or on day 4, but litter size was
significantly decreased at postnatal day 21 at 28 mg U/kg/day (5.5 vs. 8.8 in water-only controls). The
viability index (number of pups viable at day 21/number of pups born) and the lactation index (number of
pups viable at day 21/number of pups retained at day 4) were significantly decreased in the 28
mg U/kg/day group. No significant differences were observed in developmental signs (pinnae unfolding,
lower incisor eruption, eye opening), or in pup weight or body length (Domingo et al. 1989b). Structural
variations were not assessed in this report.

The offspring of male Swiss mice exposed to 2.8, 5.6, and 14 mg U/kg/day intragastrically as uranyl
acetate dihydrate for 38–60 days before mating with female mice that had received the same doses orally
for 14 days prior to mating exhibited developmental defects. The average number of total implantations
was only different in the 2.8 mg U/kg/day group. The numbers of late resorptions and dead fetuses were
significantly increased for the 14 mg U/kg/day group. Significantly reduced viability was observed in the
5.6 mg U/kg/day group. A dose-response relationship was observed for reduced offspring growth as
determined by body weight and body length (Paternain et al. 1989). Similarly, a dose-related fetotoxicity,
manifested as reduced fetal body weight and length, an increase in the incidence of stunted fetuses and
external and skeletal malformations, and developmental variations, was reported in the offspring of
20 pregnant Swiss mice given uranyl acetate dihydrate (3, 6, 14, and 28 mg U/kg/day) by gavage on
Gds 6–15 and sacrificed on Gd 18. External malformations included a significant increase in the
incidence of cleft palate ($6 mg U/kg/day) and hematomas (at 3 and 28 mg U/kg/day). Underdeveloped
renal papillae were seen in the 3 and 14 mg U/kg/day groups. An increase in the incidence of skeletal
abnormalities (bipartite sternebrae and reduced or delayed ossification of the hind limb, fore limb, skull,
and tail) were seen in the 14 and 28 mg U/kg/day groups. Embryolethality was not found at any of the
dose levels tested (Domingo et al. 1989a); however, in another study, embryolethality was found in

offspring of mice given an oral gavage dose of 14 mg U/kg/day as uranyl acetate dihydrate in a 4–8-week study (Paternain et al. 1989).

In another study, the mean litter size of the offspring of female Sprague-Dawley rats was significantly lower (p<0.05) at an oral exposure of 28 mg U/kg/day uranyl acetate dihydrate on postnatal day 21 when a group of rats were exposed to 0.028, 0.38, 2.8, or 28 mg U/kg/day for 30 days. The viability index (day 21:day 0) and lactation index were also significantly reduced at this exposure level. No differences in the developmental milestones monitored (pinna attachment, eye opening, incisor eruption) were observed in the treated animals. Treatment with uranium had no significant effect on length of gestation and sex ratios and on mean litter size at birth or postnatal day 4 as well as on body weight or pup body length throughout lactation. There was no significant effect on food consumption during the periods of late gestation and lactation (Domingo et al. 1989b).

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

2.2.2.7 Genotoxic Effects

No information was located regarding the toxic action of uranium on genetic material in humans or animals following oral exposure for any duration.

Because uranium is a predominantly alpha-emitting radionuclide, current theories on gene mutation and chromosomal aberrations by high-LET alpha radiation suggest a potential for genotoxicity from uranium's radioactivity (BEIR 1980, 1988, 1990; Leach et al. 1970; Morris et al. 1990; Muller et al. 1967; Otake and Schull 1984; Sanders 1986; Stokinger et al. 1953; UNSCEAR 1982, 1986, 1988) (see Appendix D for a review of the hazards associated with radionuclide exposure). Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No evidence linking oral exposure to uranium to human cancer has been found. Although natural, depleted, or enriched uranium and uranium compounds have not been evaluated in rodent cancer bioassays by any route by the NTP (BEIR 1980, 1988, 1990; Hahn 1989; Sanders 1986; UNSCEAR 1982, 1986, 1988), there is potential for the carcinogenicity of uranium, since it emits primarily alpha radiation. Nevertheless, no evidence has been found to associate human exposure to uranium compounds and carcinogenesis. The National Academy of Sciences has determined that bone sarcoma is the most likely cancer from oral exposure to uranium; however, their report noted that this cancer has not been observed in exposed humans and concluded that exposure to natural uranium may have no measurable effect (BEIR IV).

Similarly, the results of several oral studies with uranium in several species were negative for evidence of cancer induction (Maynard and Hodge 1949; Maynard et al. 1953; Tannenbaum and Silverstone 1951).

No studies were located that provided evidence that oral exposure of humans to uranium as an alpha-emitting radiation source causes cancer. The available human data on the relative potential of ingested radium and uranium isotopes to induce cancers in humans concluded that the cumulative lifetime risk to 1 million people, each ingesting 5 pCi of a radium isotope (^{226}Ra, ^{228}Ra, and ^{224}Ra) per day, for the induction of skeletal cancers (bone sarcomas and carcinomas of the head sinuses) is 9 bone sarcomas and 12 head carcinomas for ^{226}Ra, 22 bone sarcomas for ^{228}Ra, and 1.6 bone sarcomas for ^{224}Ra. Assuming that the risk per rad of the average skeletal dose is equal for ^{226}Ra and uranium isotopes with half-lives exceeding 1,000 years, and that the equilibrium skeletal content is 25 times the daily ingestion of ^{226}Ra but 11 times the daily ingestion of long-lived uranium, the cumulative lifespan risk to 1 million people, each ingesting 5 pCi per day of ^{234}U (0.0008 μg), ^{235}U (2.3 μg), or ^{238}U (15 μg), is estimated to be about 1.5 bone sarcomas. However, no cancers would be expected if the incidence is found to vary with the square of the dose instead of linearly (Mays et al. 1985). The BEIR IV report came to the same conclusion, but reserved the opinion that bone sarcomas might be caused by highly enriched uranium. The report estimated a lifetime risk of excess bone sarcomas per million people of 1.5 if soluble uranium isotopes were ingested at a constant daily rate of 1 pCi/day (0.037 Bq/day). The number of bone sarcomas that occur naturally in a population of a million people is 750. However, no quantitative risk coefficient estimates for developing human exposure protection benchmarks were provided in this report. In addition, the BEIR IV analysis was presumably based on generic short-lived alpha-emitting sources,

such as radon that have a higher potential for inducing cancer, and not on radionuclides with relatively longer radioactive half-lives like ^{238}U, ^{235}U, and ^{234}U. Perhaps more importantly, the BEIR IV report concluded that "...exposure to natural uranium is unlikely to be a significant health risk in the population and may well have no measurable effect" (BEIR IV 1988).

The available long-term feeding studies in rats, mice, dogs, and rabbits found no evidence of cancer induction upon histopathological examination of selected organs and tissues. The available studies tested mice, dogs, and rabbits with extreme intakes of uranium corresponding to radioactivity exposures of as high as $1.0x10^4$ nCi/kg/day ($3.7x10^5$ Bq/kg/day) ($1.5x10^4$ mg U/kg/day) for 30 days (Maynard and Hodge 1949; Tannenbaum and Silverstone 1951) or rats and dogs at $8.2x10^3$ nCi/kg/day ($3x10^5$ Bq/kg/day) ($1.2x10^4$ mg U/kg/day) for 2 years (Maynard and Hodge 1949; Maynard et al. 1953).

2.2.3   Dermal Exposure

2.2.3.1   Death

No deaths have been reported in humans as a result of dermal exposure to uranium.

Deaths have occurred in animals after dermal exposure to uranium compounds from both single and repeated exposures. Generally, the more water-soluble uranium compounds were the most toxic and the rabbit was the most sensitive species. Deaths were due to renal failure.

In a series of 4-hour exposures to uranium compounds followed by washing with detergent and a 30-day observation period, the lowest reported LD_{50} value was 28 mg U/kg as uranyl nitrate in an ethereal solution in New Zealand rabbits (Orcutt 1949). Calculated LD_{50} values for identical exposures to uranyl nitrate were 1,190 mg U/kg for guinea pigs and 4,286 mg U/kg for mice. Insufficient fatalities occurred to calculate an LD_{50} for rats, but the mortality curve fell between that of the rabbits and the guinea pigs. Deaths mainly occurred 5 to 7 days after exposure and were due to renal failure. Similar experiments with other uranium compounds in rabbits using a lanolin vehicle showed that water-soluble compounds (uranyl fluoride, uranium tetrachloride, uranium pentachloride) were the most toxic; the slightly soluble compounds (uranium trioxide, sodium diuranate, ammonium diuranate) had intermediate toxicity; and the

water insoluble compounds (uranium tetrafluoride, uranium dioxide, uranium peroxide, triuranium octoxide) caused no deaths (Orcutt 1949).

Chemically induced renal failure caused 100% mortality in male Wistar rats after 5 daily exposures to 237 or 1,928 mg U/kg/day as uranyl nitrate hexahydrate or ammonium uranyl tricarbonate, respectively, applied in a water-Vaseline® emulsion (De Rey et al. 1983). A 60% mortality rate was also reported for other male Wistar rats that received daily applications of 1,965 mg U/kg as uranyl acetate dihydrate for 1–11 days. No deaths were reported for other Wistar rats similarly treated with 2,103 mg U/kg/day as ammonium diuranate or to an unspecified dose of uranium dioxide (De Rey et al. 1983).

Intermediate-duration dermal exposure in guinea pigs indicated that smaller repeated doses were better tolerated than a large single dose when the total exposure was the same. In a 4-week experiment where exposure was to 379 mg U/kg as uranyl nitrate for 3 days per week, 14% mortality was observed (Orcutt 1949). If the same cumulative dose (4,741 mg U/kg) had been given in a single application, 86% mortality would have been expected.

The LD_{50} values for each species and other LOAEL values for mortality from exposure to uranium through the dermal route are presented in Table 2-4.

2.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans following dermal exposure to uranium compounds for acute, intermediate, or chronic durations.

No studies were located regarding the respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or endocrine effects of uranium in animals following acute-, intermediate-, or chronic-duration exposure; regarding the renal effects following intermediate- or chronic-duration exposure; regarding the dermal or body weight effects following chronic-duration exposure; or regarding ocular effects following acute- or chronic-duration exposure. The existing animal data on renal, dermal, and body weight effects are limited to acute- and intermediate-duration exposures.

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	LOAEL		Reference Chemical Form
				Less Serious (mg/kg)	Serious (mg/kg)	

ACUTE EXPOSURE

Death

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	Less Serious	Serious	Reference Chemical Form
Rat (Wistar)	1-11 d 1x/d				237 M (100% mortality in 5 days)	De Rey et al. 1983 $UO_2(NO_3)_2 \cdot 6H_2O$
Rat (Wistar)	1-11 d 1x/d				1965 M (60% mortality in 11 days)	De Rey et al. 1983 $UO_2(C_2H_3O_2)_2 \cdot 2H_2O$
Rat (Wistar)	1-11 d 1x/d				1928 M (100% mortality in 5 days)	De Rey et al. 1983 $(NH_4)_8U_2O_4(CO_3)_3$
Rat (Wistar)	4 hr (EPICU)				101 F (LD_{50})	Orcutt 1949 $UO_2(NO_3)_2 \cdot 6H_2O$
Mouse (albino)	4 hr (EPICU)				4286 F (LD_{50})	Orcutt 1949 $UO_2(NO_3)_2 \cdot 6H_2O$
Gn pig	4 hr (EPICU)				2520 (LD_{50})	Orcutt 1949 UCl_4
Gn pig (NS)	once (EPICU)				1190 (LD_{50})	Orcutt 1949 $UO_2(NO_3)_2 \cdot 6H_2O$

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	LOAEL		Reference Chemical Form
				Less Serious (mg/kg)	Serious (mg/kg)	
Rabbit (New Zealand)	4 hr (EPICU)				344 (67% mortality)	Orcutt 1949 UCl5
Rabbit (New Zealand)	4 hr (EPICU)				188 (50% mortality)	Orcutt 1949 UCl4
Rabbit (New Zealand)	4 hr (EPICU)				666 (67% mortality)	Orcutt 1949 UO3
Rabbit (New Zealand)	once 4 hr (EPICU)				198 (33% mortality)	Orcutt 1949 (NH4)2U2O7
Rabbit (New Zealand)	4 hr (EPICU)				28 (LD_{50})	Orcutt 1949 UO2(NO3)2*6H2O
Rabbit (New Zealand white, New Zealand red, checker, chinchilla, or mixed)	4hr (EPICU)				3091 (83% mortality)	Orcutt 1949 UO2F2

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

| Species/ (Strain) | Exposure/ Duration/ Frequency | System | NOAEL (mg/kg) | LOAEL | | Reference Chemical Form |
				Less Serious (mg/kg)	Serious (mg/kg)	
Systemic						
Rat (Wistar)	1-11 d 1x/d	Renal			1965 M (renal failure)	De Rey et al. 1983 UO2(C2H3O2)2*2H2O
		Bd Wt Dermal	3929 M		1965 M (70% weight loss)	
Rat (Wistar)	1-11 d 1x/d	Dermal	1928 M			De Rey et al. 1983 (NH4)8U2O4(CO3)3
		Bd Wt		1928 M (slight initial weight loss)		
Rat (Wistar)	1-11 d 1x/d	Renal			2670 M (renal failure)	De Rey et al. 1983 (NH4)2U2O7
		Dermal Bd Wt	2670 M (mild lesions)		2670 M (severe weight loss)	
Rat (Wistar)	1-11 d 1x/d	Renal			237 M (renal failure)	De Rey et al. 1983 UO2(NO3)2*6H2O
		Dermal	237 M (mild lesion)			
Rat (Wistar)	once (EPICU)	Renal		85 F (proteinuria; minimal microscopic lesions in renal tubular epithelium)		Orcutt 1949 UO2(NO3)2*6H2O
		Bd Wt		85 F (unspecified decreased body weight gain)		

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	LOAEL		Reference Chemical Form
				Less Serious (mg/kg)	Serious (mg/kg)	
Mouse (albino)	4 hr (EPICU)	Renal		948 F (moderate tubular degeneration)		Orcutt 1949 UO2(NO3)2*6H2O
		Bd Wt		948 (unspecified decreased body weight gain)		
Gn pig (NS)	4 hr (EPICU)	Renal		689 (proteinuria)		Orcutt 1949 UCl4
		Bd Wt		689 (10-20% decreased body weight gain)		
Gn pig (NS)	4 hr (EPICU)	Renal	450	616 (proteinuria)		Orcutt 1949 UO2(NO3)2*6H2O
		Bd Wt	450	616 (unspecified decreased body weight gain)		
Gn pig (NS)	4 hr (EPICU)	Renal		660 (proteinurea)		Orcutt 1949 UCl4
		Bd Wt		660 (10-20% reduction in weight gain)		
Rabbit (New Zealand)	once (EPICU)	Renal		618 (proteinuria)		Orcutt 1949 UO2F2
		Dermal	618			

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

| Species/ (Strain) | Exposure/ Duration/ Frequency | System | NOAEL (mg/kg) | LOAEL | | Reference Chemical Form |
				Less Serious (mg/kg)	Serious (mg/kg)	
Rabbit (New Zealand)	4 hr (EPICU)	Renal		344.1 (proteinuria)		Orcutt 1949 UCl5
		Dermal		344.1 (moderate skin irritation)		
Rabbit (New Zealand)	4 hr (EPICU)	Renal		666 (proteinuria)		Orcutt 1949 UO3
		Dermal	666			
Rabbit (New Zealand)	4 hr (EPICU)	Renal		195 (proteinuria)		Orcutt 1949 Na2U2O7
		Dermal	195			
Rabbit (New Zealand)	4 hr (EPICU)	Renal		169 (proteinuria)		Orcutt 1949 (NH4)2U2O7
		Dermal	169			
Rabbit (New Zealand)	4 hr (EPICU)	Renal	410			Orcutt 1949 UO4
		Dermal	410			
Rabbit (New Zealand)	4 hr (EPICU)	Renal	458			Orcutt 1949 UO2
		Dermal	458			

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

| Species/ (Strain) | Exposure/ Duration/ Frequency | System | NOAEL (mg/kg) | LOAEL | | Reference Chemical Form |
				Less Serious (mg/kg)	Serious (mg/kg)	
Rabbit (New Zealand)	4 hr (EPICU)	Renal	147			Orcutt 1949 U3O8
		Dermal	147			
Rabbit (New Zealand)	4 hr (EPICU)	Renal		1.4 (proteinuria)		Orcutt 1949 UO2(NO3)2*6H2O
		Dermal		1.4 (moderate erythema)		
		Bd Wt	6	30 (decreased body weight gain)		
Rabbit (New Zealand)	4 hr (EPICU)	Renal	98			Orcutt 1949 UF4
		Dermal	98			

Neurological

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	Less Serious (mg/kg)	Serious (mg/kg)	Reference Chemical Form
Rabbit (New Zealand)	4 hr (EPICU)				1.4 (irritability, hyperactivity, upset equilibrium, rigidity of limbs, respiratory arrest)	Orcutt 1949 UO2(NO3)2*6H2O

INTERMEDIATE EXPOSURE

Death

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	Less Serious (mg/kg)	Serious (mg/kg)	Reference Chemical Form
Gn pig (NS)	4 wk 3 d/wk (EPICU)				379 (14% mortality)	Orcutt 1949 UO2(NO3)2*6H2O

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

| Species/ (Strain) | Exposure/ Duration/ Frequency | System | NOAEL (mg/kg) | LOAEL | | Reference Chemical Form |
				Less Serious (mg/kg)	Serious (mg/kg)	
Gn pig (NS)	4 wk 6 d/wk (EPICU)				47 (12% mortality)	Orcutt 1949 UO2(NO3)2*6H2O
Systemic						
Gn pig (NS)	4 wk 3-6 d/wk (EPICU)	Renal		47 mg/kg/ day (proteinuria)		Orcutt 1949 UO2(NO3)2*6H2O
		Dermal		47 (skin irritation)		
		Bd Wt	47	161.2 (transitory weight loss)		
Rabbit (New Zealand)	5 wk 5 d/wk (EPICU)	Renal		2.3 mg/kg/ day (proteinuria)		Orcutt 1949 UO2(NO3)2*6H2O
		Dermal			2.3 (severe dermal ulcers)	
		Bd Wt		2.3 (temporary weight loss)		

Bd Wt = body weight; d = day(s); EPICU = epicuticle; F = female; Gn Pig = guinea pig; hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); NOAEL = no-observable-adverse-effect level; NS = not specified; occup = occupational; wk = week(s); x = times

2. HEALTH EFFECTS

The highest NOAEL values and all reliable LOAEL values in each species and duration category for adverse systemic effects from chemical exposure to uranium by the dermal route are presented in Table 2-4.

Renal Effects.   Rabbits, guinea pigs, rats, and mice dermally exposed to uranyl nitrate hexahydrate for 1 day showed proteinuria for up to 10 days, followed by recovery to control values. The degree of proteinuria did not correlate well with the applied dose of uranium. Rabbits had elevated blood NPN at doses over 270 mg U/kg. The animals that died from dermal exposure to uranium had microscopic renal damage typical of uranium poisoning. The kidneys of the animals that did not die were essentially normal, which may reflect repair of acute renal injury (Orcutt 1949). Chemically induced renal failure caused 100% mortality in male Wistar rats after 5 daily exposures to 237 or 1,928 mg U/kg/day as uranyl nitrate hexahydrate or ammonium uranyl tricarbonate, respectively, applied in a water-Vaseline® emulsion (De Rey et al. 1983). Deaths from renal failure were also reported in this study for male Wistar rats that received daily applications of 1,965 mg U/kg as uranyl acetate dihydrate for 1–11 days.

Dermal Effects.   No human studies were located regarding the dermal effects of uranium; however, no dermal effects were reported in studies of uranium miners, millers, and processors.

In animal studies, application of 41 mg U/kg as uranium pentachloride to the shaved backs of New Zealand white rabbits resulted in mild skin irritation (Orcutt 1949). Dermally applied uranium was also damaging to the epidermis in other animal studies. Application of 56.4 mg U/kg as uranyl nitrate hexahydrate to another group of rabbits resulted in superficial coagulation necrosis and inflammation of the epidermis, while a dose of 4.2 mg U/kg as uranyl nitrate hexahydrate applied in single or multiple sites for 5 weeks resulted in severe dermal ulcers. No untreated controls were used in the 5-week study (Orcutt 1949). Moderate erythema was observed in male and female New Zealand white rabbits after single applications of 1.4 mg U/kg as uranyl nitrate hexahydrate to their uncovered clipped skins (Orcutt 1949). An applied dose of 2,670 mg U/kg as ammonium diuranate for 1–10 daily applications to the shaved backs of a group of rats resulted in mild lesions on the skin of the rats, while a dose of 237 mg U/kg as uranyl nitrate hexahydrate resulted in disrupted membranes in the cell, mitochondria, and cell nucleus, as revealed by transmission electron microscopy (TEM). Light microscopy revealed swollen and vacuolated epidermal cells and damage to hair follicles and sebaceous glands in the uranyl nitrate hexahydrate-treated animals (De Rey et al. 1983).

No dermal effects were seen following application of a single dose of 618 mg U/kg as uranyl fluoride, 666 mg U/kg as uranium trioxide, 195 mg U/kg as sodium diuranate, 198 mg U/kg as ammonium diuranate, 410 mg U/kg as uranium peroxide, 458 mg U/kg as uranium dioxide, or 147 mg U/kg as triuranium octaoxide in 50% aqueous solution to the shaved skin of New Zealand white rabbits (Orcutt 1949). No dermal effects were observed on the shaved backs of New Zealand white rabbits to which a single dose of 98 mg U/kg as a 65% concentration of the uranium tetrafluoride in lanolin was applied (Orcutt 1949). Similarly, application of 3,929 mg U/kg as uranyl acetate dihydrate or 2,103 mg U/kg as ammonium uranyl tricarbonate in water-Vaseline® emulsion to a 3 cm^2 shaved area of the uncovered backs of 20 male Wistar rats in 1–10 daily applications had no effect on the skin of the rats (De Rey et al. 1983).

Body Weight Effects.   In animal studies, significant weight loss was reported in rats after the following dermal applications over a 3 cm^2 area: 3,948 mg U/kg as uranyl nitrate hexahydrate, 3,929 mg U/kg as uranyl acetate dihydrate, 2,103 mg U/kg as ammonium uranyl tricarbonate, or 2,670 mg U/kg as ammonium uranate to rats for 1–10 days (De Rey et al. 1983). Weight loss was also observed after single applications of 660 or 689 mg U/kg as uranium tetrachloride to guinea pigs, 616 or 948 mg U/kg as uranyl nitrate hexahydrate to mice, 85 mg U/kg as uranyl nitrate hexahydrate to rats, and 43 mg U/kg as uranyl nitrate hexahydrate to rabbits (Orcutt 1949).

Uranium (4.2 mg U/kg/day) applied as uranyl nitrate hexahydrate to the clipped backs of New Zealand white rabbits for 5 weeks also induced significant weight loss that peaked at 10–15 days after beginning treatment (Orcutt 1949). However, in several other animal studies, no changes in body weight in New Zealand white rabbits were reported following single dermal applications of 618 or 804 mg U/kg as uranyl fluoride, 344 mg U/kg as uranium pentachloride, 666 mg U/kg as uranium trioxide or uranyl fluoride, 344 mg U/kg as uranyl pentachloride, 195 mg U/kg as sodium diuranate, 198 mg U/kg as ammonium diuranate, 410 mg U/kg as uranium peroxide, 458 mg U/kg as uranium dioxide, or 147 mg U/kg as triuranium octaoxide (Orcutt 1949).

2.2.3.3 Immunological and Lymphoreticular Effects

No information was located regarding the effects of uranium on the immunological and lymphoreticular system in humans and animals following dermal exposure for any duration.

2.2.3.4 Neurological Effects

No studies were located for humans regarding neurological effects following dermal exposure to uranium compounds; however, such effects have not been observed in studies involving workers in uranium mining, milling, and production.

In animal studies, neurological signs observed in rabbits in a test in which single dermal doses of 1.4, 3, 6, 30, or 85 mg U/kg as uranyl nitrate hexahydrate were applied included irritability, hyperactivity, upset equilibrium, limb rigidity, and respiratory arrest at all doses tested (Orcutt 1949). The LOAEL value for this study is presented in Table 2-4.

2.2.3.5 Reproductive Effects

No studies were located for humans and animals that described reproductive effects following dermal exposure to uranium for any duration.

2.2.3.6 Developmental Effects

No studies were located regarding effects of uranium on development in humans or animals following dermal exposure for any duration.

2.2.3.7 Genotoxic Effects

No information was located regarding the toxicity of uranium to genetic material in humans or animals following dermal exposure for any duration of exposure. Other genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No information on the cancer effects in humans or animals following dermal exposure to uranium for all durations of exposure was located; however, such effects have not been observed in studies involving uranium mining, milling, and production.

2.3   TOXICOKINETICS

Overview.   Absorption of uranium is low by all exposure routes (inhalation, oral, and dermal).
Absorption of inhaled uranium compounds takes place in the respiratory tract via transfer across cell
membranes. The deposition of inhalable uranium dust particles in the lungs depends on the particle size,
and its absorption depends on its solubility in biological fluids (ICRP 1994, 1996) Estimates of systemic
absorption from inhaled uranium-containing dusts in occupational settings based on urinary excretion of
uranium range from 0.76 to 5%. A comprehensive review of the available data for a pharmacokinetic
model used lung absorption factors of 2% to 4% for 3 month old children and 0.2% to 2% for adults,
based on compound absorbability (ICRP 1996). Gastrointestinal absorption of uranium can vary from
<0.1 to 6%, depending on the solubility of the uranium compound. Studies in volunteers indicate that
approximately 2% of the uranium from drinking water and dietary sources is absorbed in humans
(Leggett and Harrison 1995; Spencer et al. 1990; Wrenn et al. 1989), while a comprehensive review
indicates that the absorption is 0.2% for insoluble compounds and 2% for soluble hexavalent compounds
(ICRP 1996). Dermal absorption has not been quantified, but toxicity experiments in animals indicate
that water-soluble uranium compounds are the most easily absorbed. Once in the blood, uranium is
distributed to the organs of the body. Uranium in body fluids generally exists as the uranyl ion $(UO_2)^{2+}$
complexed with anions such as citrate and bicarbonate. Approximately 67% of uranium in the blood is
filtered in the kidneys and leaves the body in urine within 24 hours; the remainder distributes to tissues.
Uranium preferentially distributes to bone, liver, and kidney. Half-times for retention of uranium are
estimated to be 11 days in bone and 2–6 days in the kidney. The human body burden of uranium is
approximately 90 µg; it is estimated that 66% of this total is in the skeleton, 16% in the liver, 8% in the
kidneys, and 10% in other tissues. The large majority of uranium (>95%) that enters the body is not
absorbed and is eliminated from the body via the feces. Excretion of absorbed uranium is mainly via the
kidney. The case of Gulf War veterans who were exposed to depleted uranium from inhalation,
ingestion, and wounds, showed average urinary excretion, 7 years post exposure, of 0.08
µg U/g creatinine, with the highest rates around 30 µg/g (McDiarmad et al. 1999b).

2.3.1   Absorption

2.3.1.1   Inhalation Exposure

The deposition of inhalable uranium dust particles in the various regions of the lungs (extrathoracic,
tracheobronchial, and deep pulmonary or alveolar) depends on the size of the particles. Particles larger
than 10 µm are likely to be transported out of the tracheobronchial region by mucocilliary action and

swallowed. Particles that are sufficiently small to reach the alveolar region (#10 µm AMAD) may transfer rapidly or slowly into the blood, depending on the solubility of the uranium compound. According to the ICRP (1996), a more soluble compound (uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate) is likely to be absorbed into the blood from the alveoli within days and is designated inhalation Type F (fast dissolution). A less soluble compound (uranium tetrafluoride, uranium dioxide, uranium trioxide, triuranium octaoxide) is likely to remain in the lung tissue and associated lymph glands for weeks and is designated Type M (medium dissolution). A relatively insoluble compound (uranium dioxide, triuranium octaoxide) may remain in the lungs for years and is designated Type S (slow dissolution).

Analysis of excreta of active uranium mill crushermen exposed to ore dust indicated that 1–5% of uranium entering the lungs was absorbed systemically and excreted in the urine, and 95–99% was eliminated in the feces. Absorption could have taken place in the lungs or in the gastrointestinal tract from swallowed particles cleared from the lungs (Fisher et al. 1983). Uranium workers exposed to high levels of uranium dust had a very low lung burden of uranium, indicating that only a small fraction penetrates into the alveolar region (West and Scott 1969) and remains there without being cleared (or being very slowly cleared) via retrograde tracheobronchial mucus transport to the gastrointestinal tract, into lymph nodes, or dissolved into the circulating blood.

Estimates of absorption into the blood were derived from the excretion data of uranium mill workers (Wrenn et al. 1985). They estimated the daily mean absorption of inhaled uranium by mill workers at 24 µg U/day (0.34 µg U/kg for 70-kg reference man) based on measured excretion in feces and workplace ambient air concentrations. The absorption of uranium by these workers was estimated as 0.76% (range, 0.4–1.6%). Control subjects in a study of differential metabolism of [230]Th, [234]U, and [238]U inhaled in uranium ore dust included 3 retired uranium mill workers (4–14 years since last employment as uranium ore crushermen), and 3 volunteers who lived in uranium milling communities but had no uranium work history. Two consecutive 24-hour urine and fecal collections were obtained and analyzed for [234]U and [238]U. The apparent total intakes of uranium of these individuals ranged from 11 to 18 µg U/day for the controls and from 5.3 to 71 µg U/day for the retirees. Although large compared to uranium intakes estimated for city dwellers, the uranium intakes of these individuals are not unreasonable because uranium in potable waters and locally grown foods tends to be higher in uranium mining and milling

communities. The mean uranium absorption calculated for the controls (0.82%; range, 0.6–1%) was not significantly different from that calculated for the retired uranium workers (0.94%; range, 0.55–1.6%) (Wrenn et al. 1985).

Urinary excretion data was used to estimate the absorption of uranium by workers accidentally exposed to uranium hexafluoride (Fisher et al. 1990). Estimated airborne concentrations were 20 mg uranium hexafluoride/m^3 for a 1-minute exposure and 120 mg uranium hexafluoride/m^3 for a 60-minute exposure (15.2 and 91 mg U/m^3, respectively) (USNRC 1986). Initial intakes of workers involved in the accident ranged from 470 to 24,000 μg uranium.

Higher absorption of uranium occurred in animal studies using aerosols of purified uranium compounds. In these studies, as in human studies, the solubility of the uranium compound and the size of the inhaled particles determined absorption. Reported absorption of the inhaled dose was 18–40% in rats and 20–31% in guinea pigs for uranium hexafluoride (Leach et al. 1984) and 23% for uranium trioxide in dogs (Morrow et al. 1972).

2.3.1.2 Oral Exposure

Experimental studies in humans consistently show that absorption of uranium by the oral route is less than 5%. Reported fractional absorptions include a range of 0.005–0.05 (0.5–5%) in a group of four males ingesting 10.8 mg uranium in a soft drink (Hursh et al. 1969), less than 0.0025–0.04 in a group of 12 volunteers given drinking water high in uranium (Wrenn et al. 1989), and 0.005–0.05 in another drinking water study (Harduin et al. 1994). Similar results were obtained in dietary balance studies (Leggett and Harrison 1995; Spencer et al. 1990; Wrenn et al. 1989). A review of human data conducted by the ICRP determined that a fractional absorption of 0.02 for soluble compounds and 0.002 for insoluble compounds should be used in modeling the kinetics of dietary uranium in humans (ICRP 1995).

In animal studies, absorption generally increases with increasing solubility of the compound, being greatest for uranium ingested as uranyl nitrate hexahydrate, uranium hexafluoride or uranyl fluoride, about half as great for uranium tetroxide or uranium trioxide, and 1–2 orders of magnitude lower for uranium tetrachloride, triuranium octaoxide, and uranium tetrafluoride (ICRP 1995). Increased absorption of uranium has been demonstrated in neonatal rats and pigs (ICRP 1995). Fractional

absorption in 2-day-old rats given uranyl nitrate was estimated as 0.01–0.07, two orders of magnitude greater than for adults (ICRP 1995).

Evidence from several animal studies showed that the amount of uranium absorbed from the gastro-intestinal tract was about 1% (Harrison and Strather 1981; Larsen et al. 1984; LaTouche et al. 1987; Maynard et al. 1953; Sullivan 1980a). A range of gastrointestinal absorption rates of 0.038–0.078% has been estimated by others based on data from a 2-year study in which rats were fed diets containing 0.05–0.5% of soluble uranium compounds (uranyl fluoride or 0.5–2% of uranyl nitrate). The rate of absorption appeared to be independent of concentration of uranium in the diet (Wrenn et al. 1985). Absorption factors in rats that were exposed by gavage to doses of [233]U-uranyl nitrate hexahydrate (where this anthropogenic radionuclide provided increased sensitivity without competition with natural isotopes) increased 3.4 times over normal in rats that were iron-deficient (Sullivan and Ruemmler 1988), doubled in rats that were fasted (Sullivan et al. 1986), and increased 3.6 times in neonates as compared to adults (Sullivan 1980b). Adult baboons (fed normally) absorbed about 0.5%, whereas fasted baboons absorbed an average of 4.5% (Bhattacharyya et al. 1989) Consistent with the results in baboons, fed and 24-hour fasted male B6CF$_1$/ANL mice absorbed 0.069% and 0.80%, respectively (Bhattacharyya et al. 1989).

2.3.1.3 Dermal Exposure

Absorption of uranium through the skin has not been characterized in humans. Dermal absorption in animal models can be inferred from the appearance of toxicity in mice, rats, rabbits, and guinea pigs after dermal exposure to uranium compounds (Orcutt 1949). Absorption was also shown to occur through the conjunctival sac of the eye.

Electron microscopy and X-ray microanalytical methods showed that uranium as uranyl nitrate hexahydrate penetrated the stratum corneum within 15 minutes and accumulated in the intracellular space between the viable epidermis and the stratum corneum (De Rey et al. 1983). As is the case with inhalation and oral absorption, water solubility is an important determinant of absorption, and no penetration was observed with the insoluble compounds uranium dioxide, uranyl acetate, or ammonium diuranate. After 48 hours, uranium applied as uranyl nitrate was no longer found in the skin and toxicity developed, indicating that the uranium had been absorbed into the blood.

2.3.2 Distribution

Absorbed uranium is found in all human tissues, but preferentially deposits in bone and kidney, regardless of the route of exposure (ICRP 1995, 1996). Although uranium also distributes significantly to liver, this organ is not a major repository for uranium; however, for modeling purposes, tissue contents are often normalized to liver concentration because the latter is reported in almost all studies of uranium biokinetics. The normal adult's body burden is considered to be approximately 90 µg. It is estimated that about 66% of this total is in bone, 16% in the liver, 8% in the kidneys, and 10% in other tissues (ICRP 1979, 1995, 1996). It is not known if maternal bone stores of uranium (like those of calcium and lead) are mobilized during pregnancy and lactation. Uranium can cross the placenta after parenteral administration in animals; no information was located on distribution of uranium in breast milk for either humans or animals.

2.3.2.1 Inhalation Exposure

Autopsy data from individuals occupationally exposed to uranium indicates that bone is the primary site of long term retention of absorbed uranium (ICRP 1995). Inhalation exposure may also result in some retention of insoluble uranium particles in the lungs. An evaluation of the postmortem data from a uranium worker who had inhaled a total of 220 mg (147 pCi) uranium over a 3-year period found 11 µg (7 pCi) uranium in the lungs 13 years after the end of exposure. The total calculated dose equivalent from the inhaled uranium was 35 rem (0.35 Sv) (Keane and Polednak 1983).

In a comprehensive study of tissues from two long-time residents of New Mexico without known occupational exposure, the skeleton was the primary depot for uranium (Kathren 1997). Approximately 80 soft tissue samples and 90 bone samples were analyzed from each subject. The mean uranium concentrations in bone were 4.8 and 5.8 ng/g wet weight for the two subjects, respectively. Highest concentrations of uranium in soft tissues were in the tracheobronchial and other pulmonary related lymph nodes indicating uranium-bearing particulate clearance from the lungs. Concentrations in pulmonary lymph nodes ranged from 16–28 ng/g in one individual to 29–259 ng/g wet weight in the other.

Urinary excretion data were used in a kinetic model to estimate the maximum uranium kidney concentrations of workers accidentally exposed to uranium hexafluoride (Fisher et al. 1990). Initial intakes of workers involved in the accident ranged from 470 to 24,000 µg uranium. The model estimated the

maximum kidney concentrations in the workers as ranging from 0.048 to 2.5 µg U/g in kidney tissue; renal toxicity was not observed in any of the workers (Fisher et al. 1990).

In animals, uranium that has been absorbed from the lungs leaves the blood very quickly for distribution to body tissues. The insoluble compounds (uranium tetrafluoride, uranium dioxide) were found to accumulate in the lungs and lymph nodes with the amount retained dependent on the exposure concentration and duration. In a continuous exposure study, more than 90% of the uranium retained at the end of the first year of exposure to a uranium dioxide aerosol was cleared by the end of the second year despite continued inhalation of uranyl nitrate. All of the uranium retained following one year of inhalation of uranyl hexafluoride was cleared by the end of the second year. For uranyl nitrate inhalation, no retention was found in the soft tissues. Uranium has also been shown to accumulate in the tracheo-bronchial lymph nodes, lungs, bones, and kidneys of rats, dogs, and monkeys exposed to uranium dioxide at 5 mg U/m^3 for 1–5 years. Total radiation absorbed dose in dog lungs was around 600 rads (6 Gy). Up to 7,000 rads (70 Gy) were absorbed by monkey lymph nodes (Leach et al. 1973). In rats exposed to yellowcake, the U_3O_8 portion of the yellowcake cleared from the lung with a half-time of 110–240 days (Damon et al. 1984). Mice given inhaled doses of U_3O_8 equivalent to about 0.2 mg U/kg exhibited uranium tissue distribution (in µg/g tissue) as follows: lung, 6.05; liver, 0.051; spleen, 1.45; kidney, 0.536; tibia, 0.731; urine, 0.519; and feces, 2.20 (Walinder 1989). In an inhalation study using highly enriched uranium dioxide particles (92.8% ^{235}U), rat lungs were found to clear the uranium particles at a rate of 0.28% per day over a period of 720 days. At 720 days postexposure, 82% of the uranium remained in the lungs and thoracic lymph nodes of the rats. The highest mass of extrapulmonary uranium dioxide was detected in rats sacrificed up to 11 days postexposure. This was mainly found in the intestinal tract and the carcass. The authors found that the pulmonary clearance rate of highly enriched uranium dioxide particles was about the same as the clearance rate for natural or unenriched uranium dioxide particles (Morris et al. 1990), as would be expected since they are the same chemical compound.

One site of deposition for the soluble compounds (uranyl nitrate, uranium tetrachloride, uranium hexafluoride) in animals was the skeleton, but accumulation was not seen in bone at levels below 0.25 mg U/m^3 over a period of 2 years in rats exposed to soluble compounds (uranyl nitrate, uranium tetrachloride, uranium hexafluoride) in one study. The insoluble compounds (uranium hexafluoride, uranium dioxide) were found to accumulate in the lungs and lymph nodes after the inhalation exposure. For uranyl nitrate exposure, no retention was found in the soft tissues. Accumulation of uranium was also

found in the skeleton (Stokinger 1953). The amount distributed in the skeleton has been reported to be
23–45% of the intake in dogs (Morrow et al. 1972); 28–78% in rats (Leach et al. 1984); and 34–43% in
guinea pigs (Leach et al. 1984). A biological half-time of 150–200 days (Ballou et al. 1986) or 70 days
(Morrow et al. 1982) in the skeleton has been reported following inhalation exposure to soluble uranium
compounds (e.g., uranium hexafluoride).

A 5-year exposure of Beagle dogs and monkeys, and a 1-year exposure of rats, to 5.8 mg uranium
dioxide/m^3 (5.1 mg U/m^3) as uranium dioxide dust (AMAD=1 μm) resulted in rapid lung buildup during
the first few months, which approached maximal values of 2, 3.6, and 0.8 mg U/g in dogs, monkeys, and
rats, respectively, at the end of year 1. Buildup in the tracheobronchial lymph nodes reached peak values
in year 4 of 50–70 mg U/g in both dogs and monkeys. For each, the peak radiation dose rates reached 1.8
and 3.3 rads/week (0.018 and 0.033 Gy/week) to lungs, and 55 and 64 rads/week (0.55 and 0.65
Gy/week) to lymph nodes, while the total radiation dose for the 5 years approached 500 and 900 rads (5
and 9 Gy) to lungs and 10,000 rads (10 Gy) to the lymph nodes. Renal damage was not observed in
either the dog or monkey, but fibrosis was found in the monkey lung and both necrosis and fibrosis were
found in the dog and monkey lymph nodes. It was not clear whether the damage was chemically or
radiologically induced, but the presence of lung and lymph node damage in the absence of renal effects
was suggestive to the authors of long-term radiation damage (Leach et al. 1970). A reevaluation of the
study data also showed a rapid accumulation of uranium in the lungs and tracheobronchial lymph nodes
during the first few months of exposure. The accumulation in these organs was highest (0.8 mg/g in
lungs and 1.5 mg/g in lymph nodes) at the end of 1 year of exposure. The uranium content in the lungs
decreased with a half -time of approximately 480 days. In the lymph nodes, uranium depletion showed a
trend similar to the lungs in dogs exposed for 2 and 5 years and a biphasic pattern in dogs exposed for
1 year. Comparatively low levels of uranium were found in the kidney, femur, liver, and spleen, and
these decreased with time (Leach et al. 1973).

In other studies, no significant accumulation was found in the spleen or liver of rats, dogs, or guinea pigs
(Ballou et al. 1986; Diamond et al. 1989; Leach et al. 1973, 1984; Morrow et al. 1972; Wrenn et al.
1987).

2.3.2.2 Oral Exposure

Uranium levels have been measured in tissues from humans, with no occupational exposure where the source of uranium was assumed to be dietary and environmental.

In a comprehensive study of tissues from two long-time residents of New Mexico, the skeleton was the primary depot for uranium (Kathren 1997). Approximately 80 soft tissue samples and 90 bone samples were analyzed from each subject. The mean uranium concentrations in bone were 4.8 and 5.8 ng/g wet weight for the two subjects, respectively. Highest concentrations of uranium in soft tissues were in the tracheobronchial and other pulmonary related lymph nodes, indicating uranium-bearing particulate clearance from the lungs. Concentrations in pulmonary lymph nodes ranged from 16–28 ng/g in one individual to 29–259 ng/g wet weight in the other. An unexpectedly high concentration was found in the thyroid of one subject. In both subjects, uranium was widely distributed among the soft tissues; liver concentrations were lower than those in the kidney (approximately 0.1 ng/g and 0.9 ng/g wet weight, respectively).

The concentrations of uranium in human blood from New York City donors averaged 0.14 mg U/kg in both whole blood and red cells, compared to values ranging from <0.04 to 86 mg U/kg globally (Fisenne and Perry 1985). The median concentrations of uranium in the lungs, liver, kidneys, and vertebra from New York City residents among all age groups were reported to be 0.33, 0.13, 0.32, and 0.29 mg U/kg, respectively (Fisenne and Welford 1986). The concentration of uranium in human fat with no known occupational exposure was 0.6 ng/g (EPA 1985).

In an evaluation of two human skeletal tissues, it was observed that the sacrum contained the highest concentrations of ^{238}U and ^{234}U (4.9 mBq/g ash) (0.13 pCi/g ash) (0.20 μg/g ash). The concentration of ^{238}U was lowest (0.1 mBq/g ash) (0.0027 pCi/g ash) (0.004 μg/g ash) in the right femur (Singh et al. 1987b). In the United Kingdom, the uranium concentration in wet bone was reported to be 3 mg U/kg (2 nCi U/kg) (Fisenne and Welford 1986).

Data on laboratory animals indicate that a substantial portion of uranium leaving the blood may initially distribute throughout soft tissues, but a few days after absorption or injection into the blood, most of the systemic content is found in the kidneys and skeleton (Bhattacharyya et al. 1989; ICRP 1995).

In animals, a substantial fraction of plasma uranium is associated with the ultrafilterable low-molecular-weight fraction, and the remainder is weakly associated with transferrin and other plasma proteins. Data on baboons indicate that 50% or more of the uranium in blood is associated with the red blood cells during the period 10–1,000 hours after injection. These data have been interpreted to mean that about 0.7% of the uranium leaving the plasma attaches to red blood cells and is returned to plasma with a half-time slightly greater than 1 day (ICRP 1995).

In animals, absorbed uranium is osteotropic, accumulating largely on the surface of all types of bone of the animals. Eventually, the uranium on the bone surface diffuses into the mineral portion of the bone. Autoradiography provides confirming evidence that, in the long term, uranium is a bone volume seeker (Wrenn et al. 1987). Kinetic models of uranium distribution predict that, for the short-term, uranium distributes to the bone surface and bone marrow while the deep bone is the long-term depot (Sontag 1986). These results suggest that the macro distribution of uranium in the human skeleton is not uniform.

In some ways, the skeletal behavior of uranium is quantitatively similar to that of alkaline earths. It is known that the uranyl ion (UO_2^{2+}) exchanges with Ca^{2+} on the surfaces of bone mineral crystals, although it does not participate in crystal formation or enter existing crystals. The early distribution of uranium in different parts of the skeleton is similar to that of calcium. Uranium initially deposits on all bone surfaces but is most highly concentrated in areas of growth. Depending on the microscopic structure of the bone of each species, uranium on bone surfaces may gradually diffuse into bone volume; such diffusion has been observed in dogs but not in rats or mice. As with calcium, a substantial portion of uranium deposited in bone is lost to plasma by processes that occur more rapidly than bone resorption (see Section 2.3.5). In human subjects injected with uranium, an estimated 80–90% of the original skeletal deposition was lost from bone over the first 1.5 years (ICRP 1995).

In a study with female mice exposed orally in feed to uranyl nitrate hexahydrate at a dosage of 462 mg U/kg/day for 36–44 weeks, average uranium accumulation was 6 µg per pair of kidneys, 46 µg/g bone and 0–0.5 µg in whole liver, respectively. No significant organ accumulation was found for the lower dose levels (Tannenbaum and Silverstone 1951). Maximal concentrations of 77 µg per pair of kidneys and 216 µg/g in bone were estimated at 50 weeks in male mice that were orally exposed to uranyl nitrate hexahydrate at 925 mg U/kg/day for 48 weeks. One mouse with small kidneys showed levels of 395 µg/pair of kidneys and 1,440 µg/g bone (Tannenbaum and Silverstone 1951). Average uranium

accumulation in the kidneys and bone of male mice exposed to uranyl fluoride orally at 452 mg U/kg/day for 28 weeks was 33 µg/pair of kidneys and 145 µg/g bone at 20 weeks (Tannenbaum and Silverstone 1951). Maximal concentrations of 6 µg/pair of kidneys at 50 weeks and 29 µg/g bone at 14 weeks were found in female mice given oral uranium tetrachloride at 978 mg U/kg/day for 48 weeks (Tannenbaum and Silverstone 1951).

The insoluble compounds of uranium accumulated to a lesser extent in tissues. Only small amounts of uranium were found in the kidneys (3–9 µg/pair of kidneys) of female mice that were exposed orally to uranium tetrafluoride at 4,437 mg U/kg/day for 48 weeks. No uranium was found in the bone (Tannenbaum and Silverstone 1951). Only small amounts of uranium were found in kidney (1–3 µg/pair of kidneys) of female mice that were exposed orally to triuranium octaoxide at 1,655 mg U/kg/day for 48 weeks. No uranium was found in the bone (Tannenbaum and Silverstone 1951).

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of uranium after dermal exposure in humans or animals.

2.3.2.4 Other Routes of Exposure

Intravenously injected uranium is rapidly taken up by the tissues or excreted in the urine (ICRP 1995). Typically, 25% of intravenously injected uranium (as uranyl nitrate) remained in blood of human subjects after 5 minutes, 5% after 5 hours, 1% after 20 hours, and less than 0.5% after 100 hours although inter-subject variation was high (Bassett et al. 1948; Bernard and Struxness 1957). Measurements of systemic distribution of uranium made at autopsy in one terminally ill human given a single intravenous injection of uranium indicated that the skeleton, kidneys, and other soft tissues after 2.5 hours contained about 10, 14, and 6%, respectively, of the dose. Distribution data taken from another human subject 18 hours after a single intravenous injection uranium showed that the bones, kidneys, and other soft tissues contained about 4–13%, 6%, and 4%, respectively, of the amount injected. At 566 days post-injection, uranium distribution in the skeleton, kidneys, and other soft tissues declined to about 1.4, 0.3, and 0.3%, respectively.

The distribution of uranium metal implanted in muscle has been investigated in rats (Pellmar et al. 1999a). In these experiments, pellets of depleted uranium were implanted into the gastrocnemius muscle

and uranium levels were measured in kidney, muscle, liver, spleen, brain, serum and bone at 1 day and at 6, 12, 18 months after implantation. Within 1 day uranium was measurable in kidney and bone but not in the other tissues. At later time points, significant amounts of uranium were found in the other tissues, although levels were always highest in the kidney and bone.

2.3.3 Metabolism

Uranium is usually found in compounds which can be metabolized and recomplexed to form other compounds. In body fluids, tetravalent uranium is likely to oxidize to the hexavalent form followed by formation of uranyl ion. Uranium generally complexes with citrate, bicarbonates, or protein in plasma (Cooper et al. 1982; Dounce and Flagg 1949; Stevens et al. 1980). The stability of the carbonate complex depends on the pH of the solution, which will differ in different parts of the body (BEIR IV 1988). The low-molecular-weight bicarbonate complex can be filtered at the renal glomerulus, and be excreted in urine at levels dependent on the pH of the urine. The uranium bound to the protein (primarily transferrin) is less easily filtered and is more likely to remain in blood. In the blood, the uranyl ion binds to circulating transferrin, and to proteins and phospholipids in the proximal tubule (Wedeen 1992).

2.3.4 Elimination and Excretion

Two-thirds of uranium, intravenously injected as uranyl nitrate in human subjects was typically excreted in urine in the first 24 hours. Approximately 10% more was excreted over a period of 5 days. Fecal excretion accounted for less than 1% of the excretion (ICRP 1995).

2.3.4.1 Inhalation Exposure

In a study of 7,231 uranium workers, the urinary concentration of uranium ranged from 5 µg/L in 4,556 workers to more than 100 µg/L in 32 workers. Samples were taken weekly over a 6-year period. Among a control group of 600 non-uranium workers, none had urinary uranium concentrations that exceeded 40 µg/L. The author concluded that urinary uranium concentrations greater than 100 µg/L are definitely indicative of recent absorption, and that pathological albuminuria is rare, except when the urinary uranium concentration exceeds 1,000 µg/L. Albuminuria, when seen, was transient, and did not persist (Butterworth 1955).

Urinary excretion in crushermen (about 0.2 nCi/day [7 Bq/day][0.3 mg/day]) is about 1/100th of fecal excretion (about 13.5 nCi/day [500 Bq/day][20 mg/day]). The activity of ^{234}U in urine was slightly higher than that of ^{238}U. Active crushermen excreted higher levels of ^{234}U, ^{238}U, and ^{230}Th than retired crushermen or controls (Fisher et al. 1983). Most of the inhalation doses of female employees at the Oak Ridge plant were excreted in the feces, indicating that ciliary action in the lungs, followed by fecal excretion, was an important mechanism of body clearance (West and Scott 1969).

Zhao and Zhao (1990) reported on the excretion of uranium in an occupationally exposed worker. A 23-year old man who weighed 60 kg, dressed in protective clothing, mask, and gloves, was accidentally exposed to pure uranium tetrafluoride powder for 5 minutes. The uranium tetrafluoride powder cloud was reported to contain natural uranium. Urinary excretion was reported as 112 µg/L or 156.8 µg in the first 24 hours, gradually increasing through post-accident day 60 and returning to normal at about post-accident day 1,065. The total urinary excretion of uranium through day 1,065 was calculated to be 86.7 mg. The excretion data was used to calculate total absorption and kidney content by use of a kinetic model (ICRP 1979). The kidney content on post-accident day 1 was reported as 804.2 µg or approximately 2.6 µg/g of kidney.

The biological half-time of uranium dioxide in human lungs (occupational exposure) at German fuel fabrication facilities was estimated to be 109 days. Body burden measurements of uranium taken from 12 people who handled uranium oxides for 5–15 years were used for this determination. Twice a year for 6 years, a urinalysis was conducted on workers exposed to uranium. *In vivo* lung counting was performed on the last day before and the first day after a holiday period. Levels of uranium in feces were measured during the first 3 days and the last 3 days of a holiday period and the first 3 days after the restart of work. For some employees, the levels of uranium in feces was measured during 3–4 days one-half year after the holiday period (Schieferdecker et al. 1985).

In animals, most of absorbed uranium is excreted in urine. Inhaled larger particles ($10 µm) are transported out of the respiratory system by mucocilliary action, then swallowed, and eliminated in the feces (Ballou et al. 1986; Downs et al. 1967; Morrow et al. 1982). Deposition sites of inhaled aerosols, and hence the clearance kinetics, are determined in part by particle size of the inhaled particles. As the AMAD increases, the amount deposited in the upper respiratory tract increases, and the amount deposited in the deep respiratory tracts of the lungs decreases. This study used both ^{232}U and ^{233}U dusts. The ^{233}U dust deposition in the upper respiratory tract increased from 21 to 62% of the total

amount of dust deposited with increasing particle size; deposition in the deep lung decreased from 22 to 7% with increasing particle size. The ^{232}U dust deposition in the upper respiratory tract increased from 10 to 32% with increasing particle size; deposition in the deep lung decreased from 23 to 9% with increasing particle size. The differences were less marked for ^{232}U dust, presumably, because the particle size was much more uniform than that for the ^{233}U dust. A large amount of the initial lung burden was preferentially cleared via the feces following clearance from the upper respiratory tract to the gastro-intestinal tract (higher fecal excretion with higher AMAD) by mucocilliary action. Urinary excretion was 25–50% of initial lung burden on day 1; less with larger particles. By day 7, 25–80% of the uranium uptake was cleared in urine; most of the uranium was eliminated in the feces (Ballou 1986). In one study with rats, most of the inhaled uranium, as uranium dioxide, was excreted in the urine. In dogs, less than 10% was excreted in feces (presumably cleared by mucocilliary action) (Cooper et al. 1982). About 60% of the retained uranium, as uranyl nitrate hexahydrate (Ballou et al. 1986), uranium hexafluoride (Leach et al. 1984), and uranium trioxide (Morrow et al. 1982), was excreted in urine within 1 day in other studies with rats, dogs, and guinea pigs. Most of the retained uranium in rats exposed via intra-tracheal intubation with uranium dioxide or uranyl nitrate hexahydrate was excreted in the urine. Less than 10% was excreted in feces (presumably cleared by mucocilliary action) (Cooper et al. 1982). The fraction of insoluble compounds (uranium tetrafluoride, uranium dioxide) retained in the lungs and lymph nodes was independent of the exposure concentration. More than 90% of the uranium retained at the end of the first year of exposure to uranium dioxide was cleared by the end of the second year despite continued exposure to uranyl nitrate hexahydrate. All of the uranium retained following 1 year of exposure to uranium tetrafluoride was cleared by the end of the second year. For uranyl nitrate hexahydrate exposure, no retention was found in the soft tissues (Stokinger 1953).

Once deposited in the lungs, uranium compounds clear from the various biological compartments by solubility. The ICRP lung model recognizes three clearance classification types: F, M, and S. Type F compounds (uranium hexafluoride, uranyl fluoride, uranium trioxide, possibly uranium tetrafluoride, possibly triuranium octaoxide) show 100% absorption with a half-time of 10 minutes. Type M compounds (uranyl nitrate, ammonium diuranate, possibly uranium tetrafluoride, possibly triuranium octaoxide) show 10% absorption with a half-time of 10 minutes, and 90% with a half-time of 140 days, and about 70% of the material in the alveoli eventually reached body fluid. Type S compounds (uranium dioxide) show 0.1% absorption with a half-time of 1 minute, and 99.9% with a half-time of 7,000 days,

and 10% of that deposited in the alveoli reaches body fluid (ICRP 1996). The half-time of uranium in the lungs has also been calculated to be 1–5 days for soluble compounds like uranyl nitrate hexahydrate in rats (Ballou et al. 1986), ammonium diuranate in hamsters (Stradling et al. 1984), and uranyl fluoride in dogs (Morrow et al. 1982). It is longer for the less soluble uranium dioxide: 141–289 days in rats (Downs et al. 1967) and 480 days in dogs (Leach et al. 1973). In the kidney, uranium selectively accumulates in the proximal tubule with a biological half-time of about 1 week (Wedeen 1992). The half-time of uranyl fluoride in the kidneys has been reported to be 2–5 days in rats (Diamond et al. 1989) and 9 days in dogs. In dogs, less than 1% of the uranium remained in the kidneys after 30 days (Morrow et al. 1982).

2.3.4.2 Oral Exposure

The available evidence on the excretion of ingested uranium suggests that most ($95%) is excreted in the feces, and the remainder in urine (Wrenn et al. 1985). Urinary uranium excretion rates from nonoccupationally exposed persons in 3 villages near uranium mining and refining facilities and a control village in Japan ranged from <0.02–0.24 mg U/day per person and <0.02–0.04 mg U/day per person, respectively (Masuda 1971). The half-time in the kidneys has been estimated to be 1–6 days for 99% of the uranium in the kidneys and 1,500 days for the remainder (ICRP 1979). Most of the uranium doses, given as 900 mL of water containing 90 pCi (3.3 Bq) ^{234}U and 90 pCi (3.3 Bq) ^{238}U (180 pCi or 6.6 Bq uranium) to drink over a period of 6 hours, was excreted in feces within 2 days (Singh and Wrenn 1987). Four volunteers who ingested 10.8 mg of uranium mixed with Coca Cola excreted the uranium in both feces and urine over a 25-day period (Hursh et al. 1969). Urinary excretion after oral exposure is generally low and has been estimated as 2% of total excretion (Spencer et al. 1990).

Animal studies have shown that most ingested uranium (99%) is not absorbed in rats, but is eliminated in the feces without being cycled through the bile. In rats, most of the absorbed uranium leaves the body within a few days in urine; half is excreted in 2–6 days (Durbin and Wrenn 1975), and 98% within 7 days (Sullivan 1986). About 95% of the uranium in the kidneys of rats is excreted in urine within 1 week, and very little remains in any other organ (LaTouche et al. 1987; Sullivan 1980a, 1986).

Data from parenteral studies provide further indication that uranium retention in animal kidneys is described by a 2-compartment exponential curve. Reported biological half-times for the compartments

are 2 and 50–60 days (Diamond et al. 1989), 2 and 13 days (Bentley et al. 1985), or 3 and 103 days
(Wrenn et al. 1986).

2.3.4.3 Dermal Exposure

No studies were located describing the excretion of uranium following dermal exposure in humans or
animals.

2.3.5 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 endpoints.

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 chemical 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.
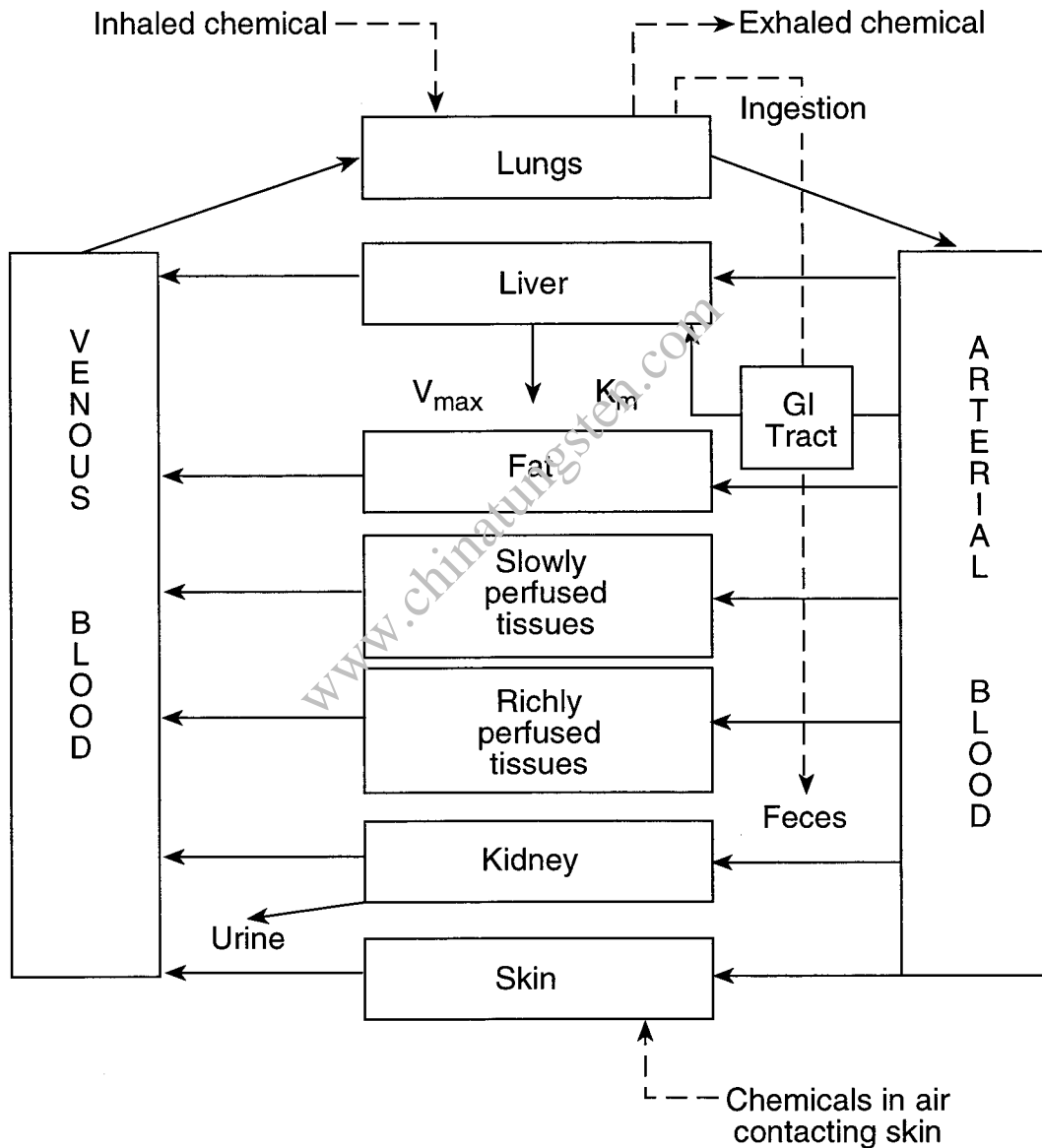
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. This simplification, however, is desirable if the uptake and disposition of the chemical substance(s) is adequately described because data are often unavailable for many biological processes and using a simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance and, thus, model validation is important.

PBPK models improve the pharmacokinetic extrapolation aspects of the risk assessment process, which seeks to identify the maximal (i.e., safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically based 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 2-4 shows a conceptualized representation of a PBPK model. The overall results and individual PBPK models are discussed in this section in terms of their use in risk assessment; tissue dosimetry; and dose, route, and species extrapolations.

The ICRP (1994, 1996) developed a Human Respiratory Tract Model for Radiological Protection which contains respiratory tract deposition and clearance compartmental models for inhalation exposure that may be applied to uranium. The ICRP (1995) also developed a biokinetic model for human oral exposure that applies to uranium. Two other compartmental models (Fisher et al. 1991; Sontag et al. 1986) are also described below. The National Council on Radiation Protection and Measurement (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 which supported the development of the human model.

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance

Inhaled chemical — — —┐   ┌— —→ Exhaled chemical

```
         ┌──────────────────┐          Ingestion
         │      Lungs        │
         └──────────────────┘
┌───┐    ┌──────────────────┐    ┌───┐
│ V │    │      Liver        │    │ A │
│ E │    └──────────────────┘    │ R │
│ N │   Vmax        Km           │ T │  ┌────────┐
│ O │    ┌──────────────────┐    │ E │  │  GI    │
│ U │    │      Fat          │   │ R │  │ Tract  │
│ S │    └──────────────────┘    │ I │  └────────┘
│   │    ┌──────────────────┐    │ A │
│ B │    │  Slowly perfused  │   │ L │
│ L │    │     tissues       │   │   │
│ O │    └──────────────────┘    │ B │
│ O │    ┌──────────────────┐    │ L │
│ D │    │  Richly perfused  │   │ O │
│   │    │     tissues       │   │ O │
│   │    └──────────────────┘    │ D │  Feces
│   │    ┌──────────────────┐    │   │
│   │    │     Kidney        │   │   │
│   │    └──────────────────┘    │   │
│   │  Urine                     │   │
│   │    ┌──────────────────┐    │   │
└───┘    │      Skin         │    └───┘
         └──────────────────┘
```

V_{max} K_m

└— —Chemicals in air contacting skin

Source: adapted from Krishnan et al. 1994

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.

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

Deposition.   The ICRP 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. ICRP provides inhalation dose coefficients which can be used to estimate the committed equivalent and effective doses to organs and tissues throughout the body based on a unit intake of radioactive material. The model applies to three levels of particle solubility, a wide range of particle sizes (approximately 0.0005–100 μm in diameter), and parameter values can be adjusted for various segments of the population (e.g., sex, age, 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 particles containing uranium, but was developed for a wide variety of radionuclides and their chemical forms.

The ICRP deposition model estimates the amount of inhaled material that initially enters each compartment (see Figure 2-5). The model was developed with 5 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 from each region and redistributed either upward into the respiratory tree or to the lymphatic system and blood by different particle removal mechanisms.

For extrathoracic deposition, the model uses experimental data, where deposition is related to particle size and airflow parameters, and scales deposition for women and children from adult male data. Similarly 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 2-5 provides reference respiratory values for the general Caucasian population under several levels of activity.

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. Figure 2-6 presents the compartmental model and is linked to the deposition model

Figure 2-5. Respiratory Tract Compartments in Which Particles May be Deposited
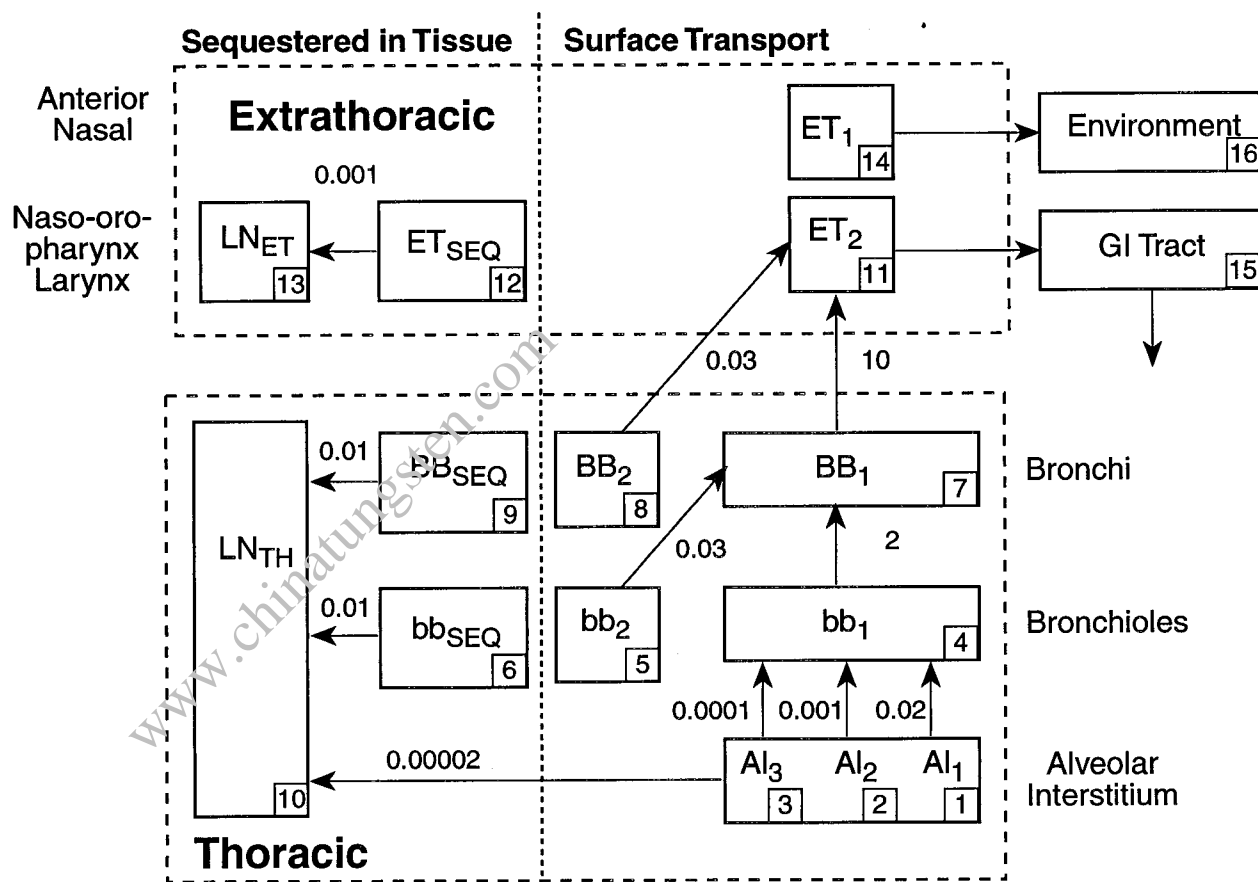
Size of arrow represents relative deposition rate

Source: ICRP 1994

Table 2-5. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity

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

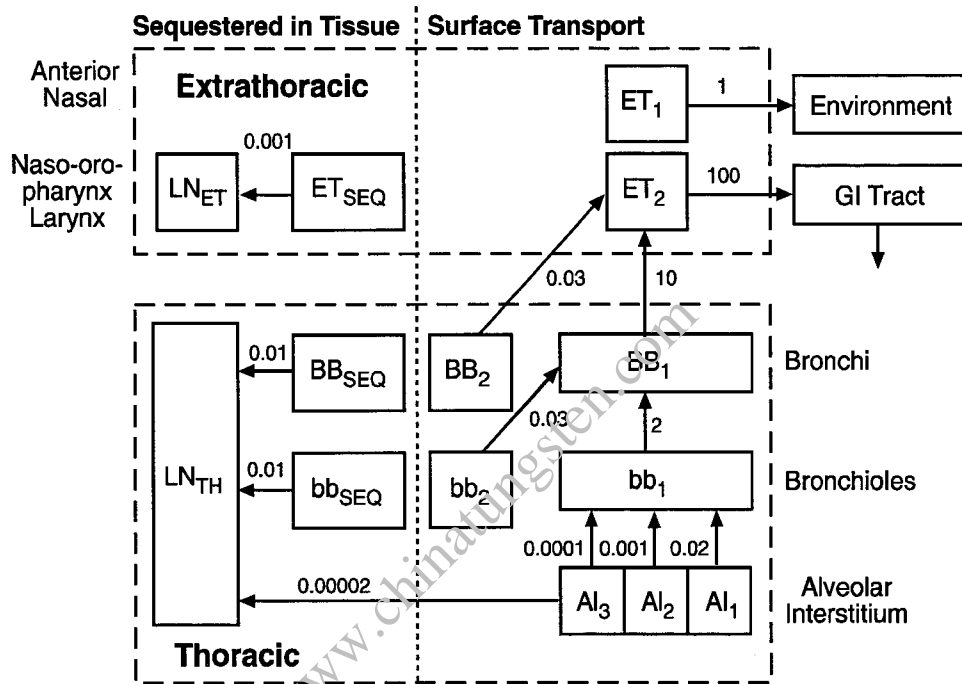[a] See Annexe B (ICRP 1994) for data from which these reference values were derived.

[b] V_T = Tidal volume, B = ventilation rate, f_R = respiration frequency.

Mo = month(s); N/A = not applicable; y =year(s)

Figure 2-6. Compartment Model to Represent Time-Dependent Particle Transport in the Respiratory Tract

Source: ICRP 1994

(See Table 2-6 for rates, half-lives, and fractions by compartment)

(Figure 2-5) and to reference values presented in Table 2-6. Table 2-6 provides clearance rates and deposition fractions for each compartment for insoluble particles. The table provides rates of insoluble particle transport for each of the compartments, expressed as a fraction per day and also as half-time. ICRP also developed modifying factors for some of the parameters, such as age, smoking and disease status.   Parameters of the clearance model are based on human evidence for the most part, although particle retention in airway walls is based on experimental data from animal experiments.

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

Particle transport from all regions is toward both the lymph nodes and the pharynx, and a majority of deposited particles 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 a few micrometers or greater, the ET_1 compartment is probably the largest deposition site. A majority of particles deposited at the back of the nasal passages and in the larynx (ET_2) are removed quickly by the fluids that cover the airways. In this region particle clearance is completed within 15 minutes.

Ciliary action removes deposited particles from both the bronchi and bronchioles. Though it is generally thought that mucocilliary action rapidly transports most particles deposited here toward the pharynx, a fraction of these particles are cleared more slowly. Evidence for this is found in human studies. For humans, retention of particles deposited in the lungs (BB and bb) is apparently biphasic. The "slow" action of the cilia may remove as many as half of the bronchi- and bronchiole-deposited particles. In human bronchi and bronchiole regions, mucus moves more slowly the closer to the alveoli it is. For the faster compartment it has been estimated that it takes about 2 days for particles to travel from the bronchioles to the bronchi and 10 days from the bronchi to the pharynx. The second (slower) compartment is assumed to have approximately equal fractions deposited between BB_2 and bb_2 and both with clearance

Table 2-6. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part A

Clearance Rates for Insoluble Particles				
Pathway	From	To	Rate (d^{-1})	Half-time[d]
$m_{1,4}$	AI_1	bb_1	0.02	35 d
$m_{2,4}$	AI_2	bb_1	0.001	700 d
$m_{3,4}$	AI_3	bb_1	0.0001	7000 d
$m_{3,10}$	AI_3	LN_{TH}	0.00002	—
$m_{4,7}$	bb_1	BB_1	2	8 h
$m_{5,7}$	bb_2	BB_1	0.03	23 d
$m_{6,10}$	bb_{seq}	LN_{TH}	0.01	70 d
$m_{7,11}$	BB_1	ET_2	10	100 min
$m_{8,11}$	BB_2	ET_2	0.03	23 d
$m_{9,10}$	BB_{seq}	LN_{TH}	0.01	70 d
$m_{11,15}$	ET_2	GI tract	100	10 min
$m_{12,13}$	ET_{seq}	LN_{ET}	0.001	700 d
$m_{14,16}$	ET_1	Environment	1	17 h

See next page for Part B

Table 2-6. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract (continued)

Part B

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

Source: ICRP 1994

[a] The half-times are approximate since the reference values are specified for the particle transport rates and are rounded in units of d^{-1}. A half-time is not given for the transport rate from AI_3 to LN_{TH}, since this rate was chosen to direct the required amount of material to the lymph nodes. The clearance half-time of compartment AI_3 is determined by the sum of the clearance rates from it.

[b] See paragraph 181, Chapter 5 (ICRP 1994) for default values used for relating f_s to d_{ae}.

[c] It is assumed that the slow-cleared fraction f_s is size-dependent. For modeling purposes f_s is taken to be:

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

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

half-times estimated at 20 days. Particle size is a primary determinant of the fraction deposited in this

slow thoracic compartment. A small fraction of particles deposited in the BB and bb regions is retained

in the airway wall for even longer periods (BB_{seq} and bb_{seq}).

If particles reach and become deposited in the alveoli, they tend to stay imbedded in the fluid on the

alveolar surface or move into the lymph nodes. The one mechanism by which particles are physically

resuspended and removed from the AI region is coughing. For modeling purposes, the AI region is

divided into 3 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 given a half-time of several hundred days. Over time, AI particle transport falls and some compounds

have been found in lungs 10–50 years after exposure.

Absorption into Blood. The ICRP model assumes that absorption into blood occurs at equivalent rates in

all parts of the respiratory tract, except in the anterior nasal passages (ET_1), where no absorption occurs.

It is essentially a 2-stage process, as shown in Figure 2-7. First, there is a dissociation (dissolution) of

particles; then the dissolved molecules or ions diffuse across capillary walls and are taken up by the

blood. Immediately following dissolution, rapid absorption is observed. For some elements, rapid

absorption does not occur because of binding to respiratory-tract components. In the absence of specific

data for specific compounds, the model uses the following default absorption rate values for those specific

compounds that are classified as Types F (fast), M (medium), and S (slow):

C   For Type F, there is rapid 100% absorption within 10 minutes of the material deposited in the BB,
     bb, and AI regions, and 50% of material deposited in ET_2. Thus, for nose breathing, there is rapid
     absorption of approximately 25% of the deposit in ET and 50% for mouth breathing. Type F
     uranium compounds include uranium hexafluoride, its mixture with uranyl fluoride, uranyl nitrate
     (which can behave as Type M), pure uranium trioxide, and uranium tetrafluoride (which can behave
     at Type M).

C   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. Type M compounds include unpure uranium trioxide, uranyl nitrate (which can behave
     as Type F), ammonium diuranate, uranium oxtaoxide (which can behave as Type S), and uranium
     tetrafluoride (which can behave as Type F).

Figure 2-7. The Human Respiratory Tract Model: Absorption into Blood
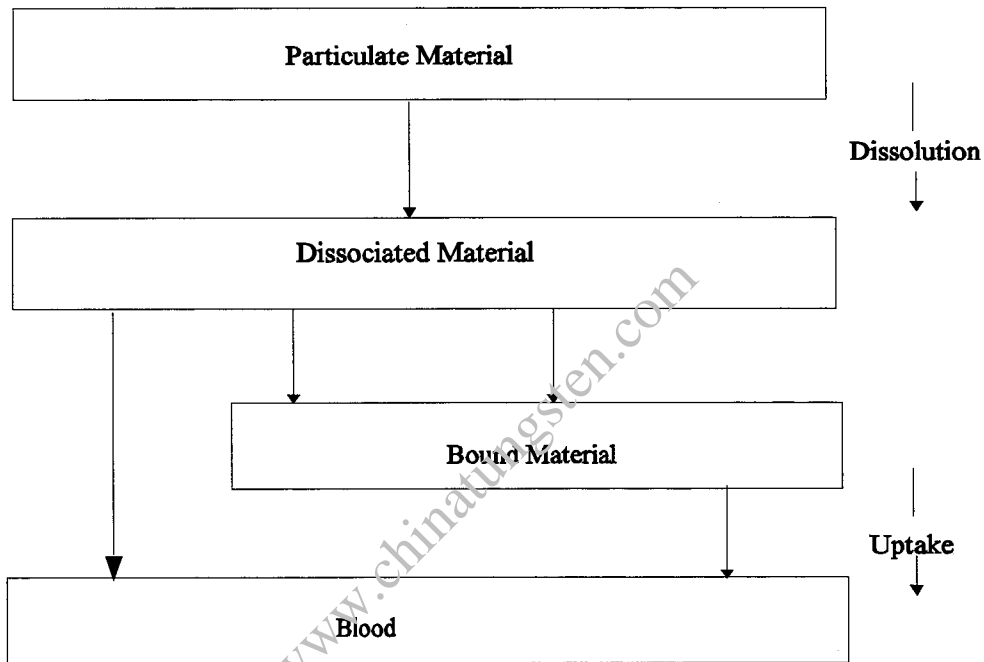
Source: ICRP 1994

C   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. Type S compounds include uranium dioxide and uranium octaoxide (which can behave
      as Type M).

Biokinetic Model for Uranium (ICRP 1995).   The ICRP biokinetic model for uranium is based on

the generic model structure for alkaline earth elements described in *Publication 67* (ICRP 1993, as cited

in ICRP 1995). Uranium (as the UO_2^{2+} ion) is similar to calcium (Ca^{2+}) with regard to skeletal kinetics.

Some transfer rates in the biokinetic model for uranium are equated with bone formation rates. The early

behavior of uranium in human circulation is represented reasonably well by treating plasma as a

uniformly mixed pool, where uranium is removed at a rate of 35 d^{-1} (ICRP 1995) and where a soft tissue

compartment (ST0) is in relatively rapid exchange with plasma (see Figure 2-8). Compartment ST0 is

assumed to receive 30% of uranium leaving plasma and to have a removal half-time of 2 hours (from ST0

to plasma). ICRP assumed that 1% of uranium leaving the circulation (or 0.7% leaving plasma) deposits

in red blood cells (ICRP 1995). The removal half-time from red blood cells to plasma is assumed to be
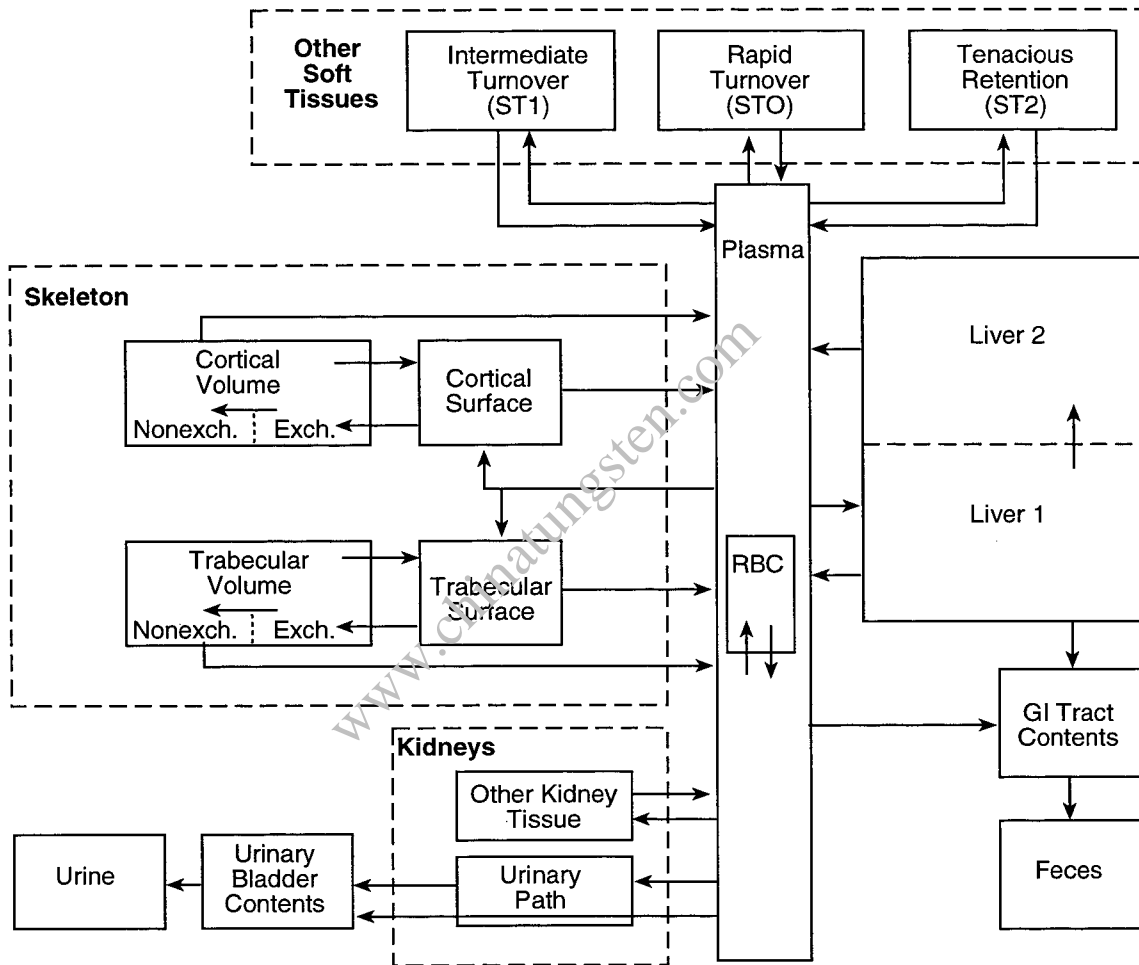
2 days.

Urinary excretion of uranium is assumed to arise from uranium moving directly from plasma to the

urinary bladder contents. Approximately 60% of uranium leaves the blood directly to the bladder and

another 12% is retained temporarily in the renal tubules before excretion. The liver is assumed to consist

of two compartments, Liver 1 and Liver 2. The liver receives an estimated 1.5% of uranium leaving the

blood, with over 90% returning to circulation.

Little direct information on the kinetics of uranium in children exists. Age-specific deposition of uranium

in the skeleton is assumed to be proportional to the deposition of the alkaline earth elements. The rate of

removal from deep bone is assumed to be the same as the age-specific bone turnover rate. Because

children have higher amounts of uranium taken up by bone, deposition in soft tissues and excreta are

likely lower in children than for adults.

Sontag (1986) Pharmacokinetic Model.   An extended multicompartmental model (see Figure 2-9)

describing the kinetic behavior of uranium (absorption, distribution, and excretion as a function of time)

in the organs of male and female rats was developed using data taken from experiments performed on

13-month-old male and female Sprague-Dawley rats intravenously injected with 1.54 mCi/kg (57 kBq/kg)

^{233}U-uranyl citrate and sacrificed at 7, 28, 84, 168, or 336 days after injection.
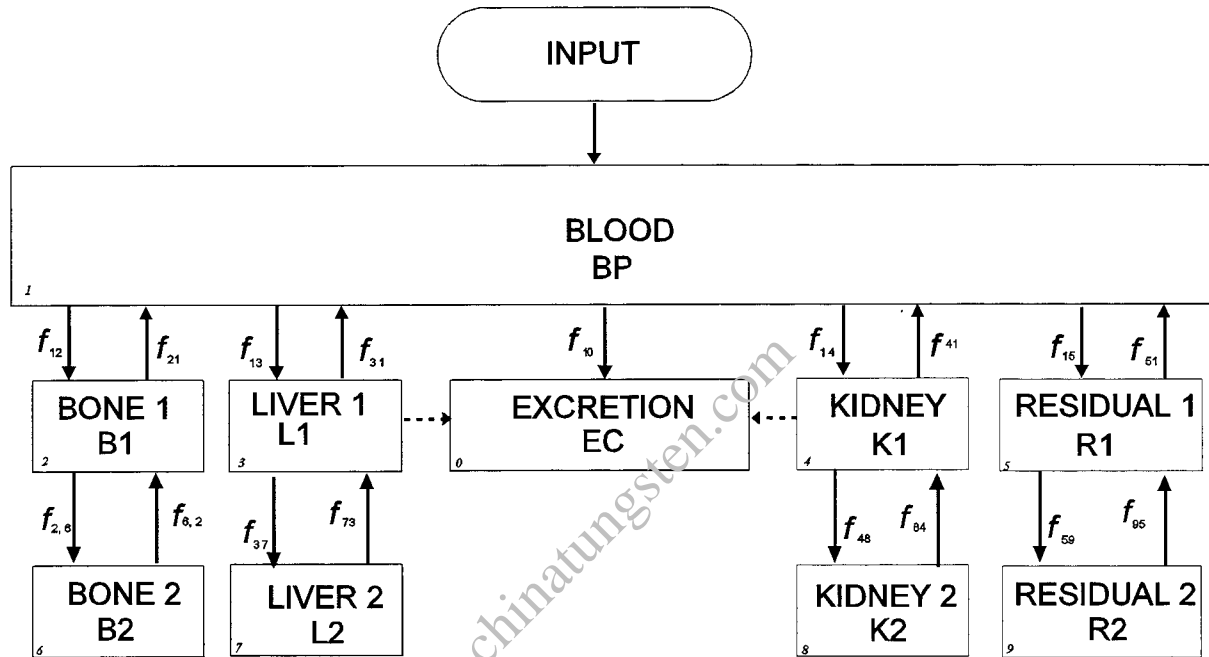
2. HEALTH EFFECTS

Figure 2-8. Biokinetic Model for Uranium after Uptake to Blood

Source: ICRP 1995

Figure 2-9. Multicompartmental Model

f = transfer coefficient (unitless)

Source: Sontag 1986

The model is composed of 10 compartments. These 10 compartments are connected by 17 linear transfer coefficients using 21 parameters. The whole system describes the flux of compounds between a central compartment (the blood) and outer compartments which connect with the central compartment only. The 10 compartments are labeled blood, bone 1, bone 2, liver 1, liver 2, kidney 1, kidney 2, residual 1, residual 2, and excretion. The organs are divided into two compartments; one compartment represents the short term and one represents the long term. For example, the short-term compartment for the bone is the bone surface and bone marrow, and the long-term compartment is the deep bone. In the liver, the short-term compartment is assumed to be the lysosomes, and the long-term compartment is assumed to be the telolysosomes. Separation of these organs into two components helps to account for the reabsorption and rapid excretion. Using the symbols BP=blood, EC=excretion, B1=bone 1, L1=liver 1, K1=kidney 1, R1=residual 1, B2=bone 2, L2=liver 2, K2=kidney, and R2=residual 2, the calculated transfer coefficients for this model are shown in Table 2-7.

Parallel evaluations produced 2 different values (ranges) for each of the 21 parameters. The maximum fractions of uranium in various compartments were as follows: bone, 0.0710 or 0.0735; liver, 0.0160 or 0.0146; kidney, 0.1777 or 0.4789; residual compartment, 0.0358 or 0.0481; and excretion compartment, 0.6995 or 0.3849 (if no back transfer to the blood compartment occurred). The time at which the maximum amount of the uranium in the organ is reduced to one-half is 0.0009 or 0.0013 days in the blood, 165 or 93 days in the bone, 6 or 7 days in the liver, 11 or 5 days in the kidney, and 5 or 6 days in the residual compartment. The cumulative radiation absorbed dose in the organ 365 days after injection of 56.6 kBq/kg body weight was 0.0002 or 0.0004 Gy to blood, 0.730 or 1.29 Gy to bone, 0.0268 or 0.0308 Gy to liver, 1.32 or 1.77 Gy to kidney, and 0.0061 or 0.0076 Gy to residual compartment. The ratio of single injection/continuous intake calculated for the same dose 1 year after the first injection was 0.018 or 0.003 to blood, 0.619 or 0.812 to bone, 0.422 or 0.355 to liver, 0.256 or 0.231 to kidney, 0.726 or 0.585 to residual compartment, and 1.024 or 1.023 to excretion compartment (Sontag 1986).

Fisher et al. (1991) Biokinetic Model   A modified biokinetic model for uranium was developed for inhaled soluble uranium based on human data from an accidental release of uranium hexafluoride in Oklahoma. Urinary excretion data from 31 exposed workers were used to test two previously published compartmental models for inhalation exposure to uranium (ICRP 1979; Wrenn et al. 1989). Urinary uranium was measured periodically for 2 years following the accident. Statistical analysis showed that the Wrenn et al. (1989) model produced a better fit to the excretion data than the ICRP (1979) model.

Table 2-7. Sensitivity and Calculated Transfer Coefficients (d^{-1})

Transfer from-to	Symbol	Experimental value 1	Experimental value 2	Sensitivity
BP-EC	f_{10}	5.55E+2	2.09E+2	0.2
BP-B1	f_{12}	5.63E+1	3.99E+1	5.9
BP-L1	f_{13}	1.27E+1	7.94E0	3.3
BP-K1	f_{14}	1..41E+2	2.60E0	1.5
BP-R1	f_{15}	2.84E+1	2.61E+1	17.5
B1-BP	f_{21}	9.79E-3	1.84E-2	1.9
L1-BP	f_{31}	1.87E-1	2.70E-1	5.6
K1-BP	f_{41}	9.48E-2	3.65E-1	0.5
R1-BP	f_{51}	2.25E-1	3.41E-1	3.4
B1-B2	f_{26}	5.65E-3	6.49E-3	2.2
L1-L2	f_{37}	8.63E-3	9.40E-3	2.7
K1-K2	f_{48}	1.14E-3	1.22E-3	2.2
R1-R2	f_{59}	1.03E-2	8.60E-3	6.1
B2-B1	f_{62}	2.61E-3	4.43E-6	5.0
L2-L1	f_{73}	2.84E-3	3.49E-3	43.7
K2-K1	f_{84}	9.72E-4	1.22E-3	4.8
R2-R1	f_{95}	7.16E-4	1.38E-3	2.3
Varinz	V	6.63E-3	4.65E-3	–

– = Not applicable

Source: Sontag 1986

Parameters of the (Wrenn et al. 1989) model were then modified to further improve the fit to the workers excretion data. Changing the retention half-time in the kidney from 15 days to 6 days and the clearance half-time in the lung from 0.5 days to 0.03 days optimized the fit of the model to the experimental data. The model may be summarized with the following 5-term exponential equation:

$$y_u(t) = 1.5e^{-2.77t} + 0.028e^{-0.116t} + 0.0069e^{-0.0347t} + (4.8 \times 10^{-7}e^{-0.000462t}) + 3.2 \times 10^{-6}e^{-0.000139t}$$

where, $y_u(t)$ is fractional daily uranium excretion rate at t days after intake; the excretion constants in the 5 exponents corresponding to compartments with retention half-times of 0.25, 6, 20, 1,500, and 5,000 days.

The model was used to estimate uranium intakes; uranium burdens in the lungs, kidneys, and bones; and effective dose equivalent for each worker in the accident. Initial intakes of workers involved in the accident ranged from 470–24,000 µg uranium. The model estimated the maximum kidney concentrations in the workers as ranging from 0.048 to 2.5 µg U/g kidney tissue, renal toxicity was not observed in any of the workers (Fisher et al. 1990, 1991).

Based on this same data base, the NRC determined that the maximum uranium dose equivalent of workers on-site was 28 mrem (0.28 mSv). The maximum uranium dose equivalent of off-site individuals was 1.4 mrem (0.014 mSv). However, these radiological doses were small compared to the background radiation level of 106 mrem/year (1.06 mSv/year) in the area from which the data were collected (USNRC 1986).

2.4   MECHANISMS OF ACTION

2.4.1   Pharmacokinetic Mechanisms

On the average, a given amount of an ingested uranium compound appears to be less toxic than the same amount of an inhaled uranium compound (Maynard and Hodge 1949; Stokinger et al. 1953). This finding may be partly attributable to the relatively low gastrointestinal absorption of uranium compounds. Only 0.1–6% of even the more soluble uranium compounds are absorbed in the gastrointestinal tract (Harrison

and Strather 1981; Hursh et al. 1969; ICRP 1979; Larsen et al. 1984; LaTouche et al. 1987; Leggett and Harrison 1995; Maynard et al. 1953; Sullivan 1980a; Wrenn et al. 1985, 1988b). The ICRP (1995) recommends a gastrointestinal absorption reference fraction of 0.02 for uranium ingested in relatively soluble form and 0.002 for insoluble compounds. On the basis of the toxicity of different uranium salts in animals, it was concluded that the relatively more soluble salts (uranyl nitrate hexahydrate, uranyl fluoride, uranium tetrachloride, uranium pentachloride) were most toxic, the slightly soluble compounds (uranium trioxide, sodium diuranate, ammonium diuranate) were of intermediate toxicity, and the insoluble compounds (uranium tetrafluoride, uranium dioxide, uranium tetrachloride, triuranium octaoxide) were nontoxic (Orcutt 1949).

In inhalation exposures, uranium compounds are usually inhalable aerosols. Thus, particle size plays a vital role in tissue dose. Particles larger than 5 μm AMAD are likely to be transported out of the tracheobronchial region by mucocilliary action and swallowed into the gastrointestinal tract, where absorption is minimal (ICRP 1979). The less soluble compounds (uranium trioxide, uranium tetrafluoride), designated Type M by the ICRP (1995), are more likely to remain in the lung tissue and associated lymph glands for weeks. The relatively insoluble compounds (uranium dioxide, triuranium octaoxide), designated Type S by the (ICRP 1995), are likely to remain in the lungs for years (Eidson 1994). This retention of uranium in the lung can lead to a significant pulmonary radiation dose.

In addition, the sequestration patterns of the different uranium compounds are important determinants for the target organ chemical and radiological toxicities of these compounds. The site of deposition for the soluble uranium compounds (uranyl nitrate, uranium tetrachloride, uranium hexafluoride) is the bone, while the insoluble compounds (uranium hexafluoride, uranium dioxide) accumulate in the lungs and lymph nodes (Stokinger 1953).

2.4.2 Mechanisms of Toxicity

The dual modes of uranium chemical and radiological toxicity are not usually separately identifiable by end point. The renal and respiratory effects from exposure of humans and animals to uranium are usually attributed to the chemical properties of uranium, while the theoretically potential excess cancers are usually attributed to the radiation properties of this substance. Although the net effects on the lungs and kidneys have been suggested to be a cooperative action of the chemical and radiation properties, with a

complementary mechanism of action, this relationship has not been demonstrated experimentally (Ballou et al. 1986; Dockery et al. 1993; Dungworth 1989; Filippova et al. 1978; Leach et al. 1984; Spiegl 1949; Spoor and Hursh 1973; Stokinger et al. 1953). UNSCEAR has considered that limits for natural (and depleted) uranium in drinking water (the most important source of human exposure) should be based on the chemical toxicity rather than on a radiological toxicity, which has not been observed in either humans or animals (UNSCEAR 1993; Wrenn et al. 1985).

The most sensitive indicator of uranium toxicity to mammals, and perhaps humans, is nephrotoxicity. While acute high level exposure to uranium compounds can clearly cause nephrotoxicity in humans (Pavlaikis et al. 1996; Zhao and Zhao 1990), the evidence for similar toxicity as the result of long-term lower level occupational exposures is equivocal. Epidemiologic studies have not noted an increase in deaths from urogenital or renal diseases (Brown and Bloom 1987; Checkoway et al. 1988; Dupree et al. 1987; Lundin et al. 1969; Polednak and Frome 1981), and follow-up studies have failed to identify significant damage to human kidneys following occupational exposure to uranium (Eisenbud and Quigley 1955; Hursh and Spoor 1973; Luessenhop et al. 1958), for which regulatory limits are set to prevent damage. A recent comparison of autopsy kidney tissue samples revealed no differences between 7 uranium workers and 6 referents with no known exposure to uranium (Russell et al. 1996). One epidemiologic study provided evidence of nephrotoxicity following occupational exposure to uranium. Nephrotoxicity, indicated by β_2-microglobulinuria and aminoaciduria due to decreased tubular reabsorption, was reported in a group of 39 male uranium mill workers exposed for more than a year to uranium concentrations exceeding the occupational standard of 3.7 Bq/m^3 (currently 5 Bq/m^3 [0.2 mg/m^3]) by #8-fold. Cement workers were used as controls in this study (Thun et al. 1985).

Many animal studies have shown that inhalation, oral, or dermal exposure to uranium results in kidney damage. The damage was histologically manifested as glomerular and tubular wall degeneration. Ultrastructural analysis showed damage to the endothelial cells in the glomerulus, such as loss of cell processes, and reduction in the density of the endothelial fenestrae (Avasthi et al. 1980; Haley 1982; Haley et al. 1982; Kobayashi et al. 1984). In the terminal segments of the proximal convoluted tubules, there was a loss of the brush border, cellular vacuolization, and necrosis. Tubular reabsorption of solutes was disrupted. Functionally, this process led to a disruption of the tubular solute reabsorption and to a decrease in the filtration rate of the glomerulus, as assessed by creatinine or inulin clearance or by proteinuria (Bentley et al. 1985; Blantz 1975; Leach et al. 1973; Morrow et al. 1982). Excessive urinary excretion of protein,

glucose, enzymes, or amino acids such as catalase or alkaline phosphatase are additional indicators of uranium-induced renal pathology (Maynard et al. 1953) by inhalation exposure (Bentley et al. 1985; Diamond et al. 1989; Haley et al. 1982; Leach et al. 1984; Maynard et al. 1953; Morrow et al. 1982).

A mechanism involving bicarbonate activity in the kidneys has been proposed for uranium-induced renal toxicity. Uranium is usually combined with either bicarbonate or a plasma protein in the blood. In the kidneys, uranium is released from bicarbonate and is free to combine to form complexes with phosphate ligands and proteins in the tubular wall to cause damage. Uranium is not tightly bound and is released again within a few days. Within a week following exposure, uranium is largely cleared from the kidneys, and the tubules begin to regenerate. Although the regenerated epithelium has histological differences from its normal state, it is often difficult to detect histological signs of kidney damage a month after exposure because all remaining functional damage is subtle. An alternative mechanism through which uranium exerts its renal toxicity has been suggested by the results of a study conducted with rabbit kidney cells *in vitro*. In this study, uranyl nitrate hexahydrate inhibited both sodium transport-dependent and independent ATP utilization and mitochondrial oxidative phosphorylation in the renal proximal tubule. Ouabain-insensitive adenosine triphosphatase (ATPase) activity exhibited the greatest sensitivity to uranyl nitrate hexahydrate and was significantly inhibited at submillimolar concentrations (Brady et al. 1989). Perhaps both of these activities combine to cause renal damage. In addition, because uranium is a predominantly alpha-emitting radionuclide, current theories on cellular necrosis by high-LET alpha radiation imply a contributory role to the cellular degenerative nephrotoxic changes (BEIR 1980, 1988, 1990; Filippova et al. 1978; Sanders 1986; UNSCEAR 1982, 1986, 1988).

Most studies of respiratory diseases reported for uranium involve noncancerous alveolar epithelium damage in type II cells. These changes are characterized by interstitial inflammation of the alveolar epithelium leading eventually to emphysema or pulmonary fibrosis in acute exposures or to hyperplasia, hypertrophy, and transdifferentiation (metaplasia) in chronic exposures (Cooper et al. 1982; Dungworth 1989; Stokinger 1981; Wedeen 1992). However, the lack of significant pulmonary injury in most inhalation animal studies indicates that other potentially toxic contaminants such as inhalable dust particles, radium, or radon may contribute to these effects.

Large doses of ionizing radiation have the actual or theoretical potential of being carcinogenic, teratogenic, and mutagenic. Since uranium has a low specific activity but emits high LET alpha particles

that are densely ionizing along their track length, studies have been conducted to determine if uranium can produce these effects in humans and animals. The 4 to 8 MeV alpha particles from uranium travel through 40–70 μm in soft tissue, incrementally transferring their kinetic energy to the series of atoms and molecules with which they interact along their short, straight paths. Consequently, only structures within this range from the site of the deposition of uranium may be affected. If a DNA molecule is intersected and damaged without resulting in cell death, a range of theoretical effects can result. DNA has been found to be the most radiosensitive biological molecule, and ionizing radiation has been observed to damage individual chromosomes. The main result from low level ionizing radiation exposure is DNA damage or fragmentation. Viable cells repair the damage, but repair errors can result which produce gene mutations or chromosomal aberrations. Such events may result in such highly rare events as carcinogenesis or teratogenesis, but there is currently no evidence for radiation mutagenesis in humans. Chromosomal aberrations following large radiation doses have been demonstrated in humans and in research animals, showing that ionizing radiation can both initiate and promote carcinogenesis, and interfere with reproduction and development. Cancer is a well-known effect of ionizing radiation exposure, but it has never been associated with exposure to uranium. Likewise, no genetic changes due to radiation have ever been observed in any human population exposed at any dose (BEIR 1980, 1988, 1990; Leach et al. 1970; Morris et al. 1990; Muller et al. 1967; Otake and Schull 1984; Sanders 1986; Stokinger et al. 1953; UNSCEAR 1982, 1986, 1988). For these reasons, UNSCEAR has stated that limits for natural (and depleted) uranium in drinking water (the most important source of human exposure) should be based on the chemical toxicity rather than on a hypothetical radiological toxicity in skeletal tissues, which has not been observed in either humans or animals (Wrenn et al. 1985).   The EPA also used chemical toxicity as the basis for their 20 μg/L interim drinking water limit for uranium published in 1991 (currently withdrawn).

2.4.3 Animal-to-Human Extrapolations

Kidney damage and respiratory disease are the most significant health effects in animals from the metallotoxicity of uranium. Because the biological systems through which these effects are mediated are common to both animals and humans (Brady et al. 1989; Cooper et al. 1982; Dungworth 1989; Stokinger 1981; Wedeen 1992), it is reasonable that animals are appropriate surrogates for humans in this regard. This assumption is consistent with evidence in humans for respiratory (Kathren and Moore 1986, Waxweiler et al. 1981a) and renal (Bernard and Struxness 1957; Fisher et al. 1991; Kathren and Moore 1986; Luessenhop et al. 1958; Thun et al. 1985; USNRC 1986; Waxweiler et al. 1981a; Zhao and Zhao

1990) effects. The data from these studies support the assumption of biological similarity in the renal toxicity of uranium in animals and humans. Nevertheless, a considerable uncertainty is associated with animal-to-human extrapolation regarding the renal toxicity of uranium exposure because the renal toxicity of animals varies with species.

2.5   RELEVANCE TO PUBLIC HEALTH

Overview.

Uranium is an alpha-emitting, radioactive, heavy metal that occurs naturally in the earth's crust at an average concentration of about 2 ppm (approximately 1 pCi/g). Uranium exists in several isotopic forms. The most toxicologically important forms are anthropogenic ^{232}U and ^{233}U and naturally occurring ^{234}U, ^{235}U, and ^{238}U. Uranium isotopes decay by alpha emission. ^{238}U decays through 16 radioactive progeny, including ^{234}U, to reach stable lead-206 (^{206}Pb), while ^{235}U decays through 13 radioactive progeny to reach stable ^{207}Pb. This profile discusses the chemical and radiological health effects of isotopes of uranium (natural, enriched, and depleted) and the various compounds in which uranium is usually found. The health effects of daughter isotopes (radium and radon) are addressed in other toxicological profiles (consult the ATSDR toxicological profiles for radium and radon for more information regarding these radionuclides).

Naturally occurring uranium is an isotopic mixture containing a large percentage of ^{238}U and very small percentages of ^{234}U and ^{235}U, by mass. The industrial process called enrichment is used to increase the percentage of ^{235}U and decrease the percentage of ^{238}U in natural uranium. This results in a continuum of additional isotope mixtures in which the percentage of ^{235}U is either larger (enriched uranium) or smaller (depleted uranium) than that of natural uranium. Natural uranium consists of 99.284% ^{238}U, 0.711% ^{235}U, and 0.005% ^{234}U by weight and has a very low specific activity (0.68 μCi/g). Uranium enrichment for commercial nuclear energy produces uranium that contains about 3% ^{235}U; this is called 3% enriched uranium. Uranium enrichment for other purposes, including nuclear weapons production, can produce uranium containing as much as 97.3% ^{235}U and having a higher specific activity (. 50 μCi/g). Depleted uranium is the byproduct of the enrichment process. Depleted uranium has even less specific activity (0.33 μCi/g) than natural uranium.

Uranium is present in the body at very low or trace concentrations and is not known to be an essential element. Human intakes are constant through very small amounts of natural uranium in food and water, and even smaller amounts in air. The following anthropogenic activities increase the potential for human exposure to uranium: mining, milling, and handling uranium; processing uranium ore end products (uranium dioxide, uranium hexafluoride); producing nuclear energy and nuclear weapons; producing phosphate fertilizers from phosphate rocks that contain much higher-than-average levels of uranium; and improperly disposing of wastes. Occupational exposure to airborne uranium ore dust occurs in uranium mines and mills and in processing plants. Typically, uranium represents only 0.2–5% by weight of the ore.

The deposition of inhaled dust particles in the lungs depends on the particle size and the absorption depends on the solubility of the compound. Very small particles, on the order of 1 μm AMAD, are deposited in the alveolar region or deep lung spaces. As particle size increases above 2–3 μm AMAD, there is an increasing likelihood of deposition in the tracheobronchial region. Dust particles that have deposited are rapidly transported out of the tracheobronchial region by mucociliary action and swallowed. The more soluble compounds are more likely to be absorbed into the blood at the alveolar level within days. Ingested uranium that has been cleared from the lungs by mucocilliary action and swallowed is only partly absorbed into the blood. This is true even for the more common soluble salts (uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate). Uranium is usually found in compounds that can break down and recomplex to form other compounds. In body fluids, tetravalent uranium is likely to oxidize to the hexavalent form, followed by formation of the uranyl ion. Uranium generally complexes with citrate, bicarbonates, or protein in plasma.

According to the ICRP (1995), the more soluble compounds (uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate) are more likely to be absorbed into the blood from the alveoli within days and are assigned to inhalation Type F (fast dissolution). The less soluble compounds (uranium tetrafluoride, uranium dioxide, uranium trioxide, triuranium octaoxide) are more likely to remain in the lung tissue and associated lymph glands for weeks and are designated Type M (medium dissolution). The relatively insoluble compounds (uranium dioxide, triuranium octaoxide) may remain in the lungs for years and are designated Type S (slow dissolution). The ICRP (1995) recommends the following absorption factors for humans for inhaled compounds that subsequently enter the gastrointestinal tract: 2% for soluble compounds and 0.2% for less soluble compounds.

The main site of long-term retention for soluble uranium compounds (uranyl nitrate, uranium tetrachloride, uranium dioxide) is the bone, while the inhaled insoluble compounds (uranium tetrafluoride, uranium dioxide) that are deposited in the deep respiratory tract tend to accumulate in the lungs and pulmonary lymph nodes.

Ingested uranium is excreted mostly in the feces; urinary excretion is generally low. The biological half-times of soluble uranium compounds (uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate) are estimated in days or weeks; those of the less soluble compounds (uranium tetrafluoride, uranium dioxide, triuranium octaoxide) are estimated in years. No information is currently available on the excretion of dermally absorbed uranium. Transdermally absorbed uranium is expected to behave identically to uranium compounds absorbed through the lungs and the gastrointestinal tract.

Because the specific activities of natural and depleted uranium are low, no remarkable noncancerous radiological health hazard is expected (and none has been observed) from exposure to natural and depleted uranium. The results of the available studies in humans and animals are consistent with this conclusion. According to the BEIR IV report, if uranium's radiation were carcinogenic in humans, the most likely carcinogenic effect in humans would be bone sarcoma. However, even highly-enriched uranium has not been found to produce cancer, including that of the bone, in exposed humans. Evidence from animal studies suggests adverse effects reported from such exposures include damage to the epithelium of the lungs (fibrosis) and cardiovascular abnormalities (friable vessels).

The chemical action of all isotopes and isotopic mixtures of uranium are identical, regardless of the specific activity, because chemical action depends only on chemical properties. Thus, the chemical toxicities of natural, depleted, and enriched uranium are identical. Current evidence from animals studies suggests that the toxicity of uranium is mainly due to its chemical damage to kidney tubular cells, leading to nephritis.

Evidence also suggests that the toxicity of uranium varies according to the route of exposure and to its compounds. This finding may be partly attributable to the relatively low gastrointestinal absorption of uranium compounds. Only <0.1–6% of even the more soluble uranium compounds are absorbed in the gastrointestinal tract. On the basis of the toxicity of different uranium salts in animals, it was concluded that the relatively more water-soluble salts (uranyl nitrate hexahydrate, uranyl fluoride, uranium pentachloride) were primarily renal and systemic toxicants. The less water-soluble compounds (uranium trioxide, sodium diuranate, ammonium diuranate) were of moderate-to-low toxicity, while the insoluble

compounds (uranium tetrafluoride, uranium dioxide, uranium peroxide, triuranium octaoxide) were primarily pulmonary toxicants. Generally, hexavalent uranium, which forms soluble compounds, is more likely to be a systemic toxicant than the less soluble tetravalent uranium. The available data on both the more important soluble and insoluble uranium compounds are sufficient to conclude that uranium has a low order of metallotoxicity in humans. This low toxicity results from the high exposures to which animals in these studies were exposed, without adverse effects in some cases. Many of the nonradioactive heavy metals such as lead, arsenic, and mercury would produce very severe, perhaps fatal, injury to animals at the levels of human exposures to uranium reported in the literature.

Particle size determines the point of deposition site of pulmonary-inhaled aerosols. The pulmonary deposition site is an important factor in determining the toxicity of an aerosol. Small particles (#2 μm AMAD) are deposited in the deep respiratory tract. Larger particles are deposited in the tracheobronchial region, where they are transported by mucociliary action to the throat and swallowed into the gastrointestinal tract where absorption is minimal. The less soluble compounds are more likely to remain in the lung tissue and associated lymph glands either for weeks (uranium trioxide, uranium tetrafluoride) or for years (uranium dioxide, triuranium octaoxide), resulting in significant pulmonary retention in inhalation-exposure toxicity and a greater dose of alpha radiation. Long-term retention of inhaled particles of insoluble compounds can cause pulmonary ailments.

The kidneys have been identified as the most sensitive target of uranium toxicosis, consistent with the metallotoxic action of a heavy metal ion, such as the uranyl ion, but epidemiological studies indicate that exposure to air concentrations within current occupational limits may not produce renal effects. The toxic action of uranium is mediated by accumulation of uranium in the renal tubular epithelium to induce cellular necrosis and atrophy in the tubular wall resulting in decreased reabsorption efficiency in the renal tubules in humans and animals. Heavy metal ions are also effective in delaying or blocking the cell division process, thereby magnifying the effects of cell necrosis. However, epidemiologic studies have not provided evidence of uranium's nephrotoxicity or urogenital toxicity in humans. One study found mild nephrotoxicity, indicated by β_2-microglobulinuria and aminoaciduria due to decreased tubular reabsorption, in 39 male uranium mill workers exposed for more than a year to uranium concentrations exceeding the occupational standard of 1.0×10^{-10} μCi/mL (3.7 Bq/m^3 or 0.15 mg/m^3) by up to 8-fold. Nephritis with edema (including nephrosis) was identified as the cause of death of 11% of a cohort of

uranium miners exposed to uranium dust (and radon daughters for an average of 821 WLM). However, the incidence was actually lower than the national average using Standard Mortality Ratio (SMR) analysis. The nephrotoxic effects of uranium in humans may include damage to the glomerulus as evidenced by histopathological changes in the kidneys of former uranium mill workers. However, the negative findings regarding renal injury among current uranium miners and mill workers exposed to dusts of both soluble and insoluble uranium compounds are particularly significant in view of the high levels of exposure.

In animal studies, observations in acute- and intermediate-duration exposures to uranium compounds provide evidence that uranium is nephrotoxic in high doses. Histopathological examination of the kidneys of these animals following oral, inhalation, or parenteral exposure revealed a thickened glomerular capsular wall, shrinkage of the glomerular capillary network, lesions, and decreased glomerular filtration rates. The damage in animals is histologically manifested as glomerular and tubular wall pathology. A mechanism involving bicarbonate activity in the kidneys has been proposed for uranium-induced renal toxicity. An alternative mechanism involving the inhibition of both sodium transport-dependent and independent ATP utilization and mitochondrial oxidative phosphorylation in the renal proximal tubule has also been proposed.

Respiratory diseases have been associated with human exposure to uranium dust, and several epidemiologic studies of uranium miners, millers, and processors are considered in this profile. Respiratory disease in uranium miners has been linked to exposure to uranium-containing dust. In several of these studies, the investigators concluded that although uranium mining clearly elevates the risk for nonmalignant respiratory disease, the etiology of the excess risk is not clearly identifiable because of concurrent exposure to known potent respiratory tract toxicants (including inhalable dust particles, silica, nickel oxide, cobalt oxide, radon daughters, and vanadium pentaoxide). Several animal studies involving uranium-containing dusts, such as carnotite mineral dust, reported serious respiratory effects. However, animals exposed to very high doses of dust-free uranium (as uranyl nitrate hexahydrate, uranium tetrachloride, uranium dioxide, uranium trioxide, uranium tetraoxide, uranyl fluoride, uranium tetrafluoride, or uranium acetate) through the inhalation or oral route in acute-, intermediate-, or chronic-duration exposures failed to develop these respiratory ailments. The lack of significant pulmonary injury in oral animal studies indicates that other factors such as diverse inorganic inhalable dust particles, radium, or radon progeny may contribute to these effects. In studies in which humans and animals inhaled uranium hexafluoride, the associated hydrofluoric acid could have been responsible for or could

have aggravated the observed respiratory effects because uranium hexafluoride is hydrolyzed on contact with water to uranyl fluoride and hydrogen fluoride, the latter of which solubilizes into hydrofluoric acid. Acute overexposures to hydrogen fluoride and hydrofluoric acid can lead to death from respiratory failure or cardiac arrythmia.

Uranium has not been implicated in the production of human lung cancer. Since uranium is weakly radioactive, it has been assumed to be potentially carcinogenic at occupational levels by NIOSH. EPA had classified uranium similarly, but has since withdrawn this classification for review. IARC has no classification for uranium. Studies do not indicate any level of uranium carcinogenicity. No significant difference in cancer (of the lungs) was found between workers occupationally exposed to uranium and control populations. Other detailed studies conducted between 1950 and 1967 on the association between uranium mining and an increased incidence of cancer found lung cancer in the miners over 6 times the rate expected. However, the miners were concurrently exposed to other known or potential cancer-causing substances such as radon and its progeny, tobacco smoke, phosgene gas, mercury, and solvents (carbon tetrachloride and trichloroethylene). Radon progeny in the mines, and not the uranium, were clearly identified as the carcinogenic agents. (For further information on cancer risks from radon, refer to the ATSDR *Toxicological Profile for Radon* [ATSDR 1990c]). Uranium also appears to be noncarcinogenic in animals. Issues relevant to children are explicitly discussed in Sections 2.6, Children's Susceptibility, and 5.6, Exposures of Children.

Minimal Risk Levels.

Minimal Risk Levels (MRLs) have been derived for the effects from inhalation and oral exposure to uranium, and those values are identified in this section and their bases are detailed in Appendix A. MRLs for radiological exposure were not calculated because:

- no data are available for use in calculating radiological MRLs for any duration because no radiological effects were identified in any of the available studies that used natural uranium as a test material;

- the MRLs for chemical effects would adequately protect against the possible radiotoxicity of natural and depleted uranium because radiological effects are not expected to occur, based on the low specific activities of these isotopic mixtures and the current toxicity data in humans and animals;

- the studies that reported potential radiological effects (severe pulmonary fibrosis, friable blood vessels) used highly enriched uranium in a single inhalation exposure (Filippova et al. 1978; Morris et al. 1989);

- UNSCEAR has considered that limits for natural (and depleted) uranium in food and drinking water (the most important sources of human exposure) should be based on the chemical toxicity rather than on a hypothetical radiological toxicity, which has not been observed in either humans or animals (UNSCEAR 1993; Wrenn et al. 1985).

Lack of radiological effects (see Tables 2-1, 2-2, 2-3, and 2-4) in studies that used natural uranium is due to the low specific activities of natural and depleted uranium, which are 0.67 and 0.3 µCi/g, respectively. In comparison, the calculated specific activity for 97.5% enriched uranium is approximately 50 µCi/g.

Table 2-8 shows the mass equivalents for natural and depleted uranium for radiation levels that caused potential radiological effects in rats exposed once for 100 minutes to airborne 92.8% enriched uranium with an estimated specific activity of 51.6 µCi/g (Morris et al. 1989). These mass equivalent values for natural and depleted uranium for the minimal concentration of radioactivity that is expected to induce potential radiological effects are well above levels that would be expected to be inhaled or ingested. In addition, the mass equivalents for natural and depleted uranium for potential radiological effects are 3,600 and 76,500 times higher, respectively, than the occupational exposure limits (short-term exposure) recommended by the National Institute for Occupational Safety and Health (NIOSH 1997). Therefore, MRLs for uranium based on studies that used enriched uranium are inappropriate.

Chemically, natural and depleted uranium are identical. Therefore, the MRLs calculated for chemical effects, based on studies that tested natural uranium, are applicable to the chemical actions of depleted uranium because the nature and extent of chemical toxicity are determined only by chemical properties.

All of the MRLs derived for uranium are based on renal effects, the most sensitive toxic end point. Uranium has been identified as a nephrotoxin, exerting its toxic effect by chemical action in the proximal tubules in humans and animals, with nephron involvement expected at higher doses. Some acute high-level exposures have resulted in renal effects in humans (Pavlaikis et al. 1996; Zhao and Zhao 1990), while others have not (Eisenbud and Quigley 1955; Fisher et al. 1990). A study of the kidney functions of past uranium mill workers chronically exposed to uranium revealed renal tubular dysfunction, as manifested by mild proteinuria; aminoaciduria; and a correlation between the excretion of β_2-microglobulin (relative to that of creatinine), and the length of time that the uranium workers had spent in the yellowcake (uranium dioxide) drying and packaging area, the work area with the highest exposures to insoluble uranium (Thun et al. 1985). Glomerular function was unaffected by uranium exposure. A number of epidemiological studies have demonstrated no relation between occupational exposure to

Table 2-8. Enriched, Natural, and Depleted Uranium Mass Equivalents for Radiological Effects

Intake duration	Effect	Highly eniched uranium radioactivity concentration[a]	Natural uranium mass equivalent[b]	Depleted uranium mass equivalent[c]	Threshold Limit Value[d]
Acute	Severe alveolar fibrosis	5 µCi/m^3 (= 0.111 g/m^3)	7.2 g/m^3	15.3 g/m^3	0.0002 g/m^3
Intermediate	No data[e]	No data	No data	No data	N/A
Chronic	No data	No data	No data	No data	N/A

[a] Value calculated from a highly ^{235}U-enriched uranium dioxide exposure of 111 mg/m^3 (97.8 mg uranium/m^3) and a specific activity of 1.91 kBq/g (51.6 µCi/g) (Morris et al. 1990)

[b] Value based on a highly ^{235}U-enriched dioxide radioactivity concentration of 5 µCi/m^3 and a specific activity of 0.7 µCi/g for natural uranium

[c] Value based on a highly ^{235}U-enriched dioxide radioactivity concentration of 5 µCi/m^3 and a specific activity of 0.33 µCi/g for depleted uranium

[d] This is a time-weighted average (TWA) concentration for short-term (8-hour) inhalation exposure to insoluble natural uranium compounds in the workplace for which no adverse effects (chemical or radiological) are expected (NIOSH 1994)

[e] Because the observations in the Morris et al. (1989) studies were made through 720 days, its conclusions may be applicable to intermediate and chronic durations

uranium and deaths from renal disease (Brown and Bloom 1987; Checkoway et al. 1988; Dupree et al. 1987; Lundin et al. 1969; Polednak and Frome 1981). The evidence is clear that exposure to uranium can cause renal effects in humans under certain conditions, threshold levels of exposure at which these effects occur have been reported over the range of 0.2 to 3 μg U/g of kidney; however, human organ concentrations are not typically measurable because of the invasive methods that are required. An extensive animal toxicity database, particularly for the inhalation route, indicates that renal effects are also the most sensitive toxic end point in several mammalian species. The effects were dose-dependent and ranged from minimal microscopic lesions in the tubular epithelium and increased urinary catalase (for low doses) to severe necrosis of the tubular epithelium (for high doses) (Dygert 1949a, 1949b, 1949c; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949a, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953).

The effects of uranium in animal experiments were also compound-dependent, the more water-soluble compounds (e.g., uranyl nitrate) causing much greater renal toxicity than insoluble compounds (e.g., uranium dioxide) when the dose contained equivalent amounts of uranium. ATSDR has determined that the toxicity database for uranium justifies the derivation of separate MRLs for soluble and insoluble forms of uranium for certain durations and routes of exposure. This is based on toxicokinetic evidence that absorption of uranium (and concentration in target tissue) is significantly greater during exposure to the more water-soluble compounds. Soluble forms include uranyl fluoride, uranium tetrachloride and uranyl nitrate hexahydrate; insoluble forms include uranium tetrafluoride, uranium dioxide, uranium trioxide, and triuranium octaoxide. Where the database is not extensive enough to allow separate MRLs, the MRL for the soluble form should be protective for health effects due to all forms of uranium.

Inhalation MRLs.

No acute-duration inhalation MRLs were developed for uranium because of the lack of suitable data.

- An MRL of 8×10^{-3} mg U/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to insoluble compounds of uranium.

This MRL is expected to be protective for soluble uranium compounds by an order of magnitude. The MRL is based on a study in which a NOAEL of 1.1 mg U/m^3 was observed for renal effects in dogs and adjusted for intermittent exposure (6 hours/day, 6 days/week) and an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability). Dogs were exposed to uranium

dioxide dust at concentrations of 1.1 mg U/m^3, 8.2 mg U/m^3, or 9.2 mg U/m^3 for 5 weeks, 6 days/week, 6 hours/day (Rothstein 1949b). Mortality, body weight changes, standard hematology (except in the 8.2-mg U/m^3 group), blood and urine chemistries, pathology, and uranium distribution in tissues were measured. No dogs died from exposure to uranium dioxide dust. Additionally, no significant weight changes, or biochemical changes in blood or urine were seen at any concentration. No hematological changes were attributable to uranium dioxide dust. Histopathological changes in the kidney were not observed in any group except for "very slight" renal tubular degeneration in 2 of 6 dogs at 8.2 mg U/m^3. A NOAEL of 1.1 mg/m^3 was identified for the study. For further details, see Appendix A.

- An MRL of 4x10^{-4} mg U/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to soluble compounds of uranium.

The intermediate-duration inhalation MRL for soluble forms of uranium is based on a study that observed a LOAEL of 0.15 mg U/m^3 for renal effects in dogs (Rothstein 1949a). The LOAEL was adjusted for intermittent exposure (6 hours/day, 6 days/week) and multiplied by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability). In this study, dogs were bodily exposed to 0.15, 2.2, or 9.2 mg U/m^3 of uranyl fluoride dust for 6 hours/day, 6 days/week for 5 weeks (Rothstein 1949a). Clinical signs of toxicity, mortality, body weight changes, hematology, and blood and urine chemistries were monitored; selected organs were histopathologically examined and uranium levels determined. Severe toxicity was observed at the highest concentration (9.2 mg U/m^3) leading to death. The two animals in this group showed signs of anorexia, rhinitis, and polydipsia. Histopathological examination of the kidney revealed "severe" tubular lesions. Dogs exposed to 0.15 or 2.2 mg U/m^3 had no clinical signs of toxicity or significant weight changes. At 0.15 mg U/m^3, blood NPN and urinary amino acid nitrogen were normal in three dogs, while one of the three had increased urinary protein (not all tests were run on all dogs). Histopathological examination of the kidneys revealed "moderate" damage at 2.2 mg U/m^3 and "slight" changes in 50% of the dogs at 0.15 mg U/m^3. A LOAEL of 0.15 mg/m^3 for minimal microscopic lesions in the renal tubules was identified for this study. For further details, see Appendix A.

- An MRL of 3x10^{-4} mg U/m^3 has been derived for chronic-duration inhalation exposure (365 days or more) to soluble compounds of uranium.

The chronic-duration inhalation MRL for soluble forms of uranium is based on a NOAEL of 0.05 mg U/m^3 for renal effects in dogs exposed to uranium tetrachloride (Stokinger et al. 1953). The NOAEL was adjusted for intermittent exposure (6 hours/day, 5.5 days/week) and multiplied by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability). In this study, dogs of both sexes were exposed via inhalation to uranium tetrachloride for 6 hours a day, Monday–Friday, and 3 hours on Saturday (5.5 days a week) for 1 year at concentrations of 0, 0.05, and 0.2 mg U/m^3. The animals were monitored for body weight alterations, clinical signs of toxicity, and biochemical alterations in the blood and urine. At the termination of the study, the animals were sacrificed and selected organs were histopathologically examined. Histological and biochemical examinations revealed a NOAEL of 0.05 mg U/m^3 and minimal microscopic lesions in the renal tubules in the 0.2 mg U/m^3 dose level dogs. For further details, see Appendix A.

Oral MRLs.

No acute- or chronic-duration oral MRLs could be developed for uranium because of a lack of suitable data.

- An MRL of 2×10^{-3} mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to soluble compounds of uranium.

The intermediate-duration oral exposure MRL was derived from a LOAEL of 0.05 mg U/kg/day observed for renal effects in New Zealand rabbits receiving uranium as uranyl acetate in drinking water for 91 days (Gilman et al. 1998b). The LOAEL was adjusted by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability). Time-weighted average (TWA) (as mg U/kg/day) calculated by the authors from fluid intake data were: males: 0, 0.05, 0.20, 0.88, 4.82, and 28.70 mg U/kg/day; females: 0, 0.49, 1.32, and 43.02 mg U/kg/day. Urinalysis was performed at 30, 60, and 91 days and dye clearance tests were performed 1 week prior to termination, using standard bromsulfophthalein (BSP) and phenolsulfonphthalein (PSP) test procedures for liver and kidney function, respectively. After 91 days, animals were sacrificed, hematological parameters and serum chemistry were analyzed, and histopathological examination was performed on 27 tissues from each animal. No significant exposure-related differences in weight gain, food consumption, water intake, hematological, or biochemical parameters were noted. Dose-dependent differences consisted of histopathological changes limited primarily to kidney and were more pronounced in males. For further information, see Appendix A.

It is likely that the MRL level for intermediate-duration oral exposure would also be protective for chronic-duration oral exposure. This is because the renal effects of uranium exposure are more dependent on the dose than on the duration of the exposure. Data from a large number of animal studies indicate that renal damage caused by threshold and sublethal doses was overcome and obscured by regeneration of the tubular epithelium, especially in the corticomedullary region, despite continuing exposure (Bentley et al. 1985; Dygert 1949a, 1949b, 1949c; Leach et al. 1984; Maynard and Hodge 1949; Maynard et al. 1953; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949c, 1949d; Russell 1996; Spiegl 1949; Stokinger et al. 1953). Such repair, once completed, is histologically indistinguishable from undamaged kidney tissue.

Death.   The lethal effects of exposure to uranium compounds have been investigated in humans and animals. Data from these studies indicate that uranium compounds have a low order of mammalian toxicity by the inhalation, oral, and dermal routes. No deaths are causally associated with prolonged occupational exposure to inhaled uranium compounds (Archer et al. 1973a, 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Cragle et al. 1988; Gottlieb and Husen 1982; Hadjimichael et al. 1983; Lundin et al. 1969; Polednak and Frome 1981; Samet et al. 1984, 1986; Scott et al. 1972; Waxweiler et al. 1983). Although accidental inhalation exposure to a high concentration of uranium hexafluoride has resulted in human fatalities, those deaths were not associated with uranium (Kathren and Moore 1986; Moore and Kathren 1985; USNRC 1986). These accidents resulted in the generation of concentrated aerosols of uranyl fluoride and highly toxic hydrofluoric acid. In all cases, deaths were attributed to injury to the respiratory tract associated with inhalation of hydrofluoric acid. No deaths have been reported in humans from oral or dermal exposure to uranium compounds. Uranium compounds have caused death in experimental animals by the inhalation, oral and dermal routes. Death was attributed to renal failure. However, the levels of uranium necessary to cause fatalities in experimental animals are far (>1,000 fold) above any plausible human exposure either in the workplace or at hazardous waste sites (Leach et al. 1984; Spiegel 1949; Maynard and Hodge 1949; Orcutt 1949). On the basis of the available data, exposure to environmental uranium or to uranium at levels found at hazardous waste sites will not be lethal to humans.

Systemic Effects.

Respiratory Effects. General damage to pulmonary structures, usually noncancerous alveolar epithelium damage of type II cells, can occur upon inhalation of insoluble reactive chemicals such as some uranium compounds (uranium tetrafluoride, uranium dioxide, uranium trioxide, triuranium octaoxide). In acute

exposures, pulmonary damage may be limited to interstitial inflammation of the alveolar epithelium leading eventually to emphysema or pulmonary fibrosis (Cooper et al. 1982; Dungworth 1989; Saccomanno et al. 1982; Stokinger 1981; Wedeen 1992). In studies of the pulmonary effects of airborne uranium dust in uranium miners (Dungworth 1989; Waxweiler et al. 1983) and in animals (Filippova et al. 1978; Leach et al. 1984; Spiegl 1949; Stokinger et al. 1953), the respiratory diseases reported were aggravated by the insoluble aerosol particles (mine dust) to which these miners were exposed because most of the noncancerous respiratory diseases reported in these studies were consistent with toxicity of inhalable dust particles other than uranium, such as silica (Dockery et al. 1993). This hypothesis is supported by the lack of respiratory diseases in laboratory animal models exposed to aerosols of uranium compounds in the absence of other aerosols (Maynard and Hodge 1949; Maynard et al. 1953; Stokinger et al. 1953; Gilman et al. 1998a; Gilman et al. 1998b; Gilman et al. 1998c). Reports of workers in the uranium-processing industry do not show increased deaths due to diseases of the respiratory system related to exposure to uranium (Brown and Bloom 1987; Cragle et al. 1988; Polednak and Frome 1981; Scott et al. 1972). Respiratory effects reported in workers acutely exposed to uranium hexafluoride were caused by hydrogen fluoride, a potent lung irritant and a spontaneous by-product of uranium hexafluoride (Kathren and Moore 1986; USNRC 1986).

Studies in humans that provide evidence for the radiotoxicity of uranium to the lungs were equivocal and unreliable for use in assessing uranium-specific hazards. The subjects in these studies were also concurrently exposed to known pulmonary toxicants and radiological agents (e.g., radon progeny), as well as to silica dust, which was identified as the etiological agent for silicosis (Dupree et al. 1987; Hadjimichael et al. 1983). Inhalation studies with animals regarding the association of respiratory disease to uranium exposure *per se* were equivocal (Cross et al. 1981a, 1981b, 1982; Leach et al. 1970, 1973, 1984; Morrow et al. 1982; Stokinger et al. 1985). No studies were found that reported respiratory effects in animals following oral or dermal exposure to uranium compounds. Thus, no adverse pulmonary effects from human exposure to uranium *per se* at or near hazardous waste sites are likely. However, prolonged exposure to high levels of insoluble uranium dust, as may occur with uranium miners, millers, and processors, or accidental exposure to high levels of soluble uranium aerosols, especially uranyl fluoride, may damage the lungs by chemical action. These conditions are unlikely at hazardous waste sites; therefore, respiratory effects are unlikely.

Cardiovascular Effects. No reliable studies were identified that associated exposure to uranium with cardiovascular effects in humans. The available studies in animals (rats, mice, guinea pigs, and rabbits) found no adverse cardiovascular effects in animals following inhalation or oral exposures to uranium (Dygert 1949c; Gilman et al. 1998a, 1998b, 1998c; Maynard and Hodge 1949; Stokinger et al. 1953). Although a study in rats that used single intratracheal instillation of 90% enriched soluble uranium salts reported dystrophied blood vessels and enlarged hearts (Filippova et al. 1978), human exposures to such high specific-activity radionuclides at hazardous waste sites are unlikely. No studies were located that reported cardiovascular effects in animals following dermal exposure to uranium compounds. Therefore, no cardiovascular effects are likely from human exposure to environmental levels or to levels expected at or near hazardous waste sites.

Gastrointestinal Effects. A case report of a 5-minute accidental occupational exposure of a male worker in China to fumes of uranium tetrafluoride described signs and symptoms of gastrointestinal distress. These signs and symptoms included loss of appetite, abdominal pain, diarrhea, tenesmus, and pus and blood in the stool (Zhao and Zhao 1990). No gastrointestinal effects were seen in animals given unenriched uranium nitrate in doses as high as 664 mg U/kg/day for 2 years (Gilman et al. 1998a, 1998b, 1998c; Maynard et al. 1949). Gastrointestinal effects are not likely following exposure to uranium at hazardous waste sites.

Hematological Effects. The available human studies (Archer et al. 1973b; Eisenbud and Quigley 1955; Vich and Kriklava 1970) provide no clear evidence that uranium exposure can cause hematological effects in humans. Although the available animal studies provide evidence that very high exposure to uranium compounds may cause disruptions in the blood (Cross et al. 1981b; Dygert 1949b, 1949c, 1949d; Leach et al. 1970, 1973; Ortega et al. 1989a; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949b, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953), others provide evidence of no detectable hematological disturbances (Gilman et al. 1998a, 1998b, 1998c). Adverse effects on the blood are not expected health outcomes from exposure to uranium at the levels found at hazardous waste sites.

Musculoskeletal Effects. No studies have reported effects of uranium on the musculoskeletal system in humans following inhalation, oral, or dermal exposure for any duration.   Laboratory animal studies support a lack of toxicological effects on the musculoskeletal system after oral exposures (Gilman et al. 1998a, 1998b, 1998c).

Hepatic Effects.   No reliable studies were located regarding the effects of uranium on the liver of humans following inhalation, oral, or dermal exposure for any duration**.**   One case report does exist which documents hepatotoxicity in one male who drank 15 g of uranyl acetate (Pavlakis et al. 1996).   Uranyl acetate is water soluble and would likely be more quickly absorbed from the gastrointestinal tract than the more insoluble forms of uranium.   The patient suffered from increasing liver dysfunction, as evidenced by increased serum ALT, AST, and GGK.   Since no liver biopsy sample was obtained, it is difficult to elaborate further on other liver changes that may have occurred.   This individual had a history of drug abuse, which may have predisposed him to hepatic toxicity.   The liver injury appeared temporary, with no residual signs of hepatotoxicity 6 months after ingestion.

No studies were located regarding the effects of uranium on the liver of animals following dermal exposure for any duration.   No indications of liver damage were reported in several animal studies (Dygert 1949c; Pozzani 1949; Rothstein 1949c; Stokinger et al. 1953).   However, inhalation exposure to relatively high concentrations of uranium compounds has resulted in mild liver disturbances, although the etiology is not clear.   These disturbances include increased bromosulfalein retention, indicative of impaired biliary function, in a chronic-duration inhalation study in dogs (Stokinger et al. 1953); increased urinary catalase, moderate fatty livers, and a slight decrease in hepatic lactate content in rabbits (Roberts 1949; Rothstein 1949c, 1949d); and focal hepatic necrosis in rats (Dygert 1949a; Roberts 1949).   Oral exposure of animals to uranium compounds was also accompanied by indications of mild liver damage (Gilman et al. 1998a, 1998c).   These indications included microhemorrhagic foci in the liver of rats (Domingo et al. 1987); liver congestion, minimal hepatic lesions, mild degeneration, or fatty infiltration in dogs (Maynard and Hodge 1949); and increased lysosomal activity in dogs (Ortega et al. 1989a).   No changes were seen in other dog studies in which the animals were given doses as high as 7,859 mg U/kg/day as the relatively insoluble uranium acetate dihydrate for 30 days (Maynard and Hodge 1949).   Anisokaryosis, vesiculation, increased portal density, and perivenous vaculolation were observed in rats (Gilman et al. 1998a), while accentuation of zonation, variation in hepatocellular nuclear size, nuclear pyknosis, and excessive cytoplasmic vacuolization were observed in rabbits (Gilman et al. 1998c).   The data presented here suggested that uranium is a hepatotoxicant by the inhalation and oral exposure routes in both humans (limited data set) and laboratory animals. Uranium disrupts general hepatocellular function and cellular permeability; however, no mechanism for these effects has been identified from any of these studies.   On the basis of the available data, effects on the liver can occur as a result of human exposure to uranium compounds.   However, human and animal studies indicate that the

liver is an order of magnitude less sensitive than the kidney by either inhalation (Dygert 1949a, 1949d; Pozanni 1949; Rothstein 1949c; Stokinger 1953) or oral (Gilman et al. 1998a, 1998c; Maynard and Hodge 1949; Pavlikis et al. 1996) routes, for all exposure durations. Thus, it is highly unlikely that exposure to uranium compounds near hazardous waste sites could result in liver damage.

Renal Effects. Uranium has been identified as a nephrotoxic metal, exerting its toxic effect by chemical action mostly in the proximal tubules in humans and animals. There is sufficient information with high exposures to both soluble and insoluble uranium to permit the conclusion that uranium has a low order of metallotoxicity in humans in view of the high levels to which the subjects were exposed. The negative findings regarding renal injury among workers exposed to insoluble compounds are particularly significant in view of the high levels of exposure reported (Eisenbud and Quigley 1955).

Several epidemiologic studies found no increased deaths in uranium workers due to renal disease (Archer et al. 1973a, 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Polednak and Frome 1981). Also, case studies showed that workers accidentally exposed to high levels of uranium did not have renal damage even up to 38 years postexposure (Eisenbud and Quigley 1956; Kathren and Moore 1986). However, one study on the kidney function of uranium mill workers chronically exposed to soluble uranium revealed renal tubular dysfunction as manifested by mild proteinuria, aminoaciduria, and a dose-related clearance of β_2-microglobulin relative to that of creatinine. Serum β_2-microglobulin was also elevated in the serum of 22 of the 23 workers tested. The incidence and severity of these nephrotoxic signs correlated with the length of time that the uranium workers had spent in the yellowcake (insoluble) drying and packaging area (Saccomanno et al. 1982; Thun et al. 1985). The data from this study were indicative of reduced protein resorption in the proximal renal tubules consistent with the observed renal toxicity of uranium in animals. Two case reports of accidental occupational exposures to high concentrations of both soluble and insoluble uranium by inhalation or dermal routes described clinical findings of a decreased glomerular filtration rate as manifested by decreased urinary output and significantly elevated urinary proteins, nonprotein nitrogen, amino acid nitrogen/creatinine, and phenolsulfonpthalein. Renal function rapidly returned to normal in days (Zhao and Zhao 1990). Acute nephrotoxicity was attributed to a large oral intake of uranyl acetate (Pavlakis et al. 1996). Similarly, the results of animal studies indicated that nephrotoxicity is the most consistent and sensitive adverse effect following inhalation (Dygert 1949a, 1949b, 1949c, 1949d; Filippova et al. 1978; Gilman et al. 1998a, 1998b, 1998c Leach et al. 1970, 1973, 1984; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein

1949a, 1949c, 1949d; Spiegl 1949; Sprague 1949; Stokinger et al. 1953), oral (Domingo et al. 1987; Gilman et al. 1998a, 1998b, 1998c; MacDonald-Taylor 1992; Maynard and Hodge 1949; Ortega et al. 1989a), or dermal (De Rey et al. 1983; Orcutt 1949) exposures to uranium compounds. These nephrotoxic effects are consistent with the metallotoxic action of uranium in the kidneys (Goodman 1985). The pathogenesis of the kidney damage in animals indicates that regeneration of the tubular epithelium occurred following discontinuation of exposure to uranium (Bentley et al. 1985; Dygert 1949b; Maynard and Hodge 1949; Pozzani 1949; Rothermel 1949; Rothstein 1949c; Spiegl 1949; Stokinger et al. 1953). Thus, exposure to the soluble compounds of uranium at or near hazardous waste sites could result in kidney damage. Measurement of uranium in air, soil, and water at or near the site is necessary to predict the likelihood of renal effects.

The following MRLs have been calculated for exposure to uranium based on kidney effects:

- an intermediate-duration MRL of 8×10^{-5} mg/m^3 for inhalation exposure to insoluble compounds of uranium is based on renal tubule lesions in dogs (Rothstein 1949b);

- an intermediate-duration MRL of 4×10^{-4} mg/m^3 for inhalation exposure to soluble compounds of uranium is based on renal tubule lesions in dogs (Rothstein 1949a);

- a chronic-duration MRL of 3×10^{-4} mg/m^3 for inhalation exposure to soluble compounds of uranium is based on renal tubule lesions in dogs (Stokinger et al. 1953);

- an intermediate-duration MRL of 2×10^{-3} mg/kg/day for oral exposure to soluble compounds of uranium is based on renal tubule lesions in rabbits (Gilman et al. 1998b);

See the MRL discussion earlier in this section and in the MRL Worksheets in Appendix A for further details on the derivation of these MRLs.

Endocrine Effects. No endocrine effects were reported in humans following inhalation, oral, or dermal exposure to uranium compounds. No endocrine effects were reported in most of the available studies of animals following inhalation or oral exposure to uranium compounds (Gilman et al. 1998a, 1998b, 1998c; Ortega et al. 1989a; Maynard and Hodge 1949; Stokinger et al. 1953). A later study by Gilman et al. (1998a) using uranyl nitrate also identified endocrine organ changes that were limited to multifocal reductions in follicular size, increased epithelial cell height, and decreased amounts and densities of colloid in the thyroids of male but not female rats. Endocrine effects are not a significant health concern to individuals living at or near hazardous waste sites containing uranium.

Dermal Effects. No significant dermal effects were observed in animals given inhalation or oral doses of
uranium compounds (Spiegl 1949; Stokinger et al. 1953). However, dermal application of uranium
compounds resulted in mild skin irritation, severe dermal ulcers, or superficial coagulation necrosis and
inflammation of the epidermis in rabbits (Orcutt 1949). Dermal application resulted in swollen,
vacuolated epidermal cells and damage to hair follicles and sebaceous glands in rats (De Rey et al. 1983).
The effects or symptoms of acute dermal exposure to ionizing radiation included erythema (redness of the
skin) and epilation (loss of hair) (Upton 1993). The alpha particle emitted by uranium will not penetrate
the dead keratinized outer layer of the skin, so there is minimal concern for dermal effects from skin
contact with uranium. Dermal effects were not seen in studies of uranium miners, millers, and processors.
The observed skin damage reported in animals dermally exposed to excessive quantities of uranium
compounds is not expected to occur in human exposures at hazardous waste sites. Such exposures, if they
occur, are expected to be at or less than the levels at which uranium miners, millers, and processors are
exposed (levels at which no attributable dermal health effects were reported).

Ocular Effects. No ocular effects attributable to uranium exposure were reported in the available human
studies. In animal studies, dogs exposed to 13 mg U/m^3 as uranium hexafluoride for 30 days exhibited
encrusted eyes and conjunctivitis prior to death. However, these signs were considered nonspecific
indications of poor health by the investigators of the study (Spiegl 1949). Consequently, no ocular effects
are expected from human exposure to uranium compounds.

Body Weight Effects. Body weight loss was not reported in any of the human studies regarding
inhalation, oral, or dermal exposure to uranium compounds. Similarly, the available studies in animals
that evaluated this end point did not find any significant changes following inhalation exposure to
uranium compounds (Cross et al. 1981b; Dygert 1949c, 1949d; Leach et al. 1970, 1973; Pozzani 1949;
Rothermel 1949; Rothstein 1949a, 1949b, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). Similar lack
of body weight effects were found in rats in 28- and 91-day using uranium nitrate in the drinking water
(Gilman et al. 1998a). The initial or reversible loss of body weight observed in animals exposed to high
concentrations of uranium in the diet in acute-, intermediate-, and chronic-duration studies was
accompanied by decreased food consumption due to taste aversion (Maynard and Hodge 1949, 1953;
Tannenbaum and Silverstone 1951). This initial effect reversed, and the animals returned to their normal
body weight as normal food intake resumed. Thus, the changes in body weight seen in such studies may
be due more to reduction in food consumption due to bad taste than to uranium-specific toxicity. This

effect may not be relevant to humans. It is more likely that significant weight loss in rabbits following application of excessive dermal doses (as high as 1,917 mg U/kg) (Orcutt 1949) may be a response to exceeding the maximally tolerated dose in these animals and consequently overwhelming the physiological mechanisms in these species (Orcutt 1949). Therefore, no significant effect on body weight is expected from human exposure to uranium compounds at or near hazardous waste sites.

Metabolic Effects. No studies were located regarding the metabolic effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation, oral, or dermal exposure to uranium and uranium compounds. Consequently, it is not known whether human exposure to uranium and uranium compounds could result in adverse metabolic effects; however, such effects would not be anticipated, based on the absence of endocrine effects.

Other Systemic Effects. No studies were located that reported other systemic effects in humans or animals following inhalation, oral, or dermal exposure to uranium. Consequently, no other systemic effects are expected from human exposure to uranium compounds at or near hazardous waste sites.

Immunological and Lymphoreticular Effects.   No adverse immunological or lymphoreticular effects were reported in human studies following exposure to uranium through the inhalation, oral, or dermal route for any duration (Brown and Bloom 1987; Checkoway et al. 1988; Cragle et al. 1988; Keane and Polednak 1983; Polednak and Frome 1981; Vich and Kriklava 1970). Similarly, no significant uranium-induced immunological or lymphoreticular changes were observed in animals exposed to uranium for acute, intermediate, or chronic durations (Filippova et al. 1978; Gilman et al. 1998a, 1998b, 1998c; Leach et al. 1970, 1973; Malenchenko et al. 1978; Maynard et al. 1953; Stokinger et al. 1953; Tannenbaum and Silverstone 1951). Sinus hyperplasia of the spleen was noted in rats in one 91-day uranium nitrate drinking water study (Gilman et al. 1998a). No significant immunological or lymphoreticular injury is expected from human exposure to uranium compounds at or near hazardous waste sites.

Neurological Effects.   Although no neurological functions were evaluated in most of the available human studies, no damage to structures of the central or peripheral nervous system and no overt neuropathology were reported in humans following exposure to natural or enriched uranium compounds by the inhalation, oral, or dermal route (Brown and Bloom 1987; Carpenter et al. 1988; Cragle et al. 1988;

Kathren and Moore 1986; Polednak and Frome 1981; Reyes et al. 1984; USNRC 1986). Clinical signs in one man following acute exposure to uranium did include dizziness and anorexia 6 days after exposure for 5 minutes to uranium tetrafluoride by inhalation (Zhao and Zhao 1990), and may have been related to rapidly developing renal disease. No etiology could be determined for increased central and peripheral nervous system diseases found in workers in a nuclear fuels fabrication plant (Hadjimichael et al. 1983). A series of studies by Gilman et al. (1999a, 1998b, 1998c) reported no brain lesions associated with ingestion of uranium in the drinking water. However, in other high-dose animal studies, neurological signs were reported in dogs, cats, rats, and guinea pigs. These signs included instability of gait indicative of neurological dysfunction in dogs and cats (Dygert 1949a); severe muscle weakness and lassitude from inhalation exposures in dogs and cats (Rothstein 1949a); central cholinergic neurological symptoms (piloerection, tremors, hypothermia, pupillary size decrease, exophthalmos) in rats from oral exposures (Domingo et al. 1987); and irritability, hyperactivity, upset equilibrium, rigidity of limbs, and respiratory arrest in rabbits from 4-hour dermal exposures (Orcutt 1949). However, no neurological effects were observed in rabbits orally exposed to 20 times larger oral doses of the same compound for 91 days. In view of the findings of the human and animal studies, it is doubtful that human exposure to uranium compounds at or near hazardous waste sites could result in damage to the nervous system.

Recent studies suggest that intramuscular deposition of uranium metal may result in neurological effects. Implantation of depleted uranium pellets in rats resulted in measurable uranium in the brain at 6–18 months after implantation (Pellmar et al. 1999a) and was accompanied by electrophysiological changes in hippocampal slices from the treated animals at 6 months (Pellmar et al. 1999b). In addition, military veterans with retained depleted uranium shrapnel fragments had lowered performance scores on computerized tests assessing performance efficiency which correlated with their urinary uranium levels (McDiarmid et al. 1999a). The etiology of these effects is unclear, although central nervous system toxicity due to other heavy metals (e.g., lead, mercury) is well documented. Further research is needed to confirm these results and determine the relevance of the effects from this unique exposure pathway to inhalation, oral, and dermal exposure.

Reproductive Effects.   The existing human data from studies of uranium miners, millers, and processors (Muller et al. 1967; Waxweiler et al. 1981b; Wiese 1981) and most data from animal studies (Gilman et al. 1998a, 1998b; Leach et al. 1970; Llobet et al. 1991; Paternain et al. 1989) do not associate reproductive effects with uranium exposure.. Relatively high doses of uranium compounds (which also

produced significant mortality in some cases) have resulted in some reproductive abnormalities manifested as significantly reduced sperm counts (Lloblet et al. 1991), reduced implantations and increased fetal resorptions and dead fetuses, maternal (reduced weight gain and food consumption, increased relative liver weight) and fetal toxicity (Domingo et al. 1989a); testicular lesions and degeneration and decreased testes weight (at near-lethal doses for long periods) (Malenchenko et al. 1978; Maynard et al. 1953); and reduced litter size (at a dose that produced 16% mortality) (Maynard et al. 1953) following intake of uranium compounds. However, no reproductive effects were found in a series of 28-day and 91-day uranium drinking water studies in rats and rabbits (Gilman et al. 1998a, 1998b, 1998c; Paternain et al. 1989).

In view of the lack of findings of reproductive effects in uranium miners, millers, and processors in numerous human studies and the equivocal findings in high-dose animal studies, it is doubtful that human exposure to uranium compounds at or near hazardous waste sites could result in interference with normal reproduction.

Developmental Effects.   The present theories on the susceptibility of cells (with a high mitotic index such as are found in the embryo, fetus, and neonate) to damage by the DNA-adducting chemical action of uranium (as a heavy metal) (Cooper et al. 1982; Dungworth 1989; Stokinger 1981; Wedeen 1992) and ionization by high-LET, high specific-activity radiation (BEIR 1980, 1988, 1990; Muller et al. 1967; Otake and Schull 1984; Sanders 1986; Stokinger et al. 1953; UNSCEAR 1982, 1986, 1988) suggest that uranium may potentially interfere with normal development and may be teratogenic. However, no studies were located regarding the chemical or radiological effects of uranium on development in humans or animals following inhalation or dermal exposure for any duration.

Evidence for potential developmental toxicity is provided by results from oral animal studies in which the following effects were reported for uranyl acetate: increased fetal mortality, reduced survivability, and reduced growth (Paternain et al. 1989); decreased litter size, decreased viability and lactation indices, and pup liver weights (Domingo et al. 1989b); reduced fetal body weight and length, an increased incidence of stunted fetuses, increases in external and skeletal malformations and developmental variations, an increased incidence of cleft palate, underdeveloped renal papillae, and bipartite sternebrae, reduced or delayed ossification of the hind limb, fore limb, skull, and tail, an increase in the relative brain weight of the offspring, and reduced viability and lactation index (Domingo et al. 1989a); and embryotoxicity (Paternain et al. 1989). These effects were seen at relatively high doses far above any plausible human exposure.

The investigators of a study in which relative liver weights were significantly decreased at all exposure levels (p<0.05 in the 0.028–0.28 mg U/kg/day group and p<0.01 in the 2.8–28 mg U/kg/day group) in offspring of rats exposed to 0.028, 0.28, 2.8, or 28 mg U/kg/day for 30 days concluded that these effects were not uranium induced. Decreases in the relative liver weights (noted at 0.028 mg U/kg/day) and relative brain weight (noted only at 0.28 mg U/kg/day) were not considered significant effects of uranium exposure since the investigators concluded that the NOAEL for this study was 2.8 mg U/kg/day for fetotoxicity with a LOAEL of 28 mg U/kg/day (Domingo et al. 1989b). In addition, there is a lack of plausible biological validity for hepatic effects at such low doses of uranium because the other available studies with rats in which uranium acetate was administered orally for a similar duration either showed no significant effect on the liver (Maynard and Hodge 1949) at a uranium acetate dosage of 7,859 mg U/kg/day or resulted in only liver congestion (Ortega et al. 1989a) at a uranium acetate exposure of 9 mg U/kg/day. Further, the kidney rather than the liver is the most sensitive organ of uranium toxicity in both humans (Thun et al. 1985) and animals (Domingo et al. 1987; Maynard and Hodge 1949; Ortega et al. 1989a). No kidney effects were reported in this study. In previous research, the same investigators (Domingo et al. 1989a) found the opposite effect (increased relative liver weight) at all dose levels.

In view of the lack of findings of developmental effects in the offspring of uranium miners, millers, and processors in numerous human studies and the equivocal findings in animal studies, it is doubtful that human exposure to uranium compounds at or near hazardous waste sites could result in interference with normal development.

Genotoxic Effects.   No information was located showing metallotoxic or radiotoxic effects of uranium on genetic material in humans or animals following dermal exposure for any duration. In human studies, chromosomal aberrations and aberrant DNA consistent with radiation damage were found in uranium miners. However, the etiology of the effects on the chromosome and DNA could not be determined because the miners were concurrently exposed to other radioactivity (radon progeny), smoking, and potentially genotoxic microorganisms (genus *Aspergillus* and *Penicillium*).

Because uranium is a predominantly an alpha-emitting element, current theories on gene mutation and chromosomal aberrations by high-LET alpha radiation suggest a concern for genotoxicity from uranium's radioactivity (BEIR 1980, 1988, 1990; Leach et al. 1970; Morris et al. 1990; Muller et al. 1967; Otake and Schull 1984; Sanders 1986; Stokinger et al. 1953; UNSCEAR 1982, 1986, 1988) (see Appendix D

for a review of the hazards associated with radionuclide exposure). However, uranium does not distribute
to or accumulate in the gonads in any appreciable amount.

In animal studies, mice injected with doses ranging from 0.05 to 1.0 μg U/testis as enriched uranium
fluoride showed a general tendency for an increase in chromosome breaks with an increasing dose of
enriched uranyl fluoride. At high-dose levels, the statistically significant difference of break frequencies
between treated and control mice disappeared 60 days after treatment (Hu and Zhu 1990).

A study that investigated the effects of uranyl nitrate hexahydrate on viability, cell cycle kinetics,
micronuclei, chromosomal aberrations, and sister-chromatid exchanges in Chinese hamster ovary cells
found an increased frequency of micronuclei, sister-chromatid exchanges, and chromosomal aberrations
leading to the conclusion that uranyl nitrate hexahydrate was genotoxic under the conditions of the assay
(Lin et al. 1993).

However, it is unlikely that humans could be exposed at hazardous waste sites to such high specific-
activity radionuclides through the routes described in these studies. Table 2-9 lists the genotoxic effects
of uranium *in vivo* and Table 2-10 lists the genotoxic effects of uranium *in vitro*.

Recent studies suggest that intramuscular deposition of uranium metal may result in genotoxic effects in
animals. Implantation of depleted uranium pellets in rats resulted in an increase in the mutagenic
potential of urine towards the Salmonella tester strain TA98 (Miller et al. 1998a). Responses were dose-
and time-dependent and strongly correlated with urine uranium levels. In an *in vitro* study, uranyl
chloride prepared from depleted uranium transformed immortalized human osteoblastic cells to a
tumorigenic phenotype (Miller et al. 1998b). The etiology of these effects is unclear at this time. Further
research is needed to confirm these results and determine the relevance of the effects from this unique
exposure pathway to inhalation, oral, and dermal exposure.

Cancer.   There has been interest in the potential carcinogenicity of uranium, which emits alpha-particle
radiation, although natural, depleted, or enriched uranium or uranium compounds have not been evaluated
in rodent cancer bioassays by any route by the NTP (BEIR 1980, 1988, 1990; Hahn 1989; Otake and
Schull 1984; Sanders 1986; UNSCEAR 1982, 1986, 1988). However, there is no unequivocal evidence
that inhalation, oral, or dermal exposure induces cancers in humans because it is difficult to isolate the

Table 2-9. Genotoxicity of Uranium *In Vivo*

Species (test system)	End point	Exposure route	Results	Reference
Mammalian systems:				
Human	Chromosomal aberration	Inhalation	+	Martin et al. 1991
Human	Sister chromatid exchange	Inhalation	+	Martin et al. 1991
Mouse (BALB/c)	DNA damage	Intraperitoneal	+	Hu and Zhu 1990

– = negative result
+ = positive result

Table 2-10. Genotoxicity of Uranium *In Vitro*

Species (test system)	End point	Result	Reference
Eukaryotic cells:			
Human peripheral blood lymphocytes	Chromosomal aberration	+	Fajgelj et al. 1992
Chinese hamster cells	Sister chromatid exchange	+	Lin et al. 1993
Chinese hamster cells	Chromosomal aberrations	+	Lin et al. 1993
Chinese hamster cells	Micronucleus test	+	Lin et al. 1993

− = negative result
+ = positive result

cancer risk that may be specific to exposure to uranium and other substances such as tobacco smoke, radon and its decay products, radium, thorium, silica and other dusts, and diesel engine exhaust fumes to which the human subjects of these studies were concurrently exposed (Archer et al. 1973a, 1973b; Auerbach et al. 1978; Band et al. 1980; Chovil and Chir 1981; Cookfair et al. 1983; Cragle et al. 1988; Gottlieb and Husen 1982; Grace et al. 1980; Kusiak et al. 1993; Land et al. 1993; Lundin et al. 1969; Polednak and Frome 1981; Reyes et al. 1984; Saccomanno et al. 1971, 1976, 1982, 1988; Samet et al. 1984, 1986; Sanders 1986; Waxweiler et al. 1983; Whittemore and McMillan 1983; Wrenn and Singh 1983). Long-term animal studies with both natural and enriched uranium were negative (Cross et al. 1981b; Leach et al. 1970, 1973, 1984; Maynard and Hodge 1949; Maynard et al. 1953; Spiegl 1949; Stokinger et al. 1953; Tannenbaum and Silverstone 1951) or equivocal (Filippova et al. 1978; Leach et al. 1973; Mays et al. 1985) for carcinogenicity. No information was located on the cancer effects in humans or animals following dermal exposure to uranium for any duration.

The potential for carcinogenicity by administration by parenteral routes has been investigated in one animal study. Although the parenteral route is an unlikely route of exposure at hazardous waste sites, it is analogous to the condition in which uranium compounds enter cuts, wounds, abrasions, and ulcers in large quantities. That portion which enters the systemic circulation is expected to distribute in the same manner as uptakes by inhalation or ingestion, while any portion that remains at the entry site could produce large localized concentrations which are orders of magnitude larger than those calculated based on body weight. Rats that received 50 mg U (34 nCi or 1,200 Bq) as powdered metallic uranium injected as a single dose into the marrow cavity of the femur developed 11 injection-site sarcomas in 33 rats, 30 of which survived the minimal latent period of 6 months (Hueper et al. 1952). Other rats given intrapleural administration of metallic uranium equivalent to approximately 574 nCi/kg (21,238 Bq/kg or 860 mg U/kg) exhibited 2 sarcomas originating from the chest wall among 33 rats treated; 2 of the 13 sarcomas were bone-forming, and 6 produced metastases. All sarcomas either surrounded uranium deposits or were in the immediate vicinity of them. None of the 13 sarcomas seemed to originate from the endosteum. The sarcomas appeared either to be of periosteal origin or to stem from mesodermal elements of the thigh muscle. The investigators of the study were unable to ascertain whether the sarcomas were due to a metallocarcinogenic action of uranium or were caused by a radiocarcinogenic effect of this radioactive chemical. However, these observations demonstrate that localized uranium deposits in the tissues of rats created a high concentration of uranium in circumscribed areas, and the prolonged action of the uranium on cells in the immediate vicinity of such foci exert a definite carcinogenic effect (Hueper et al. 1952).

The BEIR IV report concluded that "...exposure to natural uranium is unlikely to be a significant health risk in the population and may well have no measurable effect" (BEIR IV 1988).

2.6 CHILDREN'S SUSCEPTIBILITY

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

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure.   Exposures of children are discussed in Section 5.6, 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 pre-natal and post-natal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975).   Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Komori 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). There may also be differences in excretion, particularly in the newborn

who has a low glomerular filtration rate and has 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 while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

Specific information is not available on whether children are more susceptible than adults to the effects of uranium. No reports were located describing toxicity in children as the result of uranium exposure. It is probable, however, that if exposure levels were high enough, signs of renal toxicity would be observed similar to those seen in adults exposed accidentally (Zhao and Zhao 1990) or intentionally (Pavlaikis 1996). No reports are available of studies where toxic responses of young animals to uranium were directly compared to those of adults.

No studies are available on whether exposure to uranium affects development in humans. The information from animal studies is limited to the oral route in a single species, and only one study examined structural malformations. Uranium has not caused teratogenic effects, although some developmental effects have been reported in mice (Domingo et al. 1989a, 1989b; Paternain et al. 1989). These effects generally occurred at gavage doses ≥6 mg U/kg/day in a soluble form as uranyl acetate. At doses of 14 mg U/kg/day but not 6 mg U/kg/day, embryolethality (increased total and late resorptions, decreased number of live fetuses) was observed on gestation day 13 in dams exposed from 14 days prior to mating through gestation (Paternain et al. 1989). Gavage exposure over gestation days 6–15 resulted in an increased incidence of skeletal abnormalities (bipartite sternebrae, reduced and/or delayed ossification) at 14 and 28 mg U/kg/day and cleft palate at 6, 14, and 28 mg U/kg/day (Domingo et al. 1989a). Underdeveloped renal papillae were also observed but were not dose-related. Exposure of dams from late pregnancy (gestation day 13) continuing throughout lactation (21 days postpartum) resulted in reduced pup viability at 28 mg U/kg/day, but not at lower doses (Domingo et al. 1989b). Postpartum

developmental events (pinna attachment, eye opening, incisor eruption) were unaffected at all doses. While developmental toxicity can be produced in animal models, the doses required are relatively high compared to known human exposures and are similar to a dose of 14.3 mg U/kg of uranyl nitrate that produced nausea, vomiting, and diarrhea in one human (Butterworth 1955).

Information on the pharmacokinetics of uranium in children is very limited. Since the skeletons of children are growing (higher rate of bone formation), it is possible that a higher fraction of circulating uranium will be deposited in bone than in adults. A study of uranium content in bone from three age groups (<13, 13–20, 20–25 years old) reported somewhat higher uranium content in the youngest compared to the oldest age group (approximately 1.5–3 fold); however, there were only 2–4 subjects in each group and the differences were not statistically significant (Broadway and Strong 1983). The fractional absorption of uranium by the oral route was higher in neonatal swine and rats than in adult animals (Sullivan 1980b; Sullivan and Gorham 1982).

Transfer of uranium across the placenta was investigated in an animal study, but no information is available for humans. In the animal study, only 0.01–0.03% of an intravenous dose of uranium to rat dams crossed the placenta (Sikov and Mahlum 1968); thus if an inhalation, oral, or dermal exposure was sufficient to raise the blood uranium level, a very limited amount of uranium might cross the placenta. No studies were located regarding uranium in breast milk. Based on the chemical properties of uranium, it seems unlikely that there would be preferential distribution from the blood to this high-fat compartment. It is not known if uranium has any effect on the active transport of calcium into breast milk. Most of the adult body burden of uranium is stored in bone (ICRP 1979, 1995, 1996). It is not known if maternal bone stores of uranium (like those of calcium and lead) are mobilized during pregnancy and lactation.

Age-related differences in the pharmacokinetics of uranium have been incorporated into existing PBPK models (ICRP 1995, 1996) so that they can be applied to children. Two adjustments were made:

1. The value for the fractional absorption of ingested uranium (f_1) was adjusted from the adult value of 0.02 (2%) to a value of 0.04 (4%) for children under the age of 1 year. This adjustment was made based on animal data (Sullivan et al. 1980b; Sullivan and Gorham 1982) and information on postnatal changes in the human gastrointestinal tract. For ages over 1 year, the adult value for fractional absorption was used.

2. Parameters for transfer of uranium into and out of bone were assumed to be proportional to those of alkaline earth elements such as calcium (the UO_2^{2+} ion can substitute for the Ca^{2+} ion at bone surfaces). Age-specific bone turnover rates developed for a generic alkaline-earth model (ICRP 1993) were incorporated into the uranium model to predict distribution to the tissues. As a result of this change, a greater proportion of uranium distributes to bone and a lesser proportion to soft tissues at ages under 25 years, compared to adults.

The mechanism for the renal toxicity observed in cases of adult exposure to uranium is believed to be due to the retention of uranium in the kidney. This is the result of the reabsorption of bicarbonate from the ultrafiltrate in the proximal tubule and the resulting release of the UO_2^{2+} ion from a bicarbonate complex. Newborn humans have relatively inefficient tubular secretion and reabsorption compared to older children or adults, and whether this would increase or decrease the susceptibility of newborns to uranium toxicity is not known.

2.7   BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. 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, or nonessential substances in all diets such as aluminum and uranium. Biomarkers of exposure to uranium are discussed in Section 2.7.1.

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 uranium are discussed in Section 2.7.2.

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 dose excretion, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9, Populations That Are Unusually Susceptible.

2.7.1   Biomarkers Used to Identify or Quantify Exposure to Uranium

Biomarkers of exposure to uranium include the chemical or radiological detection of uranium in the urine because uranium absorbed through the oral, dermal, and inhalation routes is excreted in urine mostly as uranyl ions (Ballou et al. 1986; Cooper et al. 1982; Downs et al. 1967; Leach et al. 1984; Morrow et al. 1982; Stradling et al. 1984, 1987; West and Scott 1969; Wrenn et al. 1985). Uranium urinalysis data have been shown to correlate with airborne uranium exposures when averaged over a period of time when the ingested quantity is insignificant. Thus, this method of analysis can be used to verify the adequacy of air sampling and as a noninvasive method for exposure estimates (Chase 1989; Davis 1985; Schieferdecker et al. 1985; Thind 1987). Typical chemical detection methods for uranium include fluorimetry and kinetic phosphorescence analysis (KPA), while the primary radiological method is alpha spectroscopy. Some of the more capital-intensive and sophisticated techniques that will allow isotope quantification in very small fecal, urine, or tissue samples are isotope dilution alpha spectrometry; neutron activation analysis; and isotope-dilution, inductively coupled plasma, and atomic absorption versions of mass spectrometry. The mass spectrometric, KPA, and neutron activation techniques are probably the most sensitive and accurate for the quantification of uranium isotopes (Wessman 1984).

According to *USNRC Regulatory Guide 8.22*, the acceptable methods for the quantification of uranium in urine must have a detection limit of 5 µg/mL and a precision of 30% (Kressin 1984). A urinary concentration >100 µg/L is indicative of recent absorption, while a concentration of <40 µg/L may be due either to slow uptake from the site of absorption or to bone mobilization (Butterworth 1955). Variations in background levels of uranium from drinking water in different locations may also result in higher or lower urinary concentrations of uranium.

Twenty-four-hour urine samples are preferable for analysis; spot samples gave accurate results when corrected for creatinine content, but only for individuals excreting relatively large amounts of uranium (McDiarmid et al. 1999b).

Uranium content in soft tissue and bone could also be used as biomarkers of exposure to uranium since uranium also distributes to these tissues and other organs (Ballou et al. 1986; Diamond et al. 1989; Leach et al. 1973, 1984; Morris et al. 1990; Morrow et al. 1972; Stokinger et al. 1953; Walinder 1989; Wrenn et al. 1987). Although soft tissues and bone are the most frequently analyzed biological media after urine and feces, these tissues are usually available for analysis only at autopsy. Therefore, this method is impractical and not used for routine screening purposes.

2.7.2 Biomarkers Used to Characterize Effects Caused by Uranium

Currently, there are no available biomarkers for specific exposure to the metallotoxic or radiotoxic effects of uranium.

Functional damage to the kidneys has been documented in humans (Pavlakis et al. 1996; Thun et al. 1985; Waxweiler et al. 1981a; Zhao and Zhao 1990) and in animal (Leach et al. 1970, 1973, 1984; Morrow et al. 1982; Stokinger et al. 1953) studies. Although not specific to uranium toxicity, urinary catalase as an indicator of renal damage (Luessenhop et al. 1958) could be used in conjunction with other signs of renal tubular dysfunction, including mild proteinuria, aminoaciduria, and clearance of β_2-microglobulin relative to that of creatinine, as a battery of indicators of biomarkers of exposure to uranium (Saccomanno et al. 1982; Thun et al. 1985).

Very high doses of uranium may interfere with liver function in humans (Pavlaikis et al. 1996), but renal effects are far more sensitive. No specific biomarker is currently available for the liver as a target of uranium toxicity. Because uranium has no appreciable effect on the nervous system, no biomarkers of effect are needed for this end point. For more information on biomarkers for renal effects of chemicals, see *ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage* (ATSDR/CDC 1990). Simultaneous analysis of multiple parameters, such as urinary glucose, alkaline phosphatase, and β_2-microglobulin, which may be more specific to proximal tubular damage (Limson-Zamora et al. 1996) should be considered for evaluating subjects in future studies.

2.8 INTERACTIONS WITH OTHER CHEMICALS

No information was located regarding the modulation of the toxicity of uranium by other chemicals or vice versa. It is possible that co-exposure to other heavy metal nephrotoxicants (e.g., lead, cadmium) could have an additive effect on uranium toxicity.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to uranium than will most persons exposed to the same level of uranium 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 may result in reduced detoxification or excretion of uranium, or compromised function of target organs affected by uranium. Populations who are at greater risk due to their unusually high exposure to uranium are discussed in Section 5.6, Populations with Potentially High Exposure.

Populations susceptible to uranium toxicosis would include people with impaired renal function. People with stomach ulcers are thought to have elevated absorption of some toxic metals and might be unusually susceptible to uranium toxicity. The potential for children's susceptibility is discussed in Section 2.6.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing the toxic effects of exposure to uranium. 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 uranium. When specific exposures have occurred, poison control centers, health physicists, and medical toxicologists should be consulted for medical advice. The following text provides specific information about treatment following exposures to uranium:

2.10.1 Reducing Peak Absorption Following Exposure

No specific recommendations have been reported for reducing the peak absorption following acute exposure to uranium. However, because uranium forms complexes with the bicarbonate ion (Cooper et al. 1982), there is a role for oral sodium bicarbonate in the mobilization of systemic uranium, thereby preventing uptake by critical tissues (kidney, bone).

2.10.2 Reducing Body Burden

Administration of bicarbonate is applicable to reducing uranium body burdens from acute exposures. Bicarbonate ions complex with uranium and alkalize the blood, both of which enhance the excretion from the kidneys by glomerular filtration (Cooper et al. 1982) and such an application was described in a case of prophylactic treatment (Fisher et al. 1991). Experimental evidence in animals indicates that chelation therapy may reduce the body burden of uranium. Several compounds were found to enhance the urinary and fecal excretion of uranium, if administered soon after uranium exposure. When given immediately after exposure to uranium, Tiron resulted in the greatest reduction in renal and bone levels of uranium and acute lethal effects in animals (Domingo et al. 1992; Ortega et al. 1989a). None of the chelating agents affected bone levels of uranium when given 24 hours or more after exposure to uranium (Domingo et al. 1992). Bicarbonate treatment is also limited to very near-term exposures.

2.10.3   Interfering with the Mechanism of Action for Toxic Effects

Treatment for uranium poisoning is typically in response to a known accidental exposure to uranium and is largely asymptomatic. One study found that Tiron® (sodium 4,5-dihydroxybenzene-1,3-disulphonate), gallic acid, and DTPA (diethylamine-tetramine-pentaacetic acid) were the most effective chelating agents among those tested for binding systemic uranium and removing it from the body following large acute intraperitoneal injections (Ortega et al. 1989). However, another study which tested Tiron® alone and in conjunction with either DTPA or EDHPA (ethylenediamine-N,N'-bis[2-hydroxyphenylacetic acid]) found that it reduced the uranium body burden no more than about 35%, indicating that the administration of Tiron® is of limited practical value for the treatment of uranium exposures that do not greatly exceed the permitted intake level (Stradling et al. 1991).

2.11 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 uranium 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 uranium.

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.

2.11.1   Existing Information on Health Effects of Uranium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to uranium are summarized in Figure 2-10. The purpose of this figure is to illustrate the existing information concerning the health effects of uranium. 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* (ATSDR 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 2-10 depicts the existing health effects information on uranium for a specific route and duration of exposure. There is a lack of information regarding the health effects in humans from ingested uranium. Similar information from dermal exposures is also scarce; only two studies were located in this respect. Several available studies that investigated the health effects in humans of inhalation exposure to uranium are limited to occupational settings (miners, millers, processors). The subjects of some of these studies were also concurrently exposed to other potentially toxic substances, rendering it difficult to establish the etiology for the effects reported in these studies; however, studies of processors who were not concurrently exposed to those toxicants are useful in this regard. Consequently, indications of the cancer-inducing potential of uranium in these latter workers were useful in making a determination that uranium exposure by normal routes of exposure is unlikely to be carcinogenic. Although three human studies presented limited evidence of reproductive effects (damage to sex chromosomes) in uranium mine workers, no empirical evidence was presented for evaluation. Information on the systemic effects of uranium through the inhalation, oral, and dermal routes of exposure are available. However, there is limited information regarding the reproductive and developmental effects of uranium in animals; no multigenerational studies are available. In addition, because the data from some critical studies were not clearly or sufficiently presented, the data were inadequate for use in the development of acute-duration inhalation or acute- and chronic-duration oral MRLs; however, sufficient information is available on the effects of chronic oral exposure to conclude that the intermediate-duration MRL is protective for chronic exposure. An NTP cancer bioassay and an EPA IRIS cancer classification are not available for uranium.

Available long-term animal studies characterize uranium's cancer potential as low. Definitive studies regarding the genotoxicity of uranium *in vitro* or *in vivo* are lacking. In general, there are several robust human epidemiological studies of miners, millers, and processors which strongly indicate that uranium is not carcinogenic by the inhalation route unless mixed with toxicants and carcinogens such as silica dust, diesel fumes, radon progeny, and cigarette smoke. Animal studies involving large doses have also found no

Figure 2-10. Existing Information on the Health Effects of Uranium

Human

Animal

●   Existing Studies

cancer, and the one study which superimposed a large dose of external ionizing radiation concluded that the respiratory effects which were noted were due to chemical and not radiological action. Any research investigating the radiotoxicity of uranium may be of limited importance because the radiation from natural and depleted uranium has not been shown to present a substantial radiological hazard; however, this may not be the case for the less available high specific activity isotopes such as ^{233}U and ^{234}U, that are formed during energy production or associated with weapons-grade uranium.

2.11.2   Identification of Data Needs

The available data on the more common soluble and insoluble uranium compounds are sufficient to conclude that uranium has a low order of metallotoxicity in mammals in view of the high exposures to which humans and animals in these studies were exposed without adverse effects in many cases. Many of the nonradioactive heavy metals such as lead, arsenic, and mercury would produce very severe, perhaps fatal, injury at the levels of exposure reported for uranium in the literature (Eisenbud and Quigley 1955).

The available studies identified the kidneys as the most sensitive target of uranium's chemical toxicity, mediated by accumulation of uranium in the renal tubular epithelium to induce cellular necrosis and atrophy in the tubular wall resulting in decreased reabsorption efficiency in the renal tubules in humans (Goodman 1985; Luessenhop et al. 1958; Thun et al. 1981) and animals (Diamond et al. 1989; Rothstein 1949d; Stokinger et al. 1953). Other signs of renal tubular nephrotoxicity from chemical exposure to uranium have been demonstrated in animals (Bentley et al. 1985; Blantz 1975; De Rey et al. 1983; Diamond et al. 1989; Domingo et al. 1987; Haley et al. 1982; Kobayashi et al. 1984; Leach et al. 1984; Maynard and Hodge 1949; Maynard et al. 1953; Morrow et al. 1982; Orcutt 1949; Ortega et al. 1989a; Stokinger 1981; Stokinger et al. 1953) and humans (Kathren and Moore 1986; Luessenhop et al. 1958; Thun et al. 1985; USNRC 1986; Waxweiler et al. 1981a, 1983; Zhao and Zhao 1990). The nephrotoxic effects of uranium in humans include damage to the glomerulus as evidenced by histopathological signs in the kidneys of erstwhile uranium mill workers (Thun et al. 1981). Corroborative evidence from observations in acute and intermediate exposures of rats by the oral and inhalation routes indicated that uranium exposure may also interfere with renal filtration rates by damaging the glomeruli of the kidneys of humans and animals. Histopathological examination following oral, inhalation, or parenteral exposure revealed a thickened glomerular capsular wall, shrinkage of the glomerular capillary network, lesions, and decreased glomerular

filtration rates (Avasthi et al. 1980; Blantz 1975; Dygert 1949d; Haley 1982; Kobayashi et al. 1984; Pelayo et al. 1983; Rothstein 1949c, 1949d).

Animal studies designed to examine the combined effects on the kidney of uranium and other heavy metal nephrotoxicants (lead, cadmium) would also be useful to determine whether effects are less than expected on the basis of individual toxicity, additive or synergistic. It is possible at some waste sites that multiple exposures to these metals could occur in humans.

A mechanism involving bicarbonate activity in the kidneys has been proposed for uranium-induced renal toxicity. Uranium is usually combined with either bicarbonate or a plasma protein in the blood. It has been suggested that in the kidneys, uranium is released from bicarbonate to form complexes with phosphate ligands and proteins in the tubular wall, thereby causing damage. Brady et al. (1989) proposed an alternative mechanism by which uranium exerts its renal toxicity through the inhibition of both sodium transport-dependent and -independent ATP utilization and mitochondrial oxidative phosphorylation in the renal proximal tubule. Further animal studies specifically designed to study the potential role of the inhibition of ion and nutrient transport across membranes by the uranyl ion and the effect of this phenomenon on cell death would be conducive to a more comprehensive understanding of the renal toxicity of uranium.

Although not specific to uranium toxicity, urinary catalase as an indicator of renal damage (Luessenhop et al. 1958) could be used in conjunction with other signs of renal tubular dysfunction, including mild proteinuria, aminoaciduria, and clearance of β_2-microglobulin relative to that of creatinine, as a battery of indicators of biomarkers of exposure to uranium (Limson-Zamora et al. 1996; Saccomanno et al. 1982; Thun et al. 1985). Animal studies designed to evaluate the relative sensitivities of urinary catalase and serum β_2-microglobulin as biomarkers of effect for uranium exposure would be useful in the diagnosis of human uranium exposure.

Although natural uranium has a low specific-activity of 0.67 μCi/g (25,000 Bq/g) and depleted uranium has even less (0.36 μCi/g) (10 CFR 20; Wrenn et al. 1987), it is reasonable to believe that uranium, such as highly enriched uranium with its high specific activity, may present a radiological hazard, especially in cases of human exposure (Kirk 1980; USNRC 1989). Three accidental exposure reports and health data from several years of follow-up studies are available (Kathren and Moore 1986; USNRC 1986; Zhao and

Zhao 1990). Similarly, a report from a study in which terminally ill cancer patients were injected with tetravalent and hexavalent uranium is available (Bernard and Struxness 1957). Several other human studies (Archer et al. 1973a, 1973b; Auerbach et al. 1978; Band et al. 1980; Chovil and Chir 1981; Cookfair et al. 1983; Cragle et al. 1988; Gottlieb and Husen 1982; Grace et al. 1980; Kusiak et al. 1993; Land et al. 1993; Lundin et al. 1969; Polednak and Frome 1981; Priest et al. 1982; Reyes et al. 1984; Saccomanno et al. 1971, 1976, 1982, 1988; Samet et al. 1984, 1986; Sanders 1986; Sullivan 1980a; Waxweiler et al. 1983; Whittemore and McMillan 1983; Wrenn and Singh 1983) as well as long-term animal studies with both natural and enriched uranium (Cross et al. 1981b; Filippova et al. 1978; Leach et al. 1970, 1973, 1984; Maynard and Hodge 1949; Maynard et al. 1953; Mays et al. 1985; Spiegl 1949; Stokinger et al. 1953; Tannenbaum et al. 1951) in which cancer end points were evaluated are also available. The existing studies do not show evidence of the potential radiotoxicity of uranium isotopes, particularly high specific-activity enriched uranium. Such studies in animals will be useful in a more accurate evaluation of the hazard associated with human exposure to the radiation of uranium isotopes.

Acute-Duration Exposure.   Human fatalities from acute accidental exposure to airborne uranium hexafluoride have been reported, although the deaths were attributed to the sheer force of the explosions in the accident and the highly toxic hydrofluoric acid generated from the spontaneous decomposition of uranium hexafluoride upon contact with atmospheric moisture (Kathren and Moore 1986; Moore and Kathren 1985; USNRC 1986). Two poisoning incidents, an inhalation exposure to powdered uranium tetrafluoride (Zhao and Zhao 1990), and an intentional ingestion of approximately 131 mg U/kg as uranyl acetate (Pavlakis et al. 1996) resulted in renal toxicity. Follow-up studies are normally carried out in the case of industrial accidents; this should also be done in acute ingestion cases. Periodic analysis of urine for uranium over several years would be particularly valuable for the refinement of pharmacokinetic models for use in risk assessment. Acute-duration studies in animals mainly examined lethality. Inhalation acute-duration lethality studies in rats and guinea pigs are available for uranium hexafluoride (Leach et al. 1984; Spiegl 1949); oral acute-duration lethality data are available for rats and rabbits (Domingo et al. 1987; Maynard and Hodge 1949; Orcutt 1949); and dermal acute-duration lethality studies in rats, mice, guinea pigs, and rabbits (De Rey et al. 1983; Orcutt 1949) are available. Acute-duration studies which define threshold values for renal toxicity by the inhalation and oral route would be useful for assessment of brief exposures. Dermal exposure to uranium-contaminated soil is also possible. While dermal exposure to purified uranium compounds can cause toxicity in animals (De Rey et al. 1983; Orcutt 1949), the need for

further dermal studies should be assessed after information is obtained on the bioavailability of uranium from uranium-contaminated soil.

Additional research regarding the health effects of acute-duration inhalation exposure to uranium would be useful; these studies should include toxicological end points, lung doses, and metabolic fate.

Intermediate-Duration Exposure.   No studies are available describing the effects of intermediate-duration exposure to uranium in humans for any route. However, an extensive animal database for this duration for all routes demonstrates that renal toxicity is a concern for intermediate-duration human exposure. The animal database for intermediate-duration inhalation exposure is essentially complete (Dygert 1949a, 1949b, 1949d; Roberts 1949; Rothstein 1949a, 1949b, 1949c; Spiegl 1949; Stokinger et al. 1953). Threshold values from these studies were used to derive inhalation MRLs for this duration (See Section 2.5 and Appendix A). The animal database for intermediate-duration oral exposure is less extensive in terms of species and compounds examined. Comprehensive studies are available for the effects of uranyl nitrate in rats and rabbits (Gilman et al. 1998a, 1998b, 1998c). The severity of histopathological alterations in the kidney increased with dose, although tests of kidney function (dye clearance, urinalysis) were normal in all dosed groups. Additionally, histopathological effects were seen in the lower dose groups without a significant increase in kidney uranium content over controls. No threshold for the histopathological effects was observed; the lowest dose tested (0.05 mg U/kg/day) was considered a minimal effect and was used to derive an oral MRL for this duration (See Section 2.5 and Appendix A). Further studies are needed to elucidate the time-course of the development of these histopathological effects; in rats, these changes were seen after 91 days, but not at 28 days. Dermal exposure to uranium-contaminated soil is also possible. While dermal exposure to purified uranium compounds can cause toxicity in animals (De Rey et al. 1983; Orcutt 1949), the need for further dermal studies should be assessed after information is obtained on the bioavailability of uranium from uranium-contaminated soil.

Chronic-Duration Exposure and Cancer.   A number of epidemiological studies are available for workers exposed to uranium (miners, millers, processors). Studies that reported death from lung cancers from occupational inhalation exposure of mine workers are available (Archer et al. 1973a; Gottlieb and Husen 1982; Lundin et al. 1969; Samet et al. 1984, 1986). Available studies document no lung cancers solely from inhaled uranium-bearing dust. It is generally accepted that lung cancers developed subsequent to inhalation of uranium-containing dusts were principally due to radon daughters and long-term cigarette

smoking, and not due to uranium metallotoxicity or uranium radioactive emissions. Existing epidemiologic studies that reported lung cancers in uranium miners, millers, and processors are inadequate for use in assessing the carcinogenic potential of uranium because the subjects were also concurrently exposed to other potential carcinogens such as radon progeny and thorium (Archer et al. 1973a; Auerbach et al. 1978; Cookfair et al. 1983; Howe et al. 1986; Polednak et al. 1982; Saccomanno et al. 1971, 1976, 1988; Samet et al. 1986; Wrenn and Singh 1983). The negative findings in most studies regarding renal injury among uranium-processing workers exposed to dusts of both soluble and insoluble uranium compounds are particularly significant in view of the high levels of exposure also reported (Eisenbud and Quigley 1955). Perhaps more sensitive indicators of renal damage, such as altered urinary amino acid, catalase, and phosphatase activities (Dygert 1949a; Stokinger et al. 1953), or the recently developed multiparametric simultaneous analysis of urinary glucose, alkaline phosphatase, and β_2-microglobulin, which may be more specific to proximal tubular damage (Limson-Zamora et al. 1996), should be used to evaluate the subjects in future studies. In addition, data from human (Russell et al. 1996) and animal studies indicate that any actual renal damage by sublethal doses was overcome and obscured by regeneration of the tubular epithelium, especially in the corticomedullary region, despite continuing exposure (Bentley et al. 1985; Dygert 1949a, 1949b, 1949c; Leach et al. 1984; Maynard and Hodge 1949; Maynard et al. 1953; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). Such repair, once completed, is histologically indistinguishable from undamaged kidney tissue. Therefore, future studies should examine newly employed miners, millers, and processors to detect potential renal effects before the process of repair occurs. The available studies have linked respiratory diseases, fatal in some cases, in uranium miners to exposure to dust-containing uranium (and other noxious substances) (Waxweiler et al. 1981a). In several of these studies, the investigators concluded that, although uranium mining may elevate the risk for nonmalignant respiratory disease, the etiology of the excess risk is not clearly identifiable because the miners were also concurrently exposed to known potent respiratory tract irritants such as diverse inhalable dust particles, silica, nickel oxide, cobalt oxide, and vanadium pentaoxide (Waxweiler et al. 1983).

Genotoxicity.   Very little information on the genotoxic effects of uranium in humans (Hu and Zhu 1990; Muller et al. 1967; Waxweiler et al. 1981b; Wiese 1981) and in *in vitro* studies (Fajgelj et al. 1992; Lin et al. 1993) is available. Although the BEIR III (1980) and BEIR IV (1988) reports have summarized the general genotoxic effects of high-LET radiation such as might be expected from uranium, this information is not specific to uranium. Therefore, a battery of genotoxic studies with uranium compounds (including

the Ames test and tests for chromosomal damage) are needed to determine the potential of uranium to cause genetic aberrations in humans.

Reproductive Toxicity.   Existing human data from uranium miners, millers, and processors (Muller et al. 1967; Waxweiler et al. 1981b; Wiese 1981) and some data from animals (Leach et al. 1970; Llobet et al. 1991; Paternain et al. 1989) indicate that uranium does not cause reproductive effects. However, other studies have reported reproductive abnormalities manifested as reduced implantations and increased fetal resorptions and dead fetuses (Paternain et al. 1989), maternal toxicity (reduced weight gain and food consumption [identified in other studies as taste aversion and not toxicity], and increased relative liver weight) and fetal toxicity (Domingo et al. 1989a), testicular lesions and degeneration and decreased testes weight (Malenchenko et al. 1978; Maynard et al. 1953), and reduced litter size (Maynard et al. 1953) following oral exposure to uranium compounds. The last three studies used high levels of orally administered uranyl nitrate, which is often considered to be the most toxic compound; the remaining positive indications are associated with relatively low oral levels of uranyl acetate(Domingo et al. 1987; Lloglet et al. 1991; Paternain et al. 1989). In dermal studies, however, uranyl acetate appears to be more toxic than uranyl nitrate for death from acute duration exposure, which is the only comparable end point for these compounds. Additional testing is needed to validate the relative toxicities of the acetate and nitrate in reproductivity studies, and then to exploit the acetate to assess other end point toxicities.

Developmental Toxicity.   Because uranium can cross the placenta into the fetus, it is possible that uranium may have adverse effects on fetal development, especially metallotoxicity to the embryonic kidneys or the brain (Domingo et al. 1989a, 1989b; Paternain et al. 1989). The potential for teratogenicity and general developmental toxicity of uranium was demonstrated by results from oral animal studies in which the following were reported in mice: increased fetal mortality, reduced survivability, reduced growth (Paternain et al. 1989), reduced fetal body weight and length, an increased incidence of stunted fetuses, increased external and skeletal malformations and developmental variations, an increased incidence of cleft palate, underdeveloped renal papillae, and bipartite sternebrae, reduced or delayed ossification of the hind limb, fore limb, skull, and tail, an increase in the relative brain weight of the offspring, a reduced viability and lactation index (Domingo et al. 1989a), and embryotoxicity (Paternain et al. 1989). These effects have not been observed or documented in any human study.

Further data obtained from multigenerational developmental studies are required to determine whether human fetuses are at risk.

Immunotoxicity.   Epidemiologic studies that histologically evaluated the immune system structures for the effects of inhalation exposure to uranium are available (Archer et al. 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Cragle et al. 1988; Keane and Polednak 1983; Polednak and Frome 1981; Vich and Kriklava 1970). Although these studies were not designed as immunotoxicity studies, they found no significant immunological changes in the human subjects. The available inhalation studies in animals also found no evidence of histological changes in the spleens of rats, dogs, and monkeys exposed to uranium dioxide dusts (Leach et al. 1970, 1973). Intermediate-duration exposure of rats, rabbits, guinea pigs, and dogs to dusts containing various uranium compounds for 7–12 months produced no significant histological changes in the lymph nodes, bone marrow, or spleen, and no build-up of uranium was seen in these tissues (Stokinger et al. 1953). Similarly, rats and mice exposed to oral doses of soluble or insoluble compounds of uranium for intermediate- and chronic-duration exposures suffered no immunological damage (Malenchenko et al. 1978; Maynard et al. 1953; Tannenbaum et al. 1951). No studies are available that evaluated the immunological and lymphoreticular effects in animals following acute- or intermediate-duration inhalation exposure, the oral exposure of humans for any duration, the inhalation or oral exposure of animals for acute durations, or the dermal exposure of humans and animals to uranium compounds for any duration. Additional animal studies would be useful that use current techniques to evaluate the immunological and lymphoreticular dysfunctions that may occur with exposure to uranium compounds.

Neurotoxicity.   No studies were located that specifically tested neurological functions in humans or animals following inhalation, oral, or dermal exposure to uranium. Particularly lacking in the available reports are neuropathological indicators such as narcosis or ataxia (Brown and Bloom 1987; Carpenter et al. 1988; Cragle et al. 1988; Hadjimichael et al. 1983; Kathren and Moore 1986; Polednak and Frome 1981; Reyes et al. 1984; USNRC 1986). However, the available acute-duration oral studies in rats reported dose-response neurological symptoms (piloerection, tremors, hypothermia, pupillary size decrease, exophthalmos) (Domingo et al. 1987). Available intermediate-duration animal inhalation studies reported a neurological sign (instability of gait) in dogs and cats (Dygert 1949a). Anorexia observed in another 30-day study with dogs given inhalation doses of 9.5 mg U/m^3 as uranyl nitrate hexahydrate may also have had its origin in neurological dysfunction (Roberts 1949). Similarly, cats given inhalation exposures at 18 mg U/m^3 as uranium tetrafluoride exhibited unsteady gait on the seventh day in a 30-day study (Dygert

1949a). Available chronic-duration oral data in dogs and cats also reported similar neuropathological signs (weakness and lassitude) (Rothstein 1949a). Likewise, an available acute-duration dermal exposure study in rats reported neurological signs (irritability, hyperactivity, upset equilibrium, rigidity of limbs, and respiratory arrest) (Orcutt 1949). Consequently, sensitive animal neurological battery studies of the inhalation and oral routes will be useful in evaluating and quantifying the potential for uranium to damage the nervous system in humans.

Epidemiologic and Human Dosimetry Studies. Epidemiologic studies of uranium miners, millers, and processors are available on the health effects from exposure to airborne uranium and radon daughters (Archer et al. 1973a, 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Cragle et al. 1988; Gottlieb and Husen 1982; Hadjimichael et al. 1983; Lundin et al. 1969; Polednak and Frome 1981; Samet et al. 1984, 1986; Scott et al. 1972; Waxweiler et al. 1983). However, some of the studies of miners and millers contain confounding factors and lack adequate quantitative exposure information compared with the studies of processors, which had fewer confounders and clearly identified an absence of toxic effects such as cancer. New studies that account for these confounding factors, such as effects of inhalable dust particles other than uranium, other sources of ionizing radiation, and other potentially pulmonary-toxic substances to which these workers are concurrently exposed, and that provide a more accurate measurement of the airborne concentrations of uranium to which these workers are exposed would be useful. Some of these studies also reported indications of kidney damage in these workers (Saccomanno et al. 1982; Thun et al. 1985). However, most of these studies either found no renal effects or failed to report renal effects in the subjects studied (Archer et al. 1973a, 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Polednak and Frome 1981). The negative findings regarding renal injury among workers exposed to insoluble compounds may be particularly significant in view of the high levels of exposure reported (Eisenbud and Quigley 1955). Additional research regarding the health effects of acute-duration inhalation exposure to depleted uranium would be useful. This should include toxicological end points, lung doses, metabolic fate, and techniques to detect and monitor lung exposures. Also, simple and accurate monitoring methods should be developed for workers which would determine the relationship among atmospheric concentration, particle size, distribution, physical properties of the uranium aerosol, body burden, and excretion rates and pathways.

Absorption, Distribution, Metabolism, and Excretion.   Information is needed on the comparative absorption of uranium compounds by the oral route, along with an assessment of its clearance from the skeleton. Quantitative data on the bioavailability of uranium from contaminated soil by the oral and dermal routes are also necessary to assess the risk of uranium-contaminated soil at hazardous waste sites.

Comparative Toxicokinetics.   Numerous species (mice, rats, rabbits, guinea pigs, dogs, and monkeys) have been tested for their response to inhaled or ingested uranium. The results from these studies clearly demonstrate that there is a considerable difference in toxic responses among species. For example, rabbits appear to be unusually susceptible to the lethal effects of uranium (Maynard and Hodge 1949; Orcutt 1949; Stokinger et al. 1953); whereas dogs developed glandular neoplasms of the lungs (Leach et al. 1973), a type of lung cancer that is not observed in humans; and guinea pigs required far greater air concentrations (15x) for 2-minute exposures than did rats to produce an effect (Leach et al. 1984).

Methods for Reducing Toxic Effects.   Uranium forms complexes with the bicarbonate ion (Cooper et al. 1982) and has been administered prophylactically after uranium exposure (Fisher et al. 1991). Bicarbonate can alkalize the blood to a degree that facilitates the excretion of uranium via the kidneys. This in turn, can prevent uptake by and deposition in critical tissues (kidney, bone). Chelation has been tested in animals and found to have a limited potential, though possibly valuable, role in reducing acute uranium toxicity. Further research is needed to validate, refute, or refine method(s) for reducing the toxic effects of uranium compounds. No verified methods for reducing the toxic effects of long-term exposure to uranium are currently available.

Children's Susceptibility.   Specific information is not available on whether children are more susceptible than adults to the effects of uranium. No reports were located describing toxicity in children as the result of uranium exposure. It is probable, however, that if exposure levels were high enough, signs of renal toxicity would be observed similar to that seen in adults exposed accidentally (Zhao and Zhao 1990) or intentionally (Pavlaikis 1996). Data needs relating to development, both pre-natal and post-natal, are discussed in the previous section on Developmental Toxicity.

A study by the oral route establishing a threshold for renal effects in weanling and adult rats of the same strain is needed to determine if susceptibility to uranium toxicity varies with age. Histopathological studies

and urinalysis should be performed, as well as measurement of uranium in excreta for both groups. At termination in this study, uranium content should be measured in tissues, particularly bone and kidney. This will provide information on whether retention of uranium in bone is age-dependent (as assumed by analogy with calcium in PBPK models) and on whether kidney burden associated with uranium toxicity is age-related.

More information is needed on the absorption of various forms of uranium in young animals. Also, studies are needed on whether maternally stored bone uranium is mobilized to blood during pregnancy and lactation and whether this can increase exposure to the fetus and neonate. Child health data needs relating to exposure are discussed in Section 5.8.1, Data Needs: Exposures of Children.

2.11.3   Ongoing Studies

A number of studies currently being conducted on the toxicity of uranium were found in the Federal Research in Progress database (FEDRIP 1999). Selected studies are listed in Table 2-11.

Table 2-11. Ongoing Studies on Health Effects of Uranium

Investigator	Affiliation	Study	Funding agency
Kathren RL	Washington State University Health Research and Education Center, Richland WA	United States transuranium and uranium registries	DOE
Saccomanno G	Saint Mary's Hospital And Medical Center, Dept of Cytopathology, Grand Junction CO	Early lung cancer detection in uranium miners with abnormal sputum cytology	DOE
Gilland, Frank	Univ of New Mexico, Albuquerque NM	Uranium miners health study	NIH, National Center for Research Resources
Sandler DP	NIEHS, NIH, Research Triangle Park NC	Cancer risk in Czech uranium miners	NIEHS
Belinsky SA	Lovelace Biomedical and Environmental Research, Albuquerque NM	Tumor suppressor gene methylation in lung adenocarcinoma	NIEHS
Spiegleman D	Harvard School of Public Health, Boston MA	Measurement error in occupational cohort studies	NCI
Saffiotti U	NCI, NIH, Bethesda MD	Respiratory carcinogenesis by chemical and physical factors	NCI, Division of Basic Sciences
Crowell R	Department of Veterans Affairs Medical Center, Albuquerque NM	Lung cancer in uranium miners: a tissue resource	Department of Veterans Affairs Research and Development
Walsh M	Department of Veterans Affairs Medical Center, Boston MA	Follow-up and monitoring of gulf war veterans with fragments of depleted uranium and other sources of depleted uranium.	Department of Veterans Affairs Research and Development
Keogh J	Department of Veterans Affairs Medical Center, Baltimore, MD	Assessment of depleted uranium exposure during the persian gulf war.	Department of Veterans Affairs Research and Development
Standiford H	Department of Veterans Affairs Medical Center, Baltimore, MD	Evaluation of gulf war veterans to determine health effects of depleted uranium.	Department of Veterans Affairs Research and Development
McDiarmid M	University of Maryland School of Medicine, Baltimore, MD	Health effects of depleted uranium in Gulf War veterans	Department of Veterans Affairs Research and Development
McClain D	Armed Forces Radiobiology Research Institute, Bethesda MD	Health Effects of Embedded Depleted Uranium	United States Department of Defense
(supervising scientist)	University of Sydney, Sydney, Australia	Uranium measurement in occupationally exposed mill workers	Commonwealth Institute of Health, Australia

DOE = Department of Energy; NCI = National Cancer Institute; NIEHS = National Institutes of Environmental Health Sciences; NIH = National Institute of Health

Source: FEDRIP 1999 and http://www.afrri.usuhs.mil/www/research/teams/teamdu.html

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Uranium is a naturally occurring element that makes up approximately 2–4 ppm of the earth's crust. It is
more plentiful than silver and about as abundant as molybdenum or arsenic. Uranium is an actinide
element, and has the highest atomic mass of any naturally occurring element. In its refined state, it is a
heavy, silvery-white metal that is malleable, ductile, slightly paramagnetic, and very dense, second only to
tungsten. In nature, it is found in rocks and ores throughout the earth, with the greatest concentrations in
the United States in the western states of Colorado, Arizona, Wyoming, Texas, Utah, and New Mexico
(EPA 1991; Lide 1994). In its natural state, crustal uranium occurs as a component of several minerals,
such as carnotite, uraninite, and pitchblend, but is not found in the metallic state. The chemical information
for uranium metal is listed in Table 3-1.

3.2 PHYSICAL, CHEMICAL, AND RADIOLOGICAL PROPERTIES

The physical properties of uranium and uranium compounds important in the nuclear fuel cycle and defense
programs are listed in Table 3-2. The percent occurrence and radioactive properties of naturally occurring
isotopes of uranium are listed in Table 3-3. The two decay series for the naturally occurring isotopes of
uranium are shown in Table 3-4.

Metallurgically, uranium metal may exist in three allotropic forms: orthorhombic, tetragonal, or body-
centered cubic (EPA 1991), and may be alloyed with other metals to alter its structural and physical
properties to suit the application. Like aluminum metal powder, uranium metal powder is autopyrophoric
and can burn spontaneously at room temperature in the presence of air, oxygen, and water. In the same
manner, the surface of bulk metal, when first exposed to the atmosphere, rapidly oxidizes and produces a
thin surface layer of UO_2 which resists oxygen penetration and protects the inner metal from oxidation.   At
temperatures of 200–400 EC, uranium powder may self-ignite in atmospheres of CO_2 and N_2. Oxidation of
uranium under certain conditions may generate sufficient energy to cause a chemical explosion (Gindler
1973).

Table 3-1. Chemical Identity of Uranium Metal

	Value	Reference
Chemical name	Uranium	
Natural isotopes	Uranium-238; uranium-235; uranium-234	EPA 1985j
Synonyms	uranium-238; uranium-234; uranium-235; U	HSDB 1995
Trade names	No data	
Chemical formula	U	HSDB 1995
Chemical structure	Not applicable	
Identification numbers		
CAS registry	7440-61-1	HSDB 1995
NIOSH RTECS	NIOSH/YR3490000	HSDB 1995
EPA hazardous waste	No data	HSDB 1995
OHM/TADS	7217196	HSDB 1995
DOT/UN/NA/IMO shipping	UN2979; uranium metal, pyrophoric	HSDB 1995
HSDB	2553	HSDB 1995
NCI	No data	HSDB 1995
STCC	4926187; uranium metal, pyrophoric (uranium metal scrap, neither irradiated nor requiring protective shielding)	HSDB 1995

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

Table 3-2. Physical and Chemical Properties of Selected Uranium Compounds

Property	Value				
	Uranium	Uranium dioxide	Uranium trioxide	Triuranium octaoxide	Uranium tetrafluoride
Atomic/molecular weight	238.0289	270.03	286.03	842.08	314.02
Chemical formula	U	UO_2	UO_3	U_3O_8	UF_4
Synonyms[a]	Uranium I	Uranium oxide	Uranyl oxide	Uranium octaoxide	Uranium fluoride
Common names		Brown oxide	Orange oxide	Yellow cake; Block oxide	
Chemical Abstracts Service Registry No.	7440-61-1	1344-57-6	1344-58-7	1344-59-8	10049-14-6
Color	Silvery	Brown-black	Yellow-red	Olive green-black	Green
Physical state	Solid	Solid	Solid	Solid	Solid
Odor	No data	No data	No data	No data	No data
Melting point, °C	1135	2878	Decomposes	Decomposes at 1300	960
Boiling point, °C	4131	No data	Not relevant	Not relevant	No data
Autoignition temperature	20% (cloud), 100 °C[e] (layer)	Not relevant	Not relevant	Not relevant	Not relevant
Solubility:					
Water	Insoluble	Insoluble	Insoluble	Insoluble	Very slightly soluble
Other solvents	Soluble in acids	Soluble in HNO_3	Soluble in HNO_3, HCl	Soluble in HNO_3, H_2SO_4	Soluble in concentrated acids and alkalis
Density, g/cm³	18.95	10.96	7.29	8.30	6.70
Partition coefficients	Not relevant	Not relevant	Not relevant	Not relevant	No data
Vapor pressure	1 mmHg at 2450° C	Not relevant	Not relevant	Not relevant	Not relevant
Henry's law constant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
Refractive index	No data	No data	No data	No data	No data
Flashpoint	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
Flammability limits	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
Conversion factor	1 µg ≡ 0.67 pCi[d]	1 µg ≡ 0.59 pCi[d]	1 µg ≡ 0.56 pCi[d]	1 µg ≡ 0.57 pCi[d]	1 µg ≡ 0.45 pCi[d]

Table 3-2. Physical and Chemical Properties of Selected Uranium Compounds (continued)

Property	Value				
	Uranium hexafluoride	Uranium tetrachloride	Uranyl[c] fluoride	Uranyl acetate, dihydrate	Uranyl nitrate hexahydrate
Atomic/molecular weight	352.02	379.84	308.03	424.15	502.13
Chemical formula	UF_6	UCl_4	UO_2F_2	$UO_2(CH_3COO)_2 \cdot 2H_2O$	$UO_2(NO_3)_2 \cdot 6H_2O$
Synonyms[b]	UN2977; uranium fluoride (fissle)	Uranium (IV) chloride	Uranium oxyfluoride; uranium fluoride oxide	bis(Acetate-B) dioxouranium	bis(Nitrate-O) dioxouranium; hexahydrate
Common names		Green salt			
CAS Registry No.	7783-81-5	10026-10-5	13536-84-0	541-09-3	13520-83-7
Color	Colorless	Dark green	Pale Yellow	Yellow	Yellow
Physical state	Solid	Solid	Solid	Solid	Solid
Odor	No data	No data	No data	No data	No data
Melting point, °C	64.5–64.8	590	Decomposes at 300 °C	Loses $2H_2O$ at 110	60.2
Boiling point, °C	56.2	792	Not relevant	Decomposes at 275	Decomposes at 100
Autoignition temperature	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
Solubility:					
Water	Decomposes	Soluble	Soluble	7.7 g/100 mL at 15 °C	Miscible in water at 60 °C
Other solvents	Soluble in CCl_4 and chloroform	Soluble in ethanol	Soluble in ethanol	Soluble in ethanol	Soluble in ethanol
Density, g/cm³	4.68 at 21 °C	4.87	6.37	2.893 at 15 °C	2.807 at 13 °C
Partition coefficients	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
Vapor pressure	115 mmHg at 25 °C[c]	No data	No data	No data	No data
Henry's law constant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
Refractive index	No data	No data	No data	No data	1.4967
Flashpoint	No data	Not relevant	No data	Not relevant	Not relevant
Flammability limits	No data	Not relevant	No data	Not relevant	Not relevant
Conversion factor	1 µg ≡ 0.45 pCi[d]	1 µg ≡ 0.42 pCi[d]	1 µg ≡ 0.52 pCi[d]	1 µg ≡ 0.38 pCi[d]	1 µg ≡ 0.32 pCi[d]

Table 3-2. Physical and Chemical Properties of Selected Uranium Compounds (continued)

	Value	
Property	Ammonium diuranate	Uranium peroxide
Atomic/molecular weight	624.22	302.03
Chemical formula	$(NH_4)_2U_2O_7$	UO_4
Synonyms[b]	Ammonium uranate(IV)	No data
CAS Registry No.	7783-22-4	19525-15-6
Color	Reddish yellow	Pale yellow
Physical state	Solid	Solid
Odor	No data	No data
Melting point, °C	No data	Decomposes
Boiling point, °C	No data	No data
Autoignition temperature	Not relevant	Not relevant
Solubility:		
Water	Practically insoluble	Decomposes
Other solvents	Soluble in acids	No data
Density, g/cm³	No data	No data
Partition coefficients	No data	No data
Vapor pressure	No data	No data
Henry's law constant	No data	No data
Refractive index	No data	No data
Flashpoint	No data	Not relevant
Flammability limits	No data	Not relevant
Conversion factor	1 µg ≡ 0.51 pCi[d]	1 µg ≡ 0.53 pCi[d]

Source: Lide 1994, unless otherwise stated
[a]Synonyms were obtained from Chemline 1989
[b]Properties were obtained from HSDB 1989
[c]Cotton and Wilkinson 1980

[d]NCRP (1984) and EPA (1985b), based on natural U (values higher for enriched compounds, lower for depleted compounds)
[e]This value is obtained from HSDB 1995

Table 3-3. Percent Occurrence and Radioactive Properties of Naturally Occurring Isotopes of Uranium

Isotope	Percent of Total Uranium in Crustal Rock		Alpha energies, MeV (abundance)	Half-life (years)
	by weight	by radioactivity		
^{234}U	0.0055	48.9	4.776 (72.5%) 4.723 (27.5%)	2.45×10^5
^{235}U	0.720	2.2	4.597 (5%) 4.395 (55%) 4.370 (6%) 4.364 (11%) 4.216 (5.7%) Others (17.3%)	7.04×10^8
^{238}U	99.2745	48.9	4.196 (77%) 4.147 (23%)	4.46×10^9

Source: Lide 1994

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-4. Uranium Isotope Decay Series Showing the Decay Products of the Naturally Occurring Isotopes of Uranium

	Uranium-238 Series, Includes 234U Series							Uranium-235 Series				
Np												
U	238U 4.5E9		234U 2.5E5y					235U 7.1E8 y				
Pa	↓	234Pa 1.2 m	↓					↓	231Pa 3.3E4 y			
Th	234Th 24 d		230Th 8E4y					231Th 25.5 h	↓	227Th 18.7 d		
Ac			↓						227Ac 21.8 y	↓		
Ra			226Ra 1600 y						↓	223Ra 11.4 d		
Fr			↓						223Fr 21.8 m	↓		
Rn			222Rn 3.82 d							219Rn 4.0 s		
At			↓	218At 2s						↓	215At 1E-4s	
Po			218Po 3.05 m	↓	214Po 1.6E-4s		210Po 138 d			215Po 1.8E-5	↓	211Po 0.5 s
Bi			↓	214Bi 19.7 m	↓	210Bi 5.0 d	↓			↓	211Bi 2.15 m	↓
Pb			214Pb 26.8 m	↓	210Pb 22.3y	↓	206Pb stable			211Pb 36.1 m	↓	207Pb stable
Tl				210Tl 1.3 m		206Tl 4.2 m					207Tl 4.79 m	

↓ alpha decay;   ↗ beta decay;   half life (d = days; m = minutes; s = seconds; y = years)

Source: NCRP 1975

Uranium can exist in five oxidation states: +2, +3, +4, +5, and +6 (Lide 1994); however, only the +4 and
+6 states are stable enough to be of practical importance. Tetravalent uranium is reasonably stable and
forms hydroxides, hydrated fluorides, and phosphates of low solubility. Hexavalent uranium is the most
stable state, and the most commonly occurring state is U_3O_8, although there are a few localized storage
locations for anthropogenic uranium hexafluoride (UF_6) (EPA 1991). Major compounds of uranium
include oxides, fluorides, carbides, nitrates, chlorides, acetates, and others. One of the characteristics of
UO_2^{+2} ions is their ability to fluoresce under ultraviolet light.

Although the element uranium was discovered in 1789 by Klaproth, who named it "uranium" after the
newly discovered planet Uranus, it was not until 1896 that Becquerel discovered that uranium is radio-
active. There are 22 known isotopes of uranium, only 3 of which occur naturally (Parrington et al. 1996).
These three isotopes, ^{234}U, ^{235}U, and ^{238}U, have relative mass abundances within the earth's undisturbed
crustal rock of 0.005%, 0.72%, and 99.275%, respectively. One gram of natural uranium having this
relative isotopic abundance has an activity of 0.67 μCi. Of this 0.67 μCi, 48.9% of the activity is
attributable to ^{234}U, 2.2% of the activity is attributable to ^{235}U, and 48.9% of the activity is attributable to
^{238}U (Lide 1994). This ratio is for undisturbed crustal rock only. Although the relative mass abundance of
^{234}U is only 0.005%, it accounts for exactly one-half of the total activity. The relative isotopic abundances
given above can be altered to some extent by natural processes that are not fully understood, but which can
cause different ratios in air, water and soil as demonstrated in EPA reports (EPA 1994a).

^{235}U is an isotope of particular interest because it is fissile (capable of being fissioned) and, consequently,
can sustain a nuclear chain reaction in the presence of appropriate energy neutrons. The predominant
isotope of uranium found in nature, ^{238}U, is not readily fissionable, but a small portion of its transformations
result in spontaneous fission rather than the typical alpha decay; these neutrons can be sufficient to initiate a
chain reaction under appropriate concentration, mass, and neutron thermalization conditions. Consequently,
for uranium to be used as a fuel in nuclear reactors, the ratio of ^{235}U to ^{238}U is increased from 0.72% to
2–4% or enriched by a process called enrichment. The enrichment process most used in the United States is
called gaseous diffusion, but other enrichment processes involving thermal, centrifuge, and laser methods
can be used, and other countries are actively involved in producing enriched uranium. Uranium ore is
processed to uranium oxide (U_3O_8) and then fluorinated to UF_6; next a stream of UF_6 gas containing all
three isotopic compounds is passed through a long series of diffusion stages through which the ^{234}U and ^{235}U
pass more quickly than the ^{238}U. Thus, the front end of the stream has an enhanced ^{235}U concentration and
is called enriched uranium hexafluoride, while the back end of the stream has a reduced ^{235}U concentration

and is called depleted uranium hexafluoride. The percent enrichment is a measure of the mass percentage of ^{235}U in the final product, and the degree of enrichment is determined by the use. Enriched UF_6 is typically converted to uranium metal or oxide for power reactor fuel or to metal for weapons applications. Depleted UF_6 is either converted to uranium metal for a variety of civilian and military applications or stored for future use. Low enriched uranium (2–4% enriched) is used in civilian nuclear power reactors, while high enriched uranium (>90% enriched) is used in special research reactors (most of which have been removed from operation) (Weigel 1983), nuclear submarine reactor cores, and nuclear weapons. Depleted uranium metal (DU) is used as radiation shielding, missile projectiles, target elements in plutonium production reactors, a gyroscope component, and counterweights or stabilizers in aircraft.

Uranium continuously undergoes transformation through the decay process whereby it releases energy to ultimately become a stable or nonradioactive element. For the uranium isotopes, this is a complex process involving the serial production of a chain of decay products, called progeny, until a final stable element is formed. The decay products of the uranium isotopes, which are also radioactive, are shown in Table 3-4. ^{238}U is the parent isotope of the uranium series (^{234}U is a decay product of ^{238}U), while ^{235}U is the parent isotope of the actinide series. All natural uranium isotopes and some of their progeny decay by emission of alpha particles; the other members of both series decay by emission of beta particles and gamma rays (Cowart and Burnett 1994). Both the uranium and the actinide decay series have three features in common. Each series begins with a long-lived parent, ^{235}U or ^{238}U, each series contains an isotope of the noble gas radon, and each series ends with a stable isotope of lead, ^{207}Pb or ^{206}Pb.

The amount of time required for one-half of the atoms of a radionuclide to transform is called its radioactive half-life. The rate of decay, and thus the half-life, for each radionuclide is unique. The half-life of ^{238}U is very long, 4.5×10^9 years; the half-lives of ^{235}U and ^{234}U are orders of magnitude lower, 7.1×10^8 years and 2.5×10^5 years, respectively. Since the activity of a given mass of uranium depends on the mass and half-life of each isotope present, the greater the relative abundance of the more rapidly decaying ^{234}U and ^{235}U, the higher the activity will be (EPA 1991). Thus, depleted uranium is less radioactive than natural uranium and enriched uranium is more radioactive.

Uranium is unusual among the elements because it is both a chemical and a radioactive material. The hazards associated with uranium are dependent upon uranium's chemical and physical form, route of intake,

and level of enrichment. The chemical form of uranium determines its solubility and, thus, transportability in body fluids as well as retention in the body and various organs. Uranium's chemical toxicity is the principal health concern, because soluble uranium compounds cause heavy metal damage to renal tissue. The radiological hazards of uranium may be a primary concern when inhaled, enriched (>90%) and insoluble uranium compounds are retained long-term in the lungs and associated lymphatics.

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

4.1 PRODUCTION

Uranium is present in the earth's crust at approximately 3 ppm (2 pCi/g) (du Preez 1989). Although there are more than 100 uranium ores, carnotite, pitchblende, coffinite, uraninite, tobernite, autunite, tyuyamunite, and a few others are the main ores of commercial interest. The main ores are described in Table 4-1. The most economically attractive uranium ores have uranium concentrations in excess of 1,000 ppm (700 pCi/g) (Stokinger 1981; Weigel 1983). In the United States, the major ore deposits are located in Colorado, Utah, Arizona, New Mexico, Wyoming, Nebraska, and Texas (EPA 1985a). The steps necessary to produce uranium for its various uses include mining, milling, conversion to uranium hexafluoride (UF_6), enrichment, reduction to metal or oxidation to uranium oxide, and fabrication into the desired shape. The steps for preparing commercial reactor grade, submarine reactor grade, or weapons-grade uranium are the same, except the last two require a more aggressive enrichment process. Depleted uranium metal is produced by reducing the depleted uranium hexafluoride byproduct.   Conventional fabrication methods are used to configure the uranium for specific uses, such as rectangular solid blocks for helicopter rotor counterbalances and parabolic or cylindrical solids for military depleted uranium projectiles.

Mining.   Open-pit mining, *in situ* leaching, and underground mining are three techniques that have been used for mining uranium-containing ores (EPA 1985a). Uranium is found in all soil and rock, but the higher concentrations found in phosphate rock, lignite, and monazite sands are sufficient in some areas for commercial extraction (Lide 1994). The two most commonly used mining methods are open-pit and underground mining. The choice of method is influenced by factors such as the size, shape, grade, depth, and thickness of the ore deposits (Grey 1993). *In situ* leaching involves leaching (or dissolving) uranium from the host rock with liquids without removing the rock from the ground and can only be carried out on unconsolidated sandstone uranium deposits located below the water table in a confined aquifer. A leaching solution is introduced into or below the deposit and pumped to the surface, where the uranium-pregnant liquor is processed in a conventional mill to precipitate the uranium as yellowcake (U_3O_8 and other oxides) (DOE 1995b; Grey 1993).

Table 4-1. Uranium Ores

Ore	Composition	Description
Uraninite	$UO_2 + UO_3$	A major ore of uranium and radium; can dissolve in acids
Pitchblende	$UO_2 + UO_3$	Essentially the same as uraninite
Carnotite	$K_2O \cdot 2U_2O_3 \cdot V_2O_5 \cdot 3 H_2O$ (uranium potassium vanadate)	
Autunite	$Ca (UO_2)_2 (PO_4)_2 \cdot 10 H_2O$	Can lose water to form meta-autunite; dissolves in acids
Torbernite	$Cu (UO_2)_2 (PO_4)_2 \cdot 10 H_2O$	Loses water easily in air forming meta-torbernite; dissolves in acids
Coffinite	$U(SiO_4)_{1-x} (OH)_{4x}$ (uranium silicate)	
Tyuyamunite	$Ca(UO_2)_2 (VO_4)_2 \cdot 5–8 H_2O$ (uranium calcium vanadate)	Closely related to carnotite

Source: Amethyst Galleries 1995; Stockinger 1981; Uranium Institute 1996

Milling.   Ore mined in an open-pit or underground mine is crushed and leached in a uranium mill. The initial step in conventional milling involves crushing, grinding, and wet and/or dry classification of the crude ore to produce uniformly sized particles that are similar in size to beach sand. A slurry generated in the grinding circuit is transferred to a series of tanks for leaching by either an alkaline or acid process. Generally, leaching is a simple process whereby uranyl ions are extracted by a solvent. Uranyl ions are stripped from the extraction solvent and precipitated as yellowcake, predominantly U_3O_8 (EPA 1995d). Yellowcake is pressed, dried, banded, and shipped for refinement and enrichment. Some of the process streams can also be used to extract other oxides, such as vanadium pentoxide. The byproduct of this process is the leftover sand, known as tailings. Thus, tailings are the original sand minus much of the uranium plus residual process chemicals and tailings are less radioactive than the original ore. (Uranium metal production in a conversion facility is done post-enrichment.) Generalized flow charts for the alkaline and acid leaching processes for ore concentration and uranium production are shown in Figure 4-1.

Enrichment.   Next, the U_3O_8 is chemically converted to UF_6. The enrichment process increases, or enriches, the percentage of the fissionable ^{235}U isotope, as well as ^{234}U. In the United States, the process used for enrichment is gaseous diffusion. The mechanism for enrichment is based on the fact that a UF_6 molecule containing ^{235}U or ^{234}U is lighter and smaller, and has, therefore, a slightly higher thermal velocity than a UF_6 molecule containing ^{238}U. As the UF_6 passes through the series of diffusion stages, the $^{234}UF_6$ and $^{235}UF_6$ molecules gradually become more concentrated downstream and less concentrated upstream, while the $^{238}UF_6$ concentrates conversely. The lead portion of the stream is collected and recycled to reach the desired enrichment. The tail portion containing a reduced $^{235}UF_6$ content called depleted UF_6 can be stored in the vicinity of the gaseous diffusion plant sites (DOE 1994b). There are an estimated 560,000 metric tons of depleted uranium currently in storage as UF_6. A second enrichment technology, gas centrifuge separation, has been used in Europe. A third technology, laser separation, is currently under development (DOE 1995b). A fourth technology, thermal separation, is inefficient and no longer used.

Fuel fabrication.   The enriched UF_6 is either reduced to metallic uranium and machined to the appropriate shape, or oxidized to uranium dioxide and formed into pellets of ceramic uranium dioxide (UO_2). The pellets are then stacked and sealed inside metal tubes that are mounted into special fuel assemblies ready for use in a nuclear reactor (DOE 1995b; Uranium Institute 1996).

Figure 4-1. Flow Chart of Uranium Ore Processing
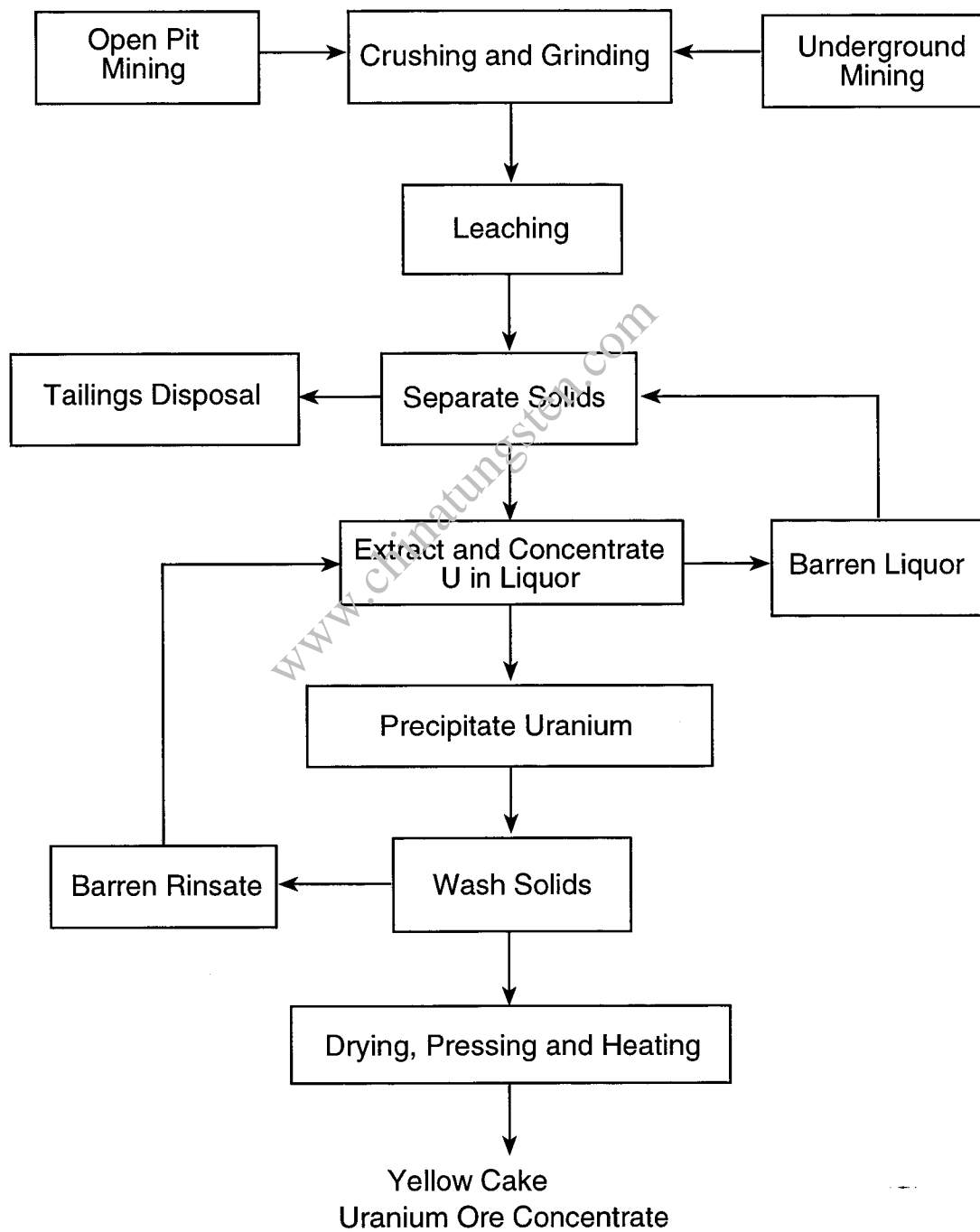
Source: ATSDR 1997; Uranium Institute 1996

Product fabrication.   Uranium metal has commercial and industrial uses due to its great density and strength. It is alloyed with a range of metals to meet other commercial and industrial needs. As with steel, uranium can be formed and fashioned by drop forging, dye casting, and machining and is often painted to minimize oxidation. Some well known uses for these products are gyroscopic wheels in guidance systems, helicopter rotor blade counterbalances, weights in airplane control surfaces, and radiation shields for high radioactivity sources (e.g. industrial radiography).

Production.   Uranium production from 1975 to 1996 is shown in Table 4-2. Peak production of uranium occurred in 1980 at 21,852 short tons (1.98×10^7 kg) and decreased until 1993. This was the same period when the planning and construction of new nuclear power plants ceased in the United States. Production of U_3O_8 had decreased to 4,443 short tons (4.03×10^6 kg) in 1990 and to 1,534 short tons (1.39×10^6 kg) in 1993, a 65% reduction (ABMS 1994; EPA 1985a). In 1996, U.S. uranium production was 3,160 (2.87×10^6 kg) short tons, an increase of 5% from the 1995 level and the highest level since 1991 (DOE 1996a). Underground and open-pit mining have been the two most commonly used methods of mining uranium ores. However, by 1994, uranium was produced primarily by *in situ* leaching methods. A summary of U.S. mine production from 1985 through 1996 (see Table 4-3) illustrates the shift from underground and open-pit mining to *in situ* leaching.

Leached uranium concentrate was produced in 1996 in Wyoming, Louisiana, Nebraska, New Mexico, and Texas. At the end of 1996, two phosphate by-product plants and five *in situ* leaching plants were in operation. In addition, seven phosphate by-product and *in situ* leaching plants were inactive, and seven conventional uranium mills were being maintained in stand-by mode (DOE 1996b).

4.2 IMPORT/EXPORT

The importation of uranium increased significantly in the 1980s (EPA 1985a). In 1983, 3,960 short tons of U_3O_8 equivalent were imported into the United States (USDOC 1984), which was about 37% of the domestic production. In 1987, the amount of U_3O_8 equivalent imported into the United States was 5,630 short tons (USDOC 1988). The amounts of uranium and uranium compounds imported into the United States during the period 1989–1997 are presented in Table 4-4 (USDOC 1995, 1997). The importation of uranium and uranium compounds peaked in 1990 at about 23 million kg (about 1 million tons) and has remained approximately the same, with some fluctuation, since that time.

Table 4-2. Uranium Production in the United States by Uranium Mills and Other Sources

Year	Short tons of U_3O_8	Kilograms of U_3O_8
1975	11600	1.05×10^7
1976	12747	1.16×10^7
1977	14939	1.35×10^7
1978	18486	1.68×10^7
1979	18736	1.70×10^7
1980	21852	1.97×10^7
1981	19237	1.74×10^7
1982	13434	1.22×10^7
1983	10579	9.60×10^6
1989	6919	6.28×10^6
1990	4443	4.03×10^6
1991	3976	3.61×10^6
1992	2823	2.56×10^6
1993	1534	1.39×10^6
1994	1676	1.52×10^6
1995	3022	2.74×10^6
1996	3160	2.87×10^6
1997	2820	2.56×10^6
1998	2550	2.13×10^6

Source: ABMS 1994; DOE 1996a, 1996b, 1999a; EPA 1985a

[a]Short ton = 2,000 pounds = 907 kilograms

Table 4-3. Uranium Mining Production, 1985–1998

Mining method	Percentage of total													
	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
Underground	52.3	77.8	81.7	56.8	54.4	W[a]	W	W	0	0	0	W	W	W
Open-pit	23.3	W	W	W	W	32.0	48.8	W	0	0	0	0	0	0
In situ leaching	No data	No data	W	W	W	W	W	W	W	96.9	95.6	93.1	86.7	77.8
Other	24.4[b]	22.2[c]	18.3[c]	43.2[c]	45.6[c]	68.0[d]	51.2[d]	100[e]	100[f]	3.1[g]	4.4[g]	6.9[h]	13.3	22.2

[a] Withheld; data included with "Other"
[b] *In situ* leach, mine water, water-treatment plant solutions
[c] Open-pit, *in situ* leach, heap leach, mine water, water-treatment plant solutions
[d] Underground, *in situ* leach, heap leach (1990), restoration
[e] Underground, open-pit, and *in situ* leach mines, uranium-bearing water from mine workings, tailing ponds, restoration
[f] *In situ* leach mines, uranium-bearing water from mine workings and restoration
[g] Production from uranium-bearing water from mine workings and restoration
[h] Production from an underground mine and uranium-bearing water from mine workings and restoration

Source: DOE 1995, 1996a, 1996b, 1999b

Table 4-4. Import of Uranium and Compounds (in kg) into the United States

Substance	Year								
	1990	1991	1992	1993	1994	1995	1996	1997	1998
U-metal (depleted)	18,343	9,673	9,008	4,458	1,735	792	1572	36,359	508
U-alloys, dispersions and ceramic materials	5	2,444	9	25	No data	No data	309,681	10	2
U-oxide (natural)	8,459,924	12,630,433	10,043,472	7,925,762	9,713,406	8,992,532	8,880,669	9,259,002	No data
U-oxide (enriched)	204,592	200,733	63,875	35,779	14,214	97,976	57,241	158,082	36,121
U-oxide (depleted)	886,853	19,410	608,472	495	0	0	11,253	0	0
U-fluoride (natural)	9,432,470	8,109,402	5,844,985	10,827,786	9,583,669	11,140,026	10,936,114	12,210,369	12,965,093
U-fluoride (enriched)	598,763	874,251	875,831	868,652	1,000,950	934,046	1,024,148	858,807	1,252,438
U-fluoride (depleted)	479,601	4,523	125,466	0	0	58,000	0	0	147,691
U-compounds (NOS)	42,277	191,221	847,425	1,275,137	121,439	86,935	324	446,812	253,211
U-compounds (NOS) (enriched)	159,220	28,950	6	6	69,063	0	6,800	29,682	No data
U-compounds (NOS) (depleted)	4,731	294	1,666	107	0	122	245	100	248
Ores and concentrates	2,763,185	1,344,927	0	0	No data	No data	0	212,434	0
Mixture (depleted)	0	0	0	4,431	No data	No data	No data	No data	No data
Spent fuel	16,401	5,033	0	115	45	0	23	306	No data

NOS = Not otherwise stated

Source: USDOC 1995, 1997, 1999

The amount of uranium and uranium compounds exported from the United States during 1989–1993 is shown in Table 4-5. The total volume of uranium and uranium compounds exported during 1989–1993 was two orders of magnitude lower than the quantities imported during this same time period. Exports in 1996 were 5.2 million kg. Most of the foreign sales (Canada, France, Germany, Japan, South Korea, United Kingdom) occurred after the uranium entered the U.S. market as imports (DOE 1999b).

4.3 USE

Uranium has been produced for use in the commercial nuclear power industry as low-enriched metal or ceramic UO_2 fuel pellets; smaller quantities of high-enriched fuel are produced for U.S. Navy ships and for weapons manufacture (EPA 1985b; Stokinger 1981). Uranium fuel lasts months to years before refueling is needed, and then only a small fraction of the uranium has actually been fissioned, making fuel reprocessing an option used in other countries. One pound of completely fissioned uranium produces the same amount of energy as 1,500 tons of coal (Lide 1994). Depleted uranium is used in the manufacture of armor-piercing ammunition for the military, in inertial guidance devices and gyro compasses, as counterbalances for helicopter rotors, as counterweights for aircraft control surfaces, as radiation shielding material, and as x ray targets (EPA 1985b; USDI 1980). Uranium dioxide is used to extend the lives of filaments in large incandescent lamps used in photography and motion picture projectors. Uranium compounds are used in photography for toning, in the leather and wood industries for stains and dyes, and in the silk and wood industries as mordants. Ammonium diuranate is used to produce colored glazes in ceramics. Uranium carbide is a good catalyst for the production of synthetic ammonia (Hawley 1981). Additionally, uranium was used in dental porcelains for many years, but this practice has been discontinued (Thompson 1976). According to the USDI (1980), the major uses of depleted uranium in 1978 were military ammunition, 71.8%; counterweights, 11.4%; radiation shielding, 13.6%; and chemical catalysts, 3.2% although this ratio may shift to support war efforts.

4.4 DISPOSAL

Radioactive waste containing uranium is usually grouped into three categories: uranium mill tailings, low-level waste, and, in the case of spent reactor fuel, high-level waste.

Table 4-5. Export of Uranium and Compounds (in kg)

Substance	Year									
	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
U-oxide (natural)	6,302	318	0	96,748	6,196	690,449	351,169	192,296	250,443	0
U-oxide (enriched)	0	0	85	26,596	64	418,873	299,175	323,990	903,810	646,984
U-fluoride (natural)	85	0	20,175	186,530	4,231	No data	No data	0	688,873	53,800
U-fluoride (enriched)	15,698	39,262	0	175,445	90,459	No data	No data	No data	No data	No data
U-compounds (NOS)	0	9,801	12,596	8,019	0	No data	No data	No data	No data	No data
U-compounds (enriched)	28,221	0	6,609	3	0	0	66,893	418,447	10,506	99,456
U-compounds (depleted)	0	90	160	0	0	246,765	379,530	406,079	30,426	41,674
U-metal	No data	No data	No data	No data	No data	270	496	299,117	3,159	0
U-ores and concentrates	No data	No data	No data	No data	No data	59,461	0	0	0	0
Alloys, Dispersions, Ceramics[a]	No data	No data	No data	No data	No data	74,712	45,424	29,759	152,920	0
Spent fuel	0	21,576	0	0	0	No data	No data	No data	No data	No data

NOS = Not otherwise stated

[a] Alloys, Dispersions (Including Cermets), Ceramic Products And Mixtures Containing Natural Uranium Compounds, Nesoi (SIC2819)

Source: USDOC 1995, 1999

Uranium mill tailings are the residual sand and trace chemicals from the processing of uranium ore. About 150 tons of enriched uranium are required per year to fuel a 1,000-megawatt electric nuclear power reactor, and about 500 times that amount of ore is required to obtain the uranium. The total accumulation of uranium mill tailings in the United States is approximately 140 million tons (Murray 1994). Tailings from mines and mills that process other metals should also be expected to contain elevated concentrations of uranium and its progeny, although this may not be readily recognized.

Disposal methods for processed uranium tailings have been discussed by Bearman (1979). In the late 1940s, mainly unconfined disposal systems were used. Untreated solid wastes were stored as open piles and, in some cases, were spread in urban areas where they were used as fill and as the sand in concrete used to build roads, walks, drives, and concrete block, and in brick mortar. As a result of the Animas River Survey in the United States, tailing control programs were instituted in 1959 to prevent airborne and waterborne dispersal of the wastes. Confined disposal methods were devised to reduce the exposure and dispersion of wastes and to reduce seepage of toxic materials into groundwater to the maximum extent reasonably achievable. Under the Uranium Mill Tailings Radiation Control Act (UMTRCA) of 1978, the U.S. Department of Energy (DOE) designated 24 inactive tailings piles for cleanup. These 24 sites contained a total of about 28 million tons of tailings and covered a total of approximately 1,000 acres (EPA 1985b). Cleanup has been completed at some sites.

In 1977, the EPA issued Environmental Radiation Protection Standards to limit the total individual radiation dose due to emissions from uranium fuel cycle facilities, including licensed uranium mills. This standard specified that the "annual dose equivalent does not exceed 25 millirems (0.25 mSv) to the whole body, 75 millirems (0.75 mSv) to the thyroid, and 25 millirems (0.25 mSv) to any other organ of any member of the public as the result of exposures of planned discharges of radioactive materials...to the general environment" (40 CFR 190). The EPA also established environmental standards for cleanup of open lands and buildings contaminated with residual radioactivity from inactive uranium processing sites (40 CFR 192).

Low-level radioactive waste (LLRW), which may contain uranium, is disposed of at DOE facilities and at commercial disposal facilities. Since 1963, six commercial LLRW facilities have operated, but only two were in operation in 1995. A 1992 report listed the total volume of LLRW buried at all 6 sites to be approximately 50 million cubic feet (Murray 1994). Only a small fraction of the LLRW contains uranium.

The method of disposal for commercial and DOE LLRW has been shallow land burial, in which the waste is disposed of in large trenches and covered. This method of disposal relies upon natural features to isolate the waste. Although U.S. Nuclear Regulatory Commission (USNRC) regulations for LLRW disposal (10 CFR 61) permit shallow land burial, many states have enacted more stringent regulations that require artificial containment of the waste in addition to natural containment (Murray 1994).   The EPA has proposed regulations for LLRW disposal that would apply to DOE facilities (EPA 1998b).

High-level radioactive waste (HLRW) includes spent fuel, which is the uranium fuel rods that have been used in a nuclear reactor. When the fuel rods are removed from the reactor for refueling, they still contain most of the original unfissioned uranium. However, the hazard from the large activity of fission products and plutonium that have been produced in the fuel rods overshadows that of uranium. Approximately 30,000 metric tons of spent fuel have been removed from U.S. power reactors through 1994 (Murray 1994). There is currently no permanent disposal facility for HLRW in the United States; these wastes are being stored at commercial nuclear power plants and DOE facilities where they were produced. The NRC has issued standards for the disposal of HLRW (10 CFR 60), and the DOE is pursuing the establishment of an HLRW facility. Efforts to establish an HLRW facility, which began over two decades ago, have experienced many delays. A facility for the permanent disposal of HLRW is not projected to be in operation before 2010 (Murray 1994).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Elevated levels of uranium have been identified in at least 54 of the 1,517 current or former EPA National Priorities List (NPL) hazardous waste sites (HazDat 1999). However, the number of sites evaluated for uranium is not known. The distribution of these sites within the United States is shown in Figure 5-1.

Uranium is a naturally occurring radioactive element that is present in nearly all rocks and soils; it has an average concentration in U.S. soils of about 2 pCi/g (3 ppm) (du Preez 1989; NCRP 1984a). Some parts of the United States, particularly the western portion, exhibit higher than average uranium levels due to natural geological formations. Most uranium ores contain between 0.05 and 0.2% uranium, up to 1,000 times the levels normally found in soil (Uranium Institute 1996).

Uranium can undergo oxidation-reduction reactions in the environment or microbial reactions to form complexes with organic matter (Premuzic et al. 1995). The only mechanism for decreasing the radioactivity of uranium is radioactive decay. Since all three of the naturally occurring uranium isotopes have very long half-lives (^{234}U, 2.4×10^5 years; ^{235}U, 7.0×10^8 years; and ^{238}U, 4.5×10^9 years), the rate at which the radioactivity diminishes is very slow (NCRP 1984a). Therefore, the activity of uranium remains essentially unchanged over periods of thousands of years.

Uranium may be redistributed in the environment by both anthropogenic and natural processes. The three primary industrial processes that cause this redistribution are operations associated with the nuclear fuel cycle that include the mining, milling, and processing of uranium ores or uranium end products; the production of phosphate fertilizers for which the phosphorus is extracted from phosphate rocks containing uranium; and the improper disposal of uranium mine tailings (Cottrell et al. 1981; Hart et al. 1986; NCRP 1984a; Yang and Edwards 1984). Essentially no uranium is released from nuclear power plants because of the fuel assembly design and the chemical and physical nature of the uranium oxide fuel. Examples of uranium redistribution by natural processes include activities and processes that move soil and rock, such as resuspension of soils containing uranium through wind and water erosion, volcanic eruptions (Kuroda et al. 1984), operation of coal-burning power plants (coal containing significant quantities of uranium), and construction of roads and dams.

Figure 5-1. Frequency of NPL Sites with Uranium (U-238) Contamination

SITES

- ⬚ 1-2
- ▨ 3-5
- ▦ 6-7

Derived from HazDat 1998

Uranium becomes airborne due to direct releases into the air from these processes. Deposition of atmospheric uranium may occur by wet (rain, sleet, or snow) or dry (gravitation or wind turbulence) processes. The rate of uranium deposition is dependent upon such factors as particle size, particle density, particle concentration, wind turbulence, and chemical form. Data are lacking on residence times of particulate uranium in the atmosphere, although UNSCEAR (1988) assumed that it behaves like atmospheric dust, for which meteorological models exist.

Uranium deposited by wet or dry precipitation will be deposited on land or in surface waters. If land deposition occurs, the uranium can be reincorporated into soil, resuspended in the atmosphere (typically factors are around 10^{-6}), washed from the land into surface water, incorporated into groundwater, or deposited on or adsorbed onto plant roots (little or none enters the plant through leaves or roots). Conditions that increase the rate of formation of soluble complexes and decrease the rate of sorption of labile uranium in soil and sediment enhance the mobility of uranium. Significant reactions of uranium in soil are formation of complexes with anions and ligands (e.g., CO_3^{-2}, OH^{-1}) or humic acid, and reduction of U^{+6} to U^{+4}. Other factors that control the mobility of uranium in soil are the oxidation-reduction potential, the pH, and the sorbing characteristics of the sediments and soils (Allard et al. 1979, 1982; Brunskill and Wilkinson 1987; Herczeg et al. 1988; Premuzie et al. 1995).

Uranium in surface water can disperse over large distances to ponds, rivers, and oceans. The transport and dispersion of uranium in surface water and groundwater are affected by adsorption and desorption of uranium on aquatic sediments. As with soil, factors that control mobility of uranium in water include oxidation-reduction potential, pH, and sorbing characteristics of sediments and the suspended solids in the water (Brunskill and Wilkinson 1987; Swanson 1985). In one study of a stream with low concentrations of inorganics, low pH, and high concentrations of dissolved organic matter, the concentration of uranium in sediments and suspended solids was several orders of magnitude higher than in the surrounding water because the uranium was adsorbed onto the surface of the sediments and suspended particles (Brunskill and Wilkinson 1987).

The levels of uranium in aquatic organisms decline with each successive trophic level because of very low assimilation efficiencies in higher trophic animals. Bioconcentration factors measured in fish were low (Mahon 1982; Poston 1982; Waite et al. 1988) and were thought to arise from the extraction of uranium from the water or simply from the accumulation of uranium on gill surfaces (Ahsanullah and Williams

1989). In plants, uptake of uranium may be restricted to the root system and may actually represent adsorption to the outer root membrane rather than incorporation into the interior of the root system (Sheppard et al. 1983). Most of this uranium may be removed by washing the vegetable surfaces; cutting away the outer membrane will essentially result in complete removal. No significant translocation of uranium from soil to the aboveground parts of plants has been observed (Van Netten and Morley 1983).

The EPA has established a nationwide network called the Environmental Radiation Ambient Monitoring System (ERAMS) for obtaining data concerning radionuclides, including natural uranium isotopes, in environmental media. Sampling locations for ERAMS were selected to provide optimal population coverage (i.e., located near population centers). Airborne uranium concentrations and precipitation levels of uranium were quite low, in the attocurie/m^3 (10^{-3} nanoBq/m^3) and 0.006–0.098 picocurie/L (0.0002–0.004 Bq/L/m^3) ranges, respectively (EPA 1994). However, both air samples and water samples taken near facilities producing uranium ore or processing uranium were found to be higher, in the pCi/L range (Eadie et al. 1979; Lapham et al. 1989; Laul 1994; NCRP 1984a; Tracy and Meyerhof 1987). The ERAMS reports document ^{234}U to ^{238}U concentration ratios in drinking water which deviate from the equilibrium value of unity found in undisturbed crustal rock. Theories proposed to account for this natural phenomenon involve water contact with soil and permeable rock containing uranium. The ^{238}U atoms transform through ^{234}Th to ^{234}U, and any process which removes either of these radionuclides from the solid changes the ^{234}U to ^{238}U ratio. ^{238}U atoms at the solid-liquid interface which emit decay alpha particles inward may experience a kinetic energy recoil sufficient to either tear the ^{234}Th progeny from the solid or fracture the surficial solid layer making the ^{234}Th more accessible for the enhanced dissolution that thorium typically experiences relative to uranium in mineral matrices. Either process can enhance the relative ^{234}U content of the liquid. Should that liquid stabilize in another location and evaporate, the localized solids could show an enhanced ^{234}U ratio.

A large drinking water study was performed in which data from the National Uranium Resource Evaluation (NURE) program plus data prepared for the EPA (Drury 1981) were compiled for a total of over 90,000 water samples. Domestic water supplies were represented by 28,000 samples and averaged 1.7 pCi/L (2.5 µg/L) uranium, with a population weighted mean value for finished waters, based on 100 measurements, of 0.8 pCi/L (1.2 µg/L). Other studies show the population weighted average concentration of uranium in U.S. community drinking water to range from 0.3 to 2.0 pCi/L (0.4–3.0 µg/L)

(Ohanian 1989), while concentrations of uranium from selected drinking water supplies analyzed by EPA laboratories were generally <1 pCi/L (1.5 µg/L) (EPA 1985j).

The uranium content of food has been studied extensively; human daily intake has been estimated to range from 0.6 to 1.0 (0.9–1.5 µg/day) pCi/day of natural uranium. Uranium is adsorbed onto the roots of plants; thus unwashed potatoes, radishes, and other root vegetables which retain their surface membrane are a primary source of uranium in the diet. Based on consumption rates, potatoes constitute the highest dietary intake of uranium (EPA 1985). One study showed that the concentration of uranium in plant roots was proportional to the uranium concentration in the soil (NCRP 1984a), while a second study did not support a linear relationship (Mortvedt 1994).

Estimates of uranium intake for drinking water vary widely, but the mean is approximately 0.8 pCi/L uranium. Drinking water intake is in the range of 0.6–1.0 pCi/day (0.9–1.5 µg/day). Uranium intake from food and water sources is approximately equal (EPA 1991b). Compared with food and drinking water, intake of uranium by the inhalation route is small, with values reported at 0.007 pCi/day (0.010 µg/day) (Cothern 1987) and at 0.0007 pCi/day (0.0010 µg/day) (UNSCEAR 1988).

Higher rates of uranium intake have been reported for some populations. The potential for uranium intake is greater for individuals who consume foods grown in areas with elevated concentrations of uranium in the soil, and for individuals with elevated concentrations of uranium in their drinking water (EPA 1985; NCRP 1984a). Workers engaged in the extraction and processing of uranium are occupationally exposed to uranium. Industries where uranium exposure are known to have occurred are uranium mining and milling, uranium conversion and enrichment, uranium fuel fabrication, and uranium weapons production (BEIR IV 1988; Miller 1977; NCRP 1984a; West et al. 1979). Other groups with the potential for exposure due to technologically enhanced natural background radioactivity include populations involved in producing and using phosphate fertilizers, and individuals living and working near fossil fuel plants (Jaworowski and Grzybowska 1977; NCRP 1984a; Tadmor 1986; Weissman et al. 1983).

5.2 RELEASES TO THE ENVIRONMENT

Throughout this chapter, the units used to express concentration or intake of uranium are the same units reported by the authors, and are sometimes followed by converted units using the conversion factor of 0.68 pCi/μg, or other multiplier based on the information provided about the isotopic mixture. In some cases, values are expressed in mass units while in other cases values are expressed as activities. In the case of natural uranium with a fixed abundance of the three isotopes, conversion from one unit to the other is possible using the conversion factor of 0.68 pCi/g (EPA 1991b). Likewise, 1 ppm is equivalent to 1 μg/g and, therefore, to 0.68 pCi/g. Other conversion values have been used, such as 0.72 pCi/μg (EPA 1985b) and 0.67 pCi/μg (NCRP 1984a). These different values are largely accounted for by the periodic refinement of values for uranium isotopic half-lives and relative percentages in crustal rock.

5.2.1 Air

Uranium is introduced into the atmosphere primarily by resuspension of soil, but also by the intentional or accidental release of uranium from mining and milling activities, by uranium processing facilities, or by burning coal.

Natural processes that involve the weathering of crustal rock and soil can change the crustal ratio of uranium isotopes. In some cases, human activities have also altered the normal crustal distribution of naturally occurring radioactive materials, resulting in what has been termed technologically enhanced naturally-occurring radioactive material (TNORM) (NCRP 1984a). No new radioactivity is produced by the enhancement, but uranium, its isotopes, and its progeny are redistributed in such a way that real exposure or the potential for human exposure may increase. A major localized source of enhanced natural uranium can result from mining and milling operations (Table 5-1).

Uranium ore with concentrations of uranium up to 1,000 times the average concentration normally found in soil (NCRP 1984a) is removed from its natural location during open-pit, *in-situ* leach, or underground mining operations. The primary sources of airborne releases from these sources are from the actual mining, from ore crushing and grinding, from high-temperature processes such as calcining or sintering, and from yellowcake drying and packaging at the mill. Ore stockpiles can also be a source of airborne emissions (NCRP 1993).

Production in the front end of the nuclear fuel cycle (uranium mining and milling) has undergone a significant reduction since its peak in the early 1980s (ABMS 1994; EPA 1985a). Currently, mining and milling activities represent a source of minimal uranium release. In the United States in 1994, uranium was mined using *in situ* leaching methods and uranium was recovered as a by-product of the processing of phosphate ore (DOE 1995). In 1995, for the third straight year, no conventional uranium mills, which recover uranium from ores mined from the ground, were in operation in the United States (DOE 1996).

As part of the nuclear fuel cycle, uranium conversion (Stelling 1980), uranium enrichment (MMES 1985), and fuel fabrication facilities also release small amounts of uranium to the atmosphere (Table 5-1). Uranium is converted to uranium hexafluoride (UF_6) prior to enrichment. There is the potential for release of some UF_6 to the atmosphere during the conversion process or from storage of the depleted UF_6. Upon release to the atmosphere, gaseous UF_6 is rapidly hydrolyzed to UO_2F_2 (particulate) and hydrofluoric acid (gas) (Bostick et al. 1985). Uranium is enriched in the United States by the gaseous diffusion process, which produces appropriate enrichments for use in both commercial and government-operated facilities. A large amount of depleted uranium is the by-product of the enrichment process; the depleted uranium is kept in storage for further potential use (DOE 1994) or used in commercial or military applications. In one study, concentrations of uranium in the air near a uranium refinery (crude U refined to highly pure UO_3) were found to be 200 times higher than background concentrations, which are typically low (Tracy and Meyerhof 1987).

In addition to gaseous diffusion operations, the DOE is involved in other activities that release uranium to the atmosphere. These include activities at two national laboratories, sites undergoing remedial actions, weapons facilities, facilities classified as waste management operations (active facilities), or environmental restoration sites (inactive and surplus facilities). DOE facilities are present in many states with operations ranging from small laboratories to large, highly complex processing plants (Figure 5-2).

Another method by which uranium may be introduced into the atmosphere is the natural process of erosion and wind activity. In geographic areas that contain higher levels of uranium in the rocks and soil, such as the western United States, additional natural uranium is introduced into the air. Wind erosion of tailings at uranium mining and milling activities will also result in the resuspension of uranium and uranium progeny (e.g., radium-226 and radon-222) (Bigu et al. 1984; Hans et al. 1979). Approximately 5–10% of the uranium initially present ends up in the mill tailing (Uranium Institute 1996).

5. POTENTIAL FOR HUMAN EXPOSURE

Figure 5-2. Major DOE Offices, Facilities, and Laboratories
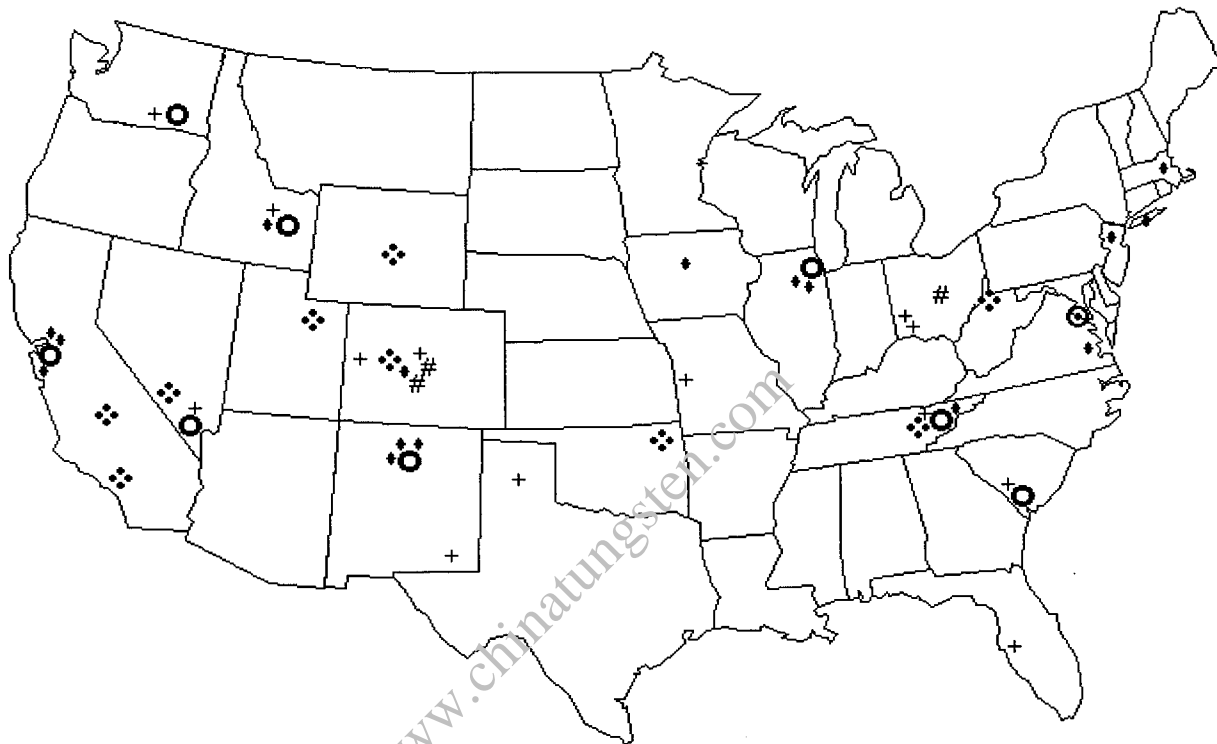
Operations Offices (⬤)
Oakland CA
Idaho Falls IH
Chicago IL
Las Vegas NV
Albuquerque NM
Savannah SC
Oak Ridge TN
Richland WA

Laboratories/National Laboratories (♦)
Lawrence Berkeley Natl
 Lab, Berkeley CA
Lawrence Livermore Natl Lab,
 Berkeley CA
Stanford Linear Accelerator
 Menlo Park CA
Natl Renewable Energy
 Lab, Golden CO
Idaho National Energy &
 Env Lab IH
Fermi Natl Accelerator
 Lab, Batavia IL
Argonne Natl Lab, Argonne IL
Ames Laboratory, Ames IA

MIT Bates Lab, Cambridge MA
Princeton Plasma Physics Lab NJ
Inhalation Toxicology Res Inst.,
 Albuquerque NM
Los Alamos Nat Lab, Los Alamos NM
Sandia Nat Labs, Albuquerque NM
Livermore CA
Brookhaven Nat Lab, Brookhaven NY
Oak Ridge Nat Lab, Oak Ridge TN
T Jefferson Natl Accelerator, Newport
 News VA
Pacific Northwest Nat Lab, Richland WA

Special Purpose Offices (❖)
Energy Technology Eng Center, LA, CA
Naval Petroleum Reserves 1&2,
 Kern Co. CA
Naval Oil Shale Reserves 1&3, Rifle CO
Yucca Mountain Project NV
Nat Petroleum Technology Office,
 Tulsa OK
Federal Energy Technology Centers,
 Pittsburgh PA, Morgantown WV
Oak Ridge Inst for Science &
 Education TN
Naval Oil Shale Reserves 2, Vernal UT
Naval Petroleum Reserve 3, Casper WY

Facilities (+)
Grand Junction CO
Rocky Flats CO
Pinellas FL
Idaho Falls IH
Kansas City Plant Kansas
 City MO
Las Vegas NV
Waste Isolation Pilot Plant,
 Carlsbad NM
Fernald Env Management
 Project, Cincinnati, OH
Miamisburg Environmental
 Managemnt Project, OH
Savannah River SC
Oak Ridge Reservation, Oak Ridge TN
Pantex Plant, Amarillo TX
Hanford WA

Field Offices (#)
Rocky Flats CO
Golden CO
Ohio (4 sites in OH, 1 site
 in New York)

Source: DOE 1999b

Volcanic eruption is another natural phenomenon that may increase the concentration of natural uranium in the air. After the eruption of Mount St. Helens, increased levels of ^{238}U were observed in rainwater at Fayetteville, Arkansas, due to precipitation of ^{238}U from the atmosphere (Essien et al. 1985; Kuroda et al. 1984). Other studies indicated that long-lived natural radionuclide (^{232}Th, ^{226}Ra, and ^{40}K) content in the ash was comparable to that of crustal material (Fruchter et al. 1980).

Uranium releases occur as a result of phosphate mining for production of phosphorous, which is used in phosphoric acid and phosphate fertilizers (NCRP 1984a). Phosphate rock from Florida, Texas, and southeastern Idaho contains as much as 120 ppm (80 pCi/g) uranium, a concentration sufficiently high to be considered as a commercial source of uranium (NCRP 1975).

Coal also contains variable amounts of uranium and other elements such as sulfur. The amount discharged to the atmosphere depends on the concentration in the coal, the amount burned, the method of combustion, the plant design, and the efficiency of fly ash recovery. Approximately 90% of the coal mass is consumed during combustion. Retained uranium concentrates in the nonvolatile fraction or ash. The uranium concentration of the fly ash, which has been quantified by several investigators (Jaworowski and Grzybowska 1977; Tadmor 1986; Weissman et al. 1983), has been found to be higher than in the original coal (NCRP 1984a), indicating that less than 90% of the uranium is released to the atmosphere. A 550 MWe plant with a coal input of 1.5 million tons/year with a uranium content of approximately 3 tons may release 0.06–0.2 Ci (90–300 kg) of ^{238}U and ^{234}U per year (NCRP 1984a), indicating that modern coal power plants release more like 10% of the uranium. A nuclear power plant by comparison releases essentially no uranium.

Raw shale oil is also known to contain uranium, and retorting operations may result in the release of uranium to the environment. Studies indicate that shale oil processing operations may increase atmospheric levels of ^{238}U and ^{234}U by a maximum of 0.04 fCi/m^3 over background levels of uranium (Gogolak 1985).

Various regulations identified in Chapter 7 are designed to limit human exposure to uranium. Guidance documents, such as the ANSI air sampling standard (ANSI 1999), are available to aid in establishing monitoring programs for assessing discharges from nuclear facilities.

5.2.2 Water

The redistribution of uranium and uranium progeny to both surface water and groundwater occurs primarily from the natural erosion of rock and soil; some redistribution also comes from the mining, milling, and, to a lesser extent, conversion portions of the nuclear fuel cycle (Table 5-1). Contamination of surface water and groundwater by effluents from uranium mining, milling, and production operations has been documented (Brandvold et al. 1981; Eadie and Kaufmann 1977; Hart et al. 1986; Swanson 1985; Yang and Edwards 1984).

Uranium is discharged to surface water and/or groundwater during mining operations. If an open-pit or underground mine extends below the water table, groundwater must be removed to permit mining operations to continue. This is usually accomplished by pumping and discharging excess water into the ground or nearby bodies of water. Since mine water is generally concentrated with uranium, its introduction into surface water bodies may produce measurable increases in uranium levels.

Waste waters from open-pit mines are typically one to two orders of magnitude greater in volume and radioactivity content than waters from shaft or underground mines (AEC 1974). A typical open-pit mine may discharge a million gallons of water daily, giving releases of approximately 0.5 mCi per day or 200 mCi per year, these releases consist of less uranium than other elements like radium and radon (AEC 1974).

Liquid releases from uranium mills have been implicated in contamination of surface water and nearby wells and groundwater (Table 5-1). Contamination of groundwater and surface water can also occur by water erosion of tailings piles (Goode and Wilder 1987; Veska and Eaton 1991; Waite et al. 1988). Since extraction of uranium ore during the milling process averages 90–95% recovery, the primary contaminants from uranium tailings disposal sites are uranium progeny (e.g., radium-226).

Generation of liquid waste from the uranium conversion process (see Table 5-1) is generally small and is handled by placing liquid effluent in lined ponds with sealed bottoms. The pond effluent is chemically neutralized to precipitate out uranium and uranium progeny in pond sludge. Water in the ponds is permitted to evaporate and sludge is disposed of as waste under controlled conditions (AEC 1974).

Liquid discharges containing uranium resulting from uranium enrichment and fuel fabrication are generally quite small (see Table 5-1).

In addition to processes of the nuclear fuel cycle, release of uranium has been detected in surface water adjacent to a radioactive waste disposal site in Massachusetts (Cottrell et al. 1981). ^{238}U measurements indicated that surface water located adjacent to the waste disposal site had concentrations of up to 155 pCi/L. Additionally, groundwater measurements of ^{238}U and ^{235}U at the disposal site were 4,400 pCi/L and 2,400 pCi/L, respectively. These values were elevated compared to values obtained in a study performed for the EPA (Drury 1981). For the EPA study, a total of 35,000 surface water samples from across the United States were analyzed; the average total uranium concentration was 1.1 pCi/L (range 0.01–582 pCi/L). Of these, 28,000 were considered samples of domestic water supplies. In this same study, 55,000 groundwater samples had a total mean uranium concentration of 3.2 pCi/L (range 0.01–635 pCi/L).

^{238}U has been detected in surface water samples at 10 of 51 hazardous waste sites and in groundwater samples at 23 of 51 hazardous waste sites where uranium has been identified in some environmental component (HazDat 1998). Examples of uranium values in groundwater and surface water include the Uravan site (uranium levels ranged from 1,500 to 16,000 pCi/L) and the tailings pond of the United Nuclear site (uranium concentrations were as high as 3,900 pCi/L). A break in the tailings pond dam in 1979 sent 93 million gallons of tailings liquid into the Rio Puerco (EPA 1988b). The distribution of Superfund NPL sites is shown in Figure 5-1.

5.2.3 Soil

Uranium is a naturally occurring radionuclide that is present in nearly all rocks and soils (soils being derived from erosion of the rocks). The average concentration in U.S. soils is about 2 pCi/g (3 ppm); however, much higher levels are found in areas such as the Colorado Plateau and lands supporting current and previous phosphate mining in Florida, Texas, and South Carolina. Lower concentrations of uranium are found in basic rocks (e.g., basalt, 0.02–0.03 pCi/g), while acidic rocks contain higher uranium concentrations (e.g., sedimentary . 1.0 pCi/g) (NCRP 1984a; Stokinger 1981). The uranium present in the rocks and soil as a natural constituent represents natural background levels.

Table 5-1. Normalized Uranium Effluent Discharges from Uranium Mining, Milling, Conversion, Enrichment, and Fuel Fabrication

Uranium-238[a]	Curies per GWy(e)[b]
Atmospheric releases	
Mining	-----
Milling	1.8×10^{-2}
Mill tailings	1.9×10^{-5}
Conversion	2.0×10^{-3}
Enrichment	9.9×10^{-4}
Fabrication	2.0×10^{-5}
Liquid releases	
Conversion	2.2×10^{-2}
Enrichment	9.9×10^{-3}
Fabrication	9.9×10^{-3}

[a]In equilibrium with progeny through U-234
[b]GWy (e) = gigawatts (10^9 watts) of electricity generated for 1 year

Source: UN 1982

Contamination of the soil can occur either from deposition of uranium originally discharged into the atmosphere, or from waste products discharged directly into or on the ground (e.g., water containing uranium from either underground or open-pit mines). Examples of industrial activities that may result in soil deposition include uranium mining and milling, uranium processing, phosphate mining, heavy metal mining, coal use, and inappropriate waste disposal.

In the process of mining uranium, when the depth of the mine is below the water table (either an open-pit or underground mine), the resulting water is pumped from the mine and often discharged directly to the ground or into surface water. For uranium milling, uranium in the ore is extracted (currently 90–95%, originally >50%) so that wastes from uranium milling contain only low levels of uranium; however, the levels of uranium progeny (e.g., radium) remain essentially unchanged. Uncontrolled erosion of these wastes from open tailings piles not protected from the weather occurred at a Shiprock, New Mexico, uranium mill site, resulting in contamination of the surrounding area (Hans et al. 1979). Uncontrolled erosion also occurred in storage areas such as the St. Louis Airport Storage Site in Missouri (Seelley and Kelmers 1985). Increased levels of uranium, radium, radon, and other decay products of uranium have also been measured around these sites, particularly in the soil. A number of controlled disposal locations on government-owned mill sites exist, but the ones identified involved uncontrolled disposal.

At various facilities that process uranium for defense programs, uranium is released to the atmosphere under controlled conditions, resulting in deposition on the soil and surface waters. Monitoring data from the area surrounding the Fernald Environmental Management Project (formerly the Fernald Feed Materials Production Center) showed that soil contained uranium released from the facility (Stevenson and Hardy 1993).

The uranium content of phosphate rock, a source of phosphorus for fertilizers and phosphoric acid for the chemical industry, ranges from several pCi/g to 130 pCi/g (several ~200 µg/g) (Boothe 1977; UNSCEAR 1977, 1982). During milling, much of the uranium content becomes concentrated in slag by-products (Melville et al. 1981). The slag by-products are often used for bedrock in the paving of roads, thus transferring the uranium-rich slag to the soil (Melville et al. 1981; Williams and Berven 1986). Because of the large amounts of phosphate fertilizer produced annually (12–15 million tons), trace amounts of uranium progeny remaining in the fertilizer result in the distribution of about 120 Ci (180 metric tons) per year over U.S. agricultural lands (Kathren 1984).

Combustion of coal is a significant source of enhanced natural radioactivity (especially combustion of coal from the western United States, which contains significantly more uranium than coal from the eastern United States). When coal is burned, some of the radioactivity is released directly to the atmosphere, but a significant fraction is retained in the bottom ash. Enhanced concentrations of uranium have been found on the ground around coal-fired power plants (UNSCEAR 1982).

Unauthorized landfill disposal of uranium processing wastes (e.g., Shpack Landfill in Norton, Massachusetts, and the Middlesex Municipal Landfill in Middlesex, New Jersey) has resulted in soil contamination (Bechtel National 1984; Cottrell et al. 1981). Also, elevated uranium concentrations have been measured in soil samples collected at 30 of 51 hazardous waste sites and in sediment samples at 16 of 51 hazardous waste sites (HazDat 1998). The HazDat data includes both Superfund and NPL sites. Elevated concentrations of uranium have been detected in soil, in surface water, in groundwater, or in all three of these environmental media from these sites. In several cases, the uranium concentrations in soils were significantly elevated. For example, uranium concentrations from the Shpack/ALI site were found to be 16,460 pCi/g (24,000 μg/g). At the United States Radium Corporation site (New Jersey), uranium concentrations ranged from 90 to 12,000 pCi/g (130–18,000 μg/g); for the Monticello site (Utah), uranium levels were reported to range from 1 to 24,000 pCi/g (1.5–36,000 μg/g) (HazDat 1998).

5.3   ENVIRONMENTAL FATE

5.3.1   Transport and Partitioning

The components of an ecosystem can be divided into several major compartments (Figure 5-3) (NCRP 1984b). None of the environmental compartments exist as separate entities; they have functional connections or interchanges between them. Figure 5-3 also shows the transport pathways between the released uranium and the environmental compartments as well as the mechanisms that lead to intakes by the population. Initial uranium deposition in a compartment, as well as exchanges between compartments (mobility), are dependent upon numerous factors such as chemical and physical form of the uranium, environmental media, organic material present, oxidation-reduction potential, nature of sorbing materials, and size and composition of sorbing particles.

Figure 5-3. Environmental Pathways for Potential Human Health Effects from Uranium
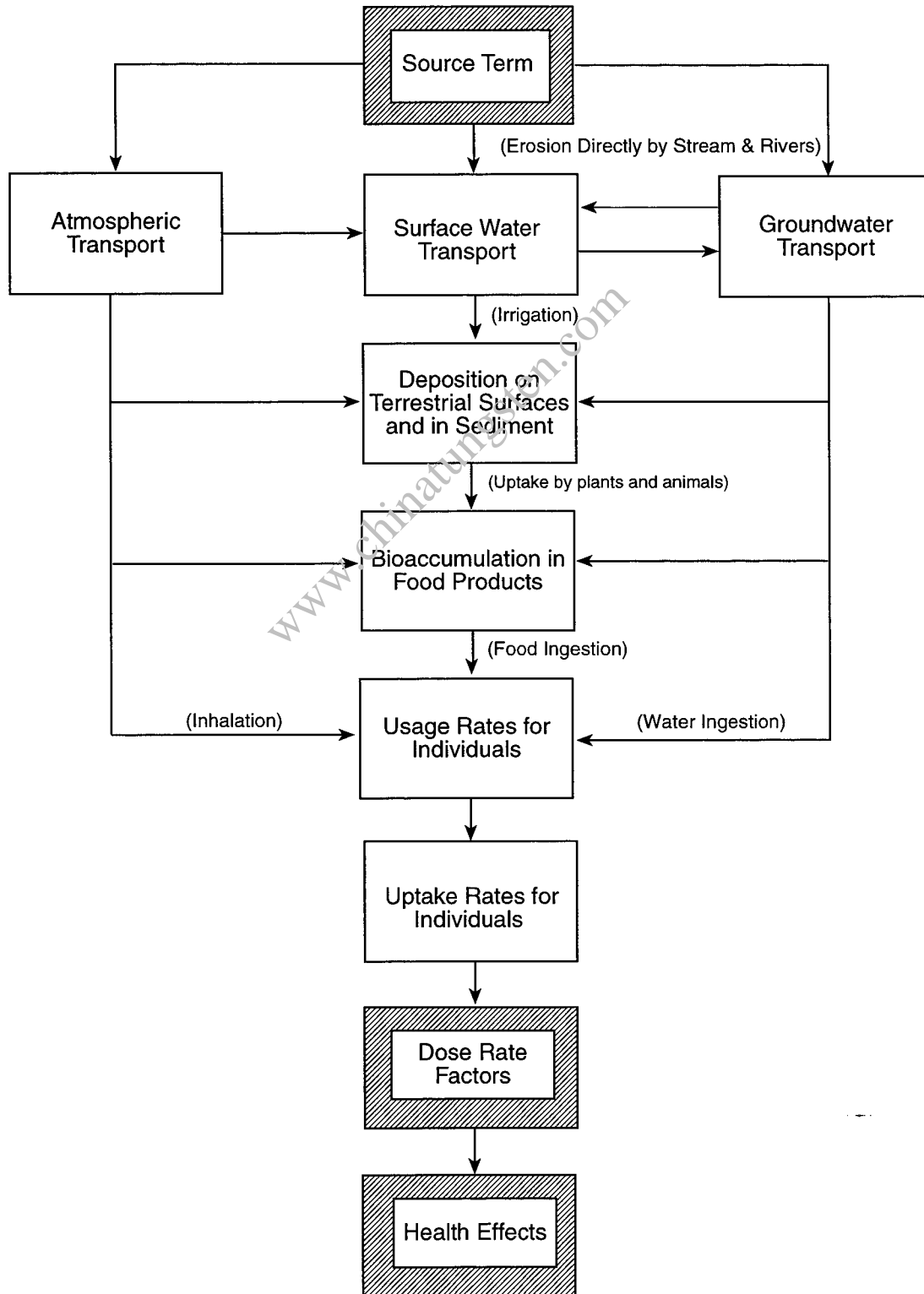
Source: NCRP 1984b

Natural processes of wind and water erosion, dissolution, precipitation, and volcanic action acting on natural uranium in rock and soil redistribute far more uranium in the total environment than the industries in the nuclear fuel cycle. However, those industries may release large quantities of uranium in specific locations, mainly in the form of solids placed on tailings piles, followed by liquids released to tailings ponds and then airborne releases, both directly from the facilities and by wind erosion of the tailings piles. Although solid releases represent the largest quantity of uranium redistribution, they remain on the facility grounds and are normally inaccessible to the public. It is the airborne (direct and wind erosion on tailings piles) and liquid releases (tailings pond runoff and water erosion of tailings) which most likely represent the important pathways for public exposure (i.e., inhalation and ingestion) if pathways can be completed.

While entrained in the air, particulate uranium represents an inhalation source for humans, the extent of which is dependent upon concentration and particle size. For particulate uranium to be an inhalation hazard to humans, the particulates must be in the size range of 1–10 µm (Bigu and Duport 1992; ICRP 1979). In some cases, the solid tailings have been removed from the site for use as fill or construction material, which can lead to external radiation exposures primarily from the uranium progeny.

Deposition of the atmospheric uranium can occur by dry deposition or wet deposition (Essien et al. 1985). Dry deposition results from gravitational settling and impaction on surfaces exposed to turbulent atmospheric flow. The rate of dry deposition is dependent upon particle size distribution, chemical form, particle density, and degree of air turbulence. Few experimental data on the particle size and residence time of uranium and uranium compounds present in ambient atmospheres are available; however, uranium particles are expected to behave like other particles for which data are available, which show that smaller uranium particles (<5 µm) travel longer distances than larger particles because of their longer residence time in the atmosphere due to their low settling velocity.

The chemical form of the uranium affects the atmospheric residence time. One uranium compound for which there are data regarding residence time and particle size is uranium hexafluoride, a soluble compound, which will hydrolyze in the atmosphere to particulate $UO_2F_2 \cdot nH_2O$ and hydrogen fluoride gas (Bostick et al. 1985). In the case of UO_2F_2, although the particles were small (<2.5 µm), its atmospheric residence time was estimated to be only 35 minutes as a result of rapid hydration and agglomeration to larger particles that have faster settling velocities (Bostick et al. 1985).

In wet deposition of airborne contaminants, the uranium is washed from the atmosphere by rain, sleet, snow or other forms of moisture. The rate of wet deposition depends upon particle size and solubility (chemical form).

Uranium thus deposited (dry or wet) will usually reside on land or be deposited on surface waters. If land deposition occurs, the uranium can incorporate into the soil or adhere to plant surfaces, be resuspended in the atmosphere as a result of wind action, or be washed from the land into surface water and groundwater. Resuspension factors are typically quite low (10^{-6}) and protective against significant exposures, but this may not apply to windy and arid areas. Resuspension into the air can be an inhalation source even after the plume or source has disappeared.

In addition to the migration of dissolved or suspended uranium due to the movement of water in the environment, the transport and dispersion of uranium in surface water and groundwater are affected by adsorption and desorption of the uranium on surface water sediments. On the other hand, migration of uranium in soil and subsoil and uptake in vegetation are usually quite local involving distances from several centimeters to several meters.

In most waters sediments act as a sink for uranium and the uranium concentrations in sediments and suspended solids are several orders of magnitude higher than in surrounding water (Brunskill and Wilkinson 1987; Swanson 1985). Factors that control the mobility of uranium from sediment to the water phase are the oxidation-reduction potential, the pH, the characteristics of complexing agents or ligands, and the nature of sorbing materials in the water. Inorganic or organic ligands that can form soluble complexes with uranium will result in mobilization of the uranium in water. However, the stability of such complexes is dependent on the pH. For example, uranium is likely to be in solution as a carbonate complex in oxygenated water with high alkalinity (Herczeg et al. 1988); however, in acidic waters (pH <6 containing low concentrations of inorganic ions and high concentrations of dissolved organic matter), the uranium is in solution as the soluble organic complex (Brunskill and Wilkinson 1987).

The oxidation-reduction potential of water is important in controlling the mobility of uranium. In anoxic waters where the aquatic environment is reductive, U(VI) will be reduced to U(IV) (e.g., changed from a soluble compound to an insoluble one). The U(IV) will be deposited into the sediment due to the insolubility of the resulting U(IV) salts (Allard et al. 1979; Herczeg et al. 1988). Mobilization and

deposition of uranium as defined by the oxidation-reduction potential of the water has been observed by several investigators (Barnes and Cochran 1993; Shaw et al. 1994). Uranium can also be removed from solution by physical adsorption processes, such as adsorption onto oxides of iron or manganese that occur as coatings on the particles of soil and sediment (Ames et al. 1982).

The mobility of uranium in soil and its vertical transport (leaching) to groundwater depend on properties of the soil such as pH, oxidation-reduction potential, concentration of complexing anions, porosity of the soil, soil particle size, and sorption properties, as well as the amount of water available (Allard et al. 1982; Bibler and Marson 1992). Retention of uranium by the soil may be due to adsorption, chemisorption, ion exchange, or a combination of mechanisms (Allard et al. 1982). Any soil property that alters the sorption mechanism will also alter the mobility of uranium in the soil. The sorption of uranium in most soils is such that it may not leach readily from soil surface to groundwater, particularly in soils containing clay and iron oxide (Sheppard et al. 1987), although other geological materials such as silica, shale, and granite have poor sorption characteristics (Bibler and Marson 1992; Erdal et al. 1979; Silva et al. 1979; Tichnor 1994).

Sorption in most soils attains a maximum when the neutral hydroxy complex of uranium is at a maximum. However, at pH 6 and above, and in the presence of high carbonate or hydroxide concentrations, uranium may form anionic complexes such as $[UO_2(OH)_4]^{-2}$. The mobility of anionic uranium complexes in soil is dependent upon the nature of the soil. For example, the decrease in sorption in soil with little anion-exchange capacity may result in increased mobility; however, increased sorption in soil with high anion-exchange may result in decreased mobility (Allard et al. 1982; Ames et al. 1982; Brookins et al. 1993; Ho and Doern 1985; Hsi and Langmuir 1985; Tichnor 1994).

Other factors also affect the mobility of uranium in soil. A field study performed near an active carbonate leach uranium mill showed that uranium in an alkali matrix can migrate to the groundwater (Dreesen et al. 1982). Uranium mobility may also be increased due to the formation of soluble complexes with chelating agents produced by microorganisms in the soil (Premuzie et al. 1995).

Uranium may be transported to vegetation by air or by water. It can be deposited on the plants themselves by direct deposition or resuspension, or it can adhere to the outer membrane of the plant's root system with potential limited absorption. Similarly, uranium deposited on aquatic plants or water may be adsorbed or taken up from the water. The plants, aquatic or terrestrial, may be eaten directly by humans or consumed

by land or aquatic animals, which provide food for humans. The uptake or bioconcentration of uranium by
plants or animals is the mechanism by which uranium in soil, air, and water enters into the food chain of
humans.

Numerous factors influence the bioaccumulation of uranium, such as the chemical and physical form of the
uranium; the season of the year and other climatic factors such as temperature, age of the organism, specific
tissue or organs involved; and the specific characteristics of the local ecosystem, such as total suspended
and dissolved solids. Bioconcentration factors for uranium have been measured by several investigators in
various aquatic organisms. Mahon (1982) measured bioconcentration factors of 1,576 and 459 in algae and
plankton, respectively. Horikoshi et al. (1981) determined bioconcentration factors in several species of
bacteria that ranged from 2,794 to 354,000. However, bioconcentration by the bacteria represented
adsorption onto the cell surfaces of the bacteria rather than true biological uptake.

Low bioconcentration factors for uranium were observed in fish. The highest bioconcentration factors
observed in fillet of rainbow trout *(Salmo gairdneri)*, white and finescale suckers *(Castastomus
catactomus),* and lake whitefish *(C. clupeaformis)* did not exceed a value of 38 (Mahon 1982; Poston 1982;
Swanson 1983, 1985). Ahsanullah and Williams (1989) concluded that the primary source of uranium for
crab *(Pachygrapsus laevimanus)* and zebra winkle *(Austrocochlea constricta)* was from water since both
fed and starved animals took up uranium at the same rate.

Uranium is transported poorly from soils to plants (Dreesen et al. 1982; Moffett and Tellier 1977). As with
aquatic organisms, the uptake of uranium by plants is dependent on the nature of the soils (soil texture and
organic content), the pH, and the concentration of uranium in the soil. Greater plant uptake is expected to
occur in soils that contain higher levels of available uranium (i.e., less sorption of uranium to soil particles
or formation of soluble uranium complexes). Swiss chard grown in sandy soils contained 80 times the
levels of uranium found in Swiss chard grown in peat soil (Sheppard et al. 1983). The uptake of uranium
by native plants, expressed as plant/soil concentration ratio (CR), grown near a mining and milling complex
was 0.8 compared to a CR of 0.09 for plants grown in soil with background levels of uranium (Ibrahim and
Wicker 1988). The effect of soil and plant type on CR values has been reviewed by Mortvedt (1994).

Reported CR values for plant/soil interaction vary widely (range, 0.0025–0.81) (Garten 1978; Ibrahim and Wicker 1988; Mortvedt 1994). Although some studies indicate that CR values in plants do not vary linearly with the concentration of uranium in the soil (Mortvedt 1994), other reported studies show a linear relationship between plant content and soil content of uranium (NCRP 1984a). It has been postulated that uranium uptake by plants may be limited to the outer membrane of the root system and may not occur on the interior of the root at all (Van Netten and Morley 1983; Sheppard et al. 1983). However, other investigators have reported the transfer of uranium from soil to the stems and leaves of plants in which the CR decreased in the following order: fruit < leaf < root (Morishima et al. 1977). Because of the higher root sorption of uranium, it has been postulated that consumption of radishes and other root vegetables grown in uranium-containing soils may be a source of human exposure (Van Netten and Morley 1983). Thorough cleansing of the plant exterior, especially if performed in conjunction with removal of the outer membrane, may remove most or all of the uranium.

5.3.2   Transformation and Degradation

5.3.2.1 Air

The presence of uranium and uranium compounds in the atmosphere results from activities associated with uranium mining, milling, processing, and use. There is limited information available regarding the abiotic transformation and degradation of uranium and uranium compounds, except for uranium hexafluoride. Uranium hexafluoride immediately hydrolyzes on contact with moisture in the air to form uranyl fluoride (UO_2F_2) and hydrofluoric acid (HF). Uranyl fluoride is hygroscopic and will absorb moisture from the air, resulting in an increased settling velocity associated with the larger particle size. The half-life of a release of airborne UF_6 is about 35 minutes (Bostick et al. 1985). Uranyl fluoride is a stable oxohalide compound of uranium which is soluble in water, a factor that will increase its mobility in the environment once deposition from the air has occurred.

5.3.2.2 Water

The principal abiotic processes that transform uranium in water are formation of complexes and oxidation-reduction reactions that have been described in Section 5.3.1. In seawater at pH 8.2, it was shown that U(IV) exists as 100% neutral hydroxo complexes, and UO_2^{+2} and U(VI) exist as 100% carbonato

complexes. In freshwater at pH 6, U(IV) was shown to exist as 100% hydroxo complexes, and UO_2^{+2} existed as 12% hydrated complexes, 18% hydroxo complexes, 8% fluoro complexes, and 60% carbonato complexes. In freshwater at pH 9, U(IV) exists as 100% hydroxo complexes, but UO_2^{+2} exists as 100% carbonato complexes (Boniforti 1987).

Oxidation-reduction conditions are important in the geologic transport and deposition of uranium. Oxidized forms of uranium (U[VI]) are relatively soluble and can be leached from the rocks to migrate in the environment. When strong reducing conditions are encountered (e.g., presence of carbonaceous materials or H_2S), precipitation of the soluble uranium will occur.

5.3.2.3 Sediment and Soil

The primary abiotic and biological processes that transform uranium in soil are oxidation-reduction reactions that convert U(VI) (soluble) to U(IV) (insoluble). Reduction of U(VI) to U(IV) can occur as a result of microbial action under anaerobic soil or sediment conditions, thereby reducing the mobility of uranium in its matrix (Barnes and Cochran 1993; Francis et al. 1989). Further abiotic and biological processes that can transform uranium in the environment are the reactions that form complexes with inorganic and organic ligands (see Section 5.3.1).

Certain microorganisms (e.g., *Thiobacillus ferrooxidans*) can facilitate the oxidation of Fe^{+2} to Fe^{+3}. The Fe^{+3} ion, in turn, can convert insoluble uranium dioxide to soluble UO_2^{+2} ions by the following reaction:

$$2Fe^{+3} \ + \ UO_2 \ 6 \ UO_2^{+2} \ + \ 2Fe^{+2}$$
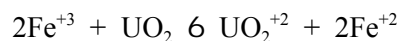
This reaction enhances the mobility of uranium in soil from mining and milling wastes (Barnes and Cochran 1993; de Siloniz et al. 1991; Scharer and Ibbotson 1982).

Uranium may be removed from the pore water of sediments under sulfate reduction conditions; microbes may control this process indirectly (Barnes and Cochran 1993).

5.4   LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

In 1973, the EPA established a nationwide network, called ERAMS, for obtaining data in environmental samples. ERAMS consists of a network of sampling stations that provide air, surface and drinking water, and milk samples that the EPA uses to obtain environmental concentrations of radioactive material. The objective of this system is to identify trends in the accumulation of long-lived radionuclides in the environment (EPA 1994). Sampling locations for ERAMS are located near primary population centers to provide optimal population coverage.

The ratio of ^{234}U to ^{238}U would be expected to be unity as long as the uranium stays locked inside undisturbed crustal rock in secular equilibrium with its progeny, but measurements show that the ratio is typically different than unity (EPA 1994). This disequilibrium occurs when the rock is disturbed by chemical or physical changes involving water. In the environment, a portion of the ^{234}U separates from the ^{238}U by what is theorized to be a physical process (alpha recoil ejection of the ^{232}Th decay product from surfaces of soil particles) or a combination of physical and chemical processes (a ^{238}U transformation at the soil particle surface fractures the surface allowing access for water to dissolve the more soluble ^{234}Th product) (NCRP 1984a). These processes can change the uranium isotope ratios in air, soil, and water.

5.4.1   Air

For airborne particles collected for the ERAMS program, ^{234}U, ^{235}U, and ^{238}U analyses are performed on semiannually composited air filters collected from continuously operating airborne particulate samplers. Following chemical separation, the uranium is quantified by α-spectroscopy.

Table 5-2 shows the results of monitoring for uranium in airborne particles for the January to June 1993 composites as published in Report 74 (EPA 1994). Results from April through June 1984 are included as well (EPA 1986). The locations of air samples with the highest total uranium concentrations were Las Vegas, Nevada; El Paso, Texas; Ross, Ohio; Lynchburg, Virginia; and Phoenix, Arizona (listed in descending concentrations of airborne total uranium). In all cases, atmospheric levels of total uranium were low, in the attocurie/m^3 range. The airborne data show ^{234}U to ^{238}U ratios that range from 1.0 to 7.4, many of which are significantly different from the one-to-one ratio found in crustal rock.

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Table 5-2. Uranium in Airborne Particles (Composites)

Location	aCi/m³					
	April-June 1984			January-June 1993		
	^{234}U	^{235}U	^{238}U	^{234}U	^{235}U	^{238}U
AK, Anchorage				11.9	0.7	9.1
AK, Juneau				12.7	0.7	10.9
AL, Mongomery	12.4[a]	1.3[a]	11.1[a]	24.6	0.4	19.3
AR, Little Rock				34.2	2.0	26.7
AZ, Phoenix				51.4	1.8	41.4
CA, Berkeley	26.6[a]	2.0[a]	19.2[a]	9.2	1.1	6.9
CA, Los Angeles	43.8[a]	2.2[a]	33.1[a]	29.8	1.8	20.4
CO, Denver	49.7[a]	1.0[a]	43.0[a]	43.2	2.0	40.1
CT, Hartford	15.8[a]	0.3[a]	11.7[a]	17.8	0.7	15.6
DE, Wilmington	14.0[a]	0.7[a]	11.3[a]	17.8	1.5	15.2
FL, Miami	17.7[a]	0.7[a]	18.0[a]	29.3	2.5	22.1
HI, Honolulu	11.7[a]	0.2[a]	6.2[a]	6.9	0.3	5.6
IA, Iowa City	23.5[a]	2.2[a]	20.3[a]	17.7	0.8	13.3
ID, Boise	35.7[a]	4.3[a]	27.3[a]	24.2	1.8	21.9
IL, Chicago	36.9[a]	0.2[a]	30.1[a]	25.1	2.2	22.6
KS, Topeka	3.9[a]	0.2[a]	2.7[a]	31.6	1.4	29.6
LA, New Orleans				17.2	1.1	17.7
ME, Augusta	17.5[a]	0.6[a]	11.5[a]	40.4	1.3	40.1
MI, Lansing	10.9[a]	0.9[a]	10.4[a]	9.7	0.4	9.6
NC, Charlotte	21.8[a]	0.6[a]	19.7[a]	31.7	1.4	25.1
ND, Bismarck	49.1[a]	0.4[a]	32.7[a]	21.6	0.9	18.5
NH, Concord	11.5[a]	0.9[a]	9.9[a]	15.5	0.7	14.6
NJ, Trenton	15.7[a]	0.0[a]	12.3[a]	9.3	0.5	9.4
NM, Santa Fe	22.1[a]	0.6[a]	18.3[a]	28.5	1.2	24.1
NV, Las Vegas	82.2[a]	0.9[a]	49.1[a]	161[b]	5.7	98.1
NY, Niagara Falls	37.9[a]	1.8[a]	49.5[a]	42.5	4.5	40.2
NY, Syracuse	2.5[a]	0.1[a]	2.0[a]	13.0	0.7	10.8
OH, Columbus	45.1[a]	2.0[a]	40.3[a]	17.1	0.5	15.3
OH, Ross				56.5	3.5	55.7
PA, Harrisburg	22.7[a]	1.4[a]	12.7[a]	11.8	0.7	11.4
SD, Pierre	20.3	1.1	17.0	13.7	0.9	12.1
TN, Knoxville	33.2	1.2	17.7	19.9	1.2	17.3
TX, Austin	39.3	1.5	33.2	11.6	0.4	9.8
TX, El Paso	132.7	3.6	105.0	77.2	1.7	65.4
VA, Lynchburg	318.6	6.3	16.5	89.3	2.8	12.1
VA, Virginia Beach	32.9	1.5	26.6	13.5	0.7	10.8
WA, Spokane	35.8	1.0	31.8	25.3	1.4	21.0

[a] Data from July-September 1984 composites
[b] Measured uranium is enriched in U^{234}, as reflected in ration of $U^{234}:U^{238}$
     = (82.2/49.1) and (161/98.1) = 1.65 > 1

aCi = attocurie, 10^{-18} curie

Source: EPA 1986d, 1994a

Uranium in airborne dust appears to result from resuspension of soil and, consequently, airborne dust has the same uranium concentration as the soil particles that produce it. Airborne dust near uranium mining or milling operations would be expected to contain higher than background levels of total uranium and have an isotope ratio the same as crustal rock as long as the surface material from which it originated had not experienced significant weathering by moisture. Some examples of airborne uranium levels near mining and milling operations when the industry was actively producing uranium ore are included below for comparison with EPA values in Table 5-2. The annual average concentration of uranium in ambient air taken near the Jackpile Open Pit mine (New Mexico) was 2.4 fCi/m^3 (Eadie et al. 1979), and the concentration of uranium in air measured near a Canadian refinery ranged between 1.3 and 134 fCi/m^3 (2–200 ng/m^3) with a geometric mean of 13 fCi/m^3 (20 ng/m^3) (Tracy and Meyerhof 1987). Air samples taken near a uranium mill tailings pile showed a uranium concentration of 1 pCi/m^3 (NCRP 1984a). Near the Paducah Gaseous Diffusion Plant in Kentucky, where uranium enrichment is performed, the maximum total air alpha activity in 1979 at one location was 0.7 pCi/m^3 (UCC 1980).

5.4.2 Water

Until the early 1980s, uranium in drinking water was not often measured except when contamination was suspected. Welford and Baird (1967) found a concentration of 0.02 pCi/L in New York City tap water. UNSCEAR (1977) reported that tap water usually contains less the 0.03 pCi/L.

A large study was performed in which data from the NURE program plus data prepared for the EPA (Drury 1981) were compiled. Over 90,000 water samples were analyzed for uranium. The total data included approximately 35,000 surface water samples that averaged 1.1 pCi/L and approximately 55,000 ground-water samples that averaged 3.2 pCi/L (NCRP 1984a). The population mean was 0.8 pCi/L, which was higher than the 0.03 pCi/L reported by UNSCEAR (1977). Ohanian (1989) reported a population-weighted average concentration of uranium in U.S. community drinking water ranging from 0.3 to 2.0 pCi/L. Another study showed that the average uranium concentrations in drinking water exceeded 2 pCi/L in South Dakota, Nevada, New Mexico, California, Wyoming, Texas, Arizona, and Oklahoma. States in which the average drinking water uranium levels exceeded 1 pCi/L are shown in Figure 5-4 (Cothern and Lappenbusch 1983; EPA 1985j). In another study based on NURE data, the mean uranium concentration in samples of more than 28,000 domestic water supplies was 1.73 pCi/L, with a median concentration range of 0.1–0.2 pCi/L (Cothern and Lappenbusch 1983). The level of uranium

Figure 5-4. Average Uranium Concentrations in Drinking Water for States Where Concentration Exceeds 1pCi/L
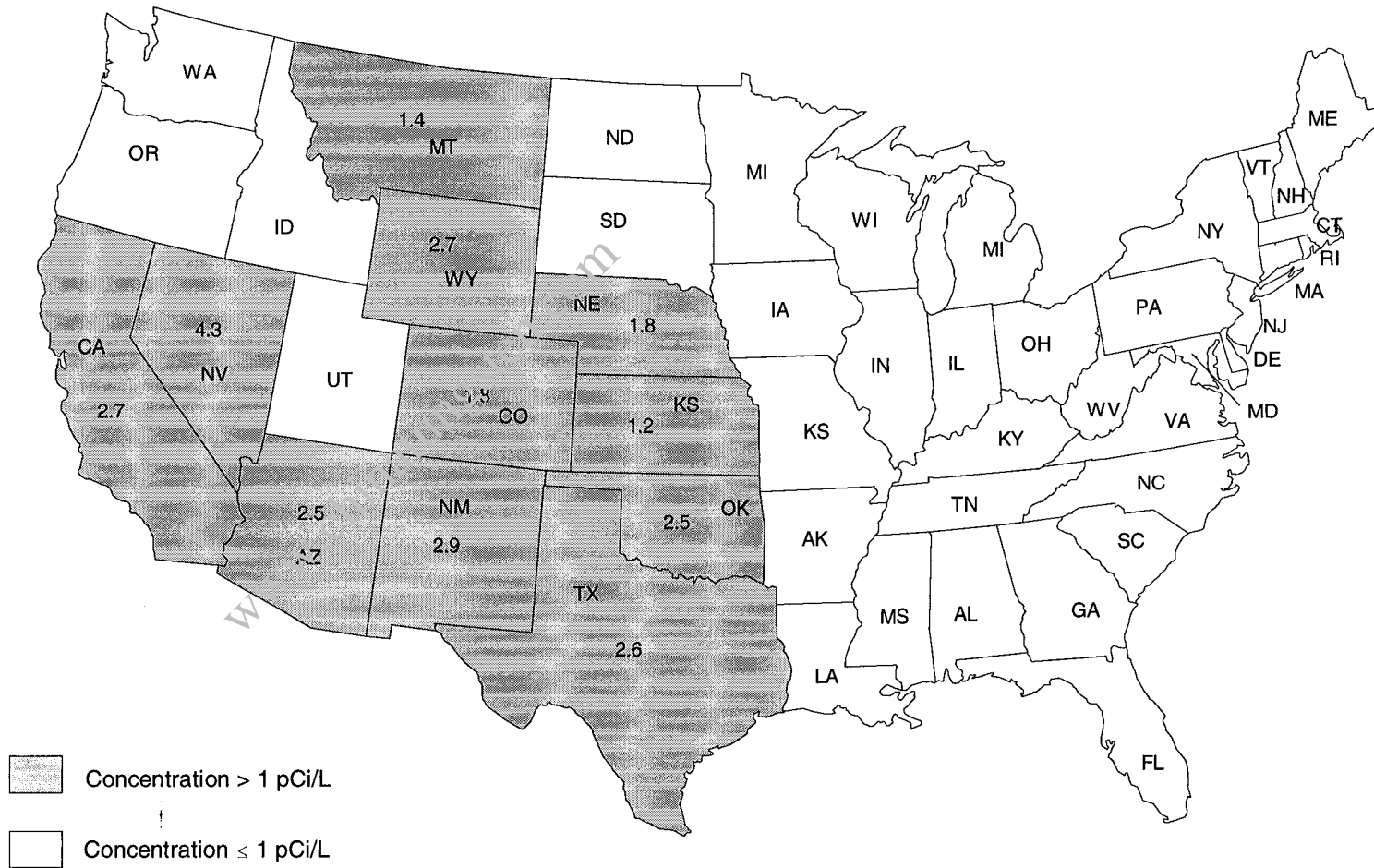
Concentration > 1 pCi/L

Concentration ≤ 1 pCi/L

Source: NCRP 1984b

in 2,228 water supplies was 10 pCi/L or more, while in 979 water supplies, the uranium concentrations were 20 pCi/L or greater. Most of these water supplies were in small towns and served less than a few thousand people (Cothern and Lappenbusch 1983;EPA 1985j).

The EPA ERAMS program measures the uranium content of precipitation. Precipitation samples are only collected during the months of March through May since these spring rain months usually contain the year's highest concentrations of uranium. The data for ^{234}U, ^{235}U, and ^{238}U for 1993 are presented in Table 5-3. The precipitation samples with the highest total uranium concentrations were obtained from Berkeley, California; Niagara Falls, New York; Santa Fe, New Mexico; Wilmington, Delaware; Salt Lake City, Utah; Jacksonville, Florida; and Denver, Colorado (listed in descending concentration of total uranium). In all cases, the uranium concentrations were low, confirming that the atmospheric content of airborne uranium is small.

In some surface waters that have been contaminated by waste discharge and in groundwaters from natural uranium-bearing aquifers, the concentrations of uranium may be higher than the average natural background levels for that area. For example, higher levels of uranium have been observed in water from Ambrosia Lake in New Mexico (uranium milling and mining) (Lapham et al. 1989), the agricultural draining and evaporation pond water of the San Joaquin Valley in California (Bradford et al. 1990), and groundwater from Rocky Flats, Colorado (Laul 1994). The concentration of uranium in creek waters that lead to the Ohio River near the Paducah Gaseous Diffusion Plant in Kentucky ranged from <0.7 to 470 pCi/L (1–700 µg/L) (UCC 1980). Mono Lake, a natural alkaline, saline lake in California, contained 185 pCi/L ^{238}U and 222 pCi/L ^{234}U during the period 1978–80 (Simpson et al. 1982). Analysis of water from the Colorado River and its tributaries during 1985 and 1986 showed that the levels of total uranium ranged from 3.4 to 60 pCi/L (Stewart et al. 1988). In the United States, the highest concentrations of uranium found in surface water and groundwater used as a source of drinking water were 582 and 653 pCi/L, respectively (Drury 1981).

Discharge of dewatering effluents from underground uranium mines and runoff from uranium mine tailings piles have contaminated surface waters and aquifers in New Mexico with elevated levels of gross alpha activity and uranium (NMHED 1989). The concentration of uranium in mine discharge water in New Mexico was 31,500 µg/L (equivalent to 22,680 pCi/L assuming the uranium content is natural uranium)

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Table 5-3. Uranium Analyses of Select Precipitation Composite Samples March–May 1993

Location	234U		235U		238U	
	pCi/L	±2σ	pCi/L	±2σ	pCi/L	±2σ
AK, Anchorage	0.073	0.005	ND	ND	0.047	0.020
AK, Juneau	0.086	0.024	0.008	0.012	0.026	0.020
AL, Montgomery	0.061	0.018	0.005	0.005	0.028	0.012
AR, Little Rock	0.083	0.021	0.001	0.004	0.032	0.013
AZ, Phoenix	0.007	0.006	0.004	0.004	0.009	0.007
CA, Berkeley	0.097	0.023	0.002	0.004	0.043	0.015
CO, Denver	0.085	0.022	0.008	0.007	0.028	0.014
CT, Hartford	0.022	0.010	0.005	0.005	0.007	0.006
DE, Wilmington	0.080	0.027	0.004	0.006	0.047	0.021
FL, Jacksonville	0.098	0.026	0.007	0.007	0.023	0.013
FL, Miami	0.063	0.023	0.010	0.009	0.032	0.015
HI, Honolulu	0.047	0.016	0.006	0.006	0.033	0.014
ID, Boise	0.054	0.018	0.004	0.005	0.038	0.015
ID, Idaho Falls	0.079	0.022	0.005	0.009	0.014	0.013
IL, Chicago	0.056	0.018	0.007	0.007	0.043	0.016
LA, New Orleans	0.053	0.016	0.004	0.004	0.036	0.014
ME, Augusta	0.071	0.021	0.003	0.004	0.034	0.015
MI, Lansing	0.076	0.022	0.002	0.005	0.037	0.015
MN, Minneapolis	0.057	0.018	0.002	0.004	0.046	0.016
MO, Jefferson City	0.063	0.017	0.002	0.003	0.032	0.012
MS, Jackson	0.064	0.020	0.006	0.006	0.030	0.014
NC, Charlotte	0.071	0.023	0.001	0.004	0.029	0.014
NC, Wilmington	0.049	0.022	0.001	0.004	0.032	0.016
ND, Bismarck	0.065	0.019	0.003	0.005	0.033	0.014
NH, Concord	0.058	0.018	0.004	0.005	0.014	0.010
NJ, Trenton	0.063	0.020	0.003	0.004	0.016	0.010
NM, Santa Fe	0.086	0.021	0.003	0.004	0.042	0.014
NV, Las Vegas	0.079	0.030	0.015	0.013	0.029	0.018

Table 5-3. Uranium Analyses of Select Precipitation Composite Samples March–May 1993 (continued)

Location	^{234}U		^{235}U		^{238}U	
	pCi/L	±2σ	pCi/L	±2σ	pCi/L	±2σ
NY, Albany	0.068	0.020	0.007	0.006	0.033	0.014
NY, Niagara Falls	0.083	0.024	0.011	0.009	0.038	0.016
NY, Yaphank	0.010	0.007	0.002	0.003	0.006	0.006
OH, Painesville	0.066	0.019	0.005	0.006	0.027	0.012
OH, Toledo	0.092	0.023	0.003	0.005	0.023	0.012
OR, Portland	0.038	0.014	ND	ND	0.022	0.011
PA, Harrisburg	0.070	0.023	0.002	0.010	0.056	0.024
SC, Barnwell	0.042	0.016	0.003	0.004	0.029	0.014
SC, Columbia	0.061	0.019	0.004	0.005	0.036	0.015
TN, Knoxville	0.063	0.019	0.003	0.004	0.034	0.014
TN, Nashville	0.055	0.019	0.009	0.007	0.027	0.013
TX, Austin	0.067	0.018	0.002	0.003	0.024	0.011
UT, Salt Lake City	0.085	0.026	0.006	0.006	0.037	0.017
VA, Lynchburg	0.068	0.024	0.007	0.009	0.042	0.019
WA, Olympia	0.077	0.024	ND	ND	0.031	0.015
WI, Madison	0.008	0.006	ND	ND	0.006	0.007

σ = Counting error; ND = Not detectable

Source: EPA 1994a

(EPA 1985j). Groundwater from an aquifer adjacent to a uranium mill tailings pile in Falls City, Texas, was also found to have concentrations of uranium above natural background levels (DOE 1994).

The concentrations of ^{234}U and ^{238}U in groundwater from Cambrian-Ordovician sandstone aquifers in Illinois range from <0.1 to 8.0 pCi/L (Gilkeson and Cowart 1987). The ratio of the activity of ^{234}U to ^{238}U ranged from 2.0 to >40. The lowest ratios were found in unconfined aquifers in primary recharge zones while ratios >20 were found in the confined zones aquifer. It was suggested that glacial recharge in unconfined zones might be responsible for the high ^{234}U to ^{238}U ratios (Gilkeson and Cowart 1987). Fifty-five groundwater samples from the Lockatong and Passaic Formation in the Newark Basin in New Jersey were analyzed during 1985–1987. These samples were found to contain 0.1–40 pCi/L total uranium, with a median value of 2.1 pCi/L (Szabo and Zepecza 1987). Uranium concentrations measured in 7 samples of groundwater from the Raymond Basin in California ranged from 5.3 to 43.7 pCi/L (Wiegand et al. 1987).

Water in a private well in Maine, thought to be of geologic origin, was reported to contain as much as 403 µg/L uranium (approximately 270 pCi/L) (Lowry et al. 1987). Elevated levels of uranium measured in waters from private wells in northern and northeastern Nebraska were thought to be due to the upward migration of uranium from bedrock and heavy use of phosphate fertilizers. Uranium values up to 110 pCi/L were measured (NEDH 1989). The concentrations of uranium in U.S. groundwaters were estimated using a conceptual model based on the geochemical and hydrological characteristics of aquifers.

The population-weighted average uranium concentration in groundwaters used as sources of drinking water in all 50 states was found to range from 0.05 to 4.6 pCi/L, with a mean value of 0.55 pCi/L (Longtin 1988). This mean is lower than the population-weighted uranium value for finished waters of 0.8 pCi/L (NCRP 1984a). Some methods which may be suitable for reducing the concentration of uranium in drinking water include lime softening, coagulation/precipitation, and filtering; however, these methods may not efficiently remove the uranium.

5.4.3 Soil

Table 5-4 shows the average concentrations of uranium in several types of rocks and soils (NCRP 1984a). The radioactivity in soils is similar to that in the rocks, usually bedrock, from which it derives. The average soil concentration of ^{234}U from Table 5-4 is 0.6 pCi/g. Since the activity of ^{234}U accounts for

Table 5-4. Uranium In Rocks and Soils

Material	pCi/g ^{238}U [a]
Igneous Rocks	
Basalt (crustal average)	0.2–0.3
Mafic[b]	0.2, 0.3
Salic[b]	1.3, 1.6
Granite (crustal average)	1
Sedimentary Rocks	
Shale	1
Sandstones	
Clean quartz	<0.3
Dirty quartz	1.0[c]
Arkose	0.3-0.7[c]
Beach Sands (unconsolidated)	1
Carbonate Rocks	0.7
Soils	0.6

[a]To obtain the series equilibrium radioactivity for total alpha, beta or approximate gamma emission
(excluding bremsstrahlung and X-rays), multiply by 8, 6, or 3, respectively.
[b]The median and mean value are given
[c]Indicates that the values are not well defined.

Source: NCRP 1975

approximately one-half of the total activity in natural uranium (see Chapter 3), the value in Table 5-4 may be multiplied by two to obtain the total uranium in soils (approximately 1.2 pCi/g).

There are wide variations from the values presented in the table, particularly in areas where uranium minerals are more concentrated. Concentrations of uranium in Louisiana soils ranged from 2.35 to 3.98 µg/g (1.6–2.7 pCi/g) (Meriwether et al. 1988), while uranium concentrations in phosphate rock in north and central Florida ranged from 4.5 to 83.4 pCi/g (6.8–124 µg/g) (EPA 1985j).

Soil samples adjacent to Los Alamos, New Mexico, taken during 1974–1977 contained total uranium in the range of 0.1–5.1 µg/g (0.067–3.4 pCi/g), with a mean concentration of 1.6 pCi/g (2.4 µg/g) (Purtymun et al. 1987). The concentrations of uranium in soils adjacent to the Hanford Fuel Fabrication Facility near Richland, Washington, that were collected during 1978–81 ranged from 0.51 to 3.1 pCi/g (0.76–4.6 µg/g), with a median value of 1.2 pCi/g (1.8 µg/g). The control samples for the Hanford Fuel Fabrication Study contained uranium at concentrations of 0.21–0.86 pCi/g (0.32–1.128 µg/g), with a median value of 0.49 pCi/g (0.73 µg/g) (Price and Kinnison 1982). Uranium in the soil within the property boundary of the Paducah Gaseous Diffusion Plant in Kentucky ranged from 3.3 to 4.8 pCi/g (4.9–7.1 µg/g), whereas off-site samples taken as far as 12 miles away contained uranium at levels of 3.8–6.0 pCi/g (6.4–9.0 µg/g) (UCC 1980). Soil monitoring data from the area surrounding the Feed Material Production Center at Fernald, Ohio, showed that the uranium concentrations within an 8-km^2 area were between 3 pCi/g and 23 pCi/g (4.5–34 µg/g) compared to an mean of 2.2 pCi/g (3.3 µg/g) for natural background levels (Stevenson and Hardy 1993). Other investigators have detected uranium levels in surface soils at the Fernald site as high as 50 times natural background levels (Miller et al. 1994).

5.4.4 Other Environmental Media

Concentrations of uranium have been determined in meat and fish (Table 5-5). The uranium content measured in tissues of cattle herds grazing in pastures close to the Rocky Flats Plant in Colorado was slightly higher than in other cattle, reflecting possible contamination from this source (Smith and Black 1975). The average concentrations of uranium in game fish (surface feeders) collected from a reservoir at locations upstream and downstream from the Los Alamos National Laboratory were 2.9 ng/g dry weight (dw) (0.0019 pCi/g) and 4.9 ng/g dw (0.0033 pCi/g), respectively (Fresquez et al. 1994). The corresponding values in nongame, bottom-feeding fish were 7.9 ng/g dw (0.0058 pCi/g) and 17.7 ng/g dw

Table 5-5. Concentrations of Uranium in Some Foods

Type of food	Uranium concentration (ng/g raw weight)	Reference
Whole grain products	1.45	NCRP 1984a
Potatoes	2.66–2.92; 15–18	NCRP 1984a; EPA 1985j
Carrots	7.7	EPA 1985j
Root vegetables	0.94–1.20	NCRP 1984a
Cabbage	4.7	EPA 1985j
Meat	0.58–1.32; 20	NCRP 1984a; EPA 1985j
Poultry	0.14–0.42	NCRP 1984a
Beef	14	EPA 1985j
Beef liver	26	EPA 1985j
Beef kidney	70	EPA 1985j
Eggs	0.23; 9.6	NCRP 1984a; EPA 1985j
Dairy products	0.08–0.31	NCRP 1984a
Cow milk	4	EPA 1985j
Milk	1–2	EPA 1985j
Fresh fish	0.43–0.85; 11	NCRP 1984a; EPA 1985j
Shellfish	9.5–31.0	NCRP 1984a
Welsh onion	69	EPA 1985j
Flour	0.25–0.68	NCRP 1984a
Wheat bread	19	EPA 1985j
Baked products	1.32–1.5; 12	NCRP 1984a; EPA 1985j
Polished rice	1.43–6.0; 15	NCRP 1984a; EPA 1985j
Macaroni	0.4–0.63	NCRP 1984a
Tea	5	EPA 1985j
Coffee	6	EPA 1985j
Parsley	60	EPA 1985j
Red pepper	5	EPA 1985j
Mustard	0.2	EPA 1985j
Table salt	40	EPA 1985j
Canned vegetables	0.09–0.18	NCRP 1984a
Fruit juices	0.04–0.12	NCRP 1984a
Canned fruits	0.18–0.29	NCRP 1984a
Fresh fruits	0.71–1.29	NCRP 1984a
Dried beans	1.5–3.67	NCRP 1984a
Fresh vegetables	0.52–0.92	NCRP 1984a

(0.012 pCi/g), respectively. The concentrations of uranium in fish muscle (dw) from a Canadian lake receiving uranium mill effluents were 7–11 times higher than in fish caught in uncontaminated lakes, but this uranium may have only been attached to the gills (Swanson 1985).

The mean uranium concentration in vegetation from Ambrosia Lake, New Mexico, (site of mining and milling activities) was measured at 0.3 pCi/g dw compared to 4 fCi/g dw for vegetation from a control site (Lapham et al. 1989). Although the concentrations of uranium in muscle from exposed cattle were indistinguishable from uranium levels in muscle from control cattle, levels of uranium in liver and kidney tissues were 4 times higher in exposed cattle than in control cattle, and levels of uranium in femur samples were 13 times higher than in controls, indicating that kidney and liver slightly bioconcentrate uranium while muscle does not (Lapham et al. 1989).

5.5   GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

General population exposure to uranium occurs by ingestion of food and drinking water and by inhalation of air. The pathways are shown in Figure 5-3.

Table 5-5 depicts uranium levels in various types of food in the United States. Measurements of normal levels of dietary ^{234}U and ^{238}U indicate that foods consumed contain about 0.3–0.5 pCi/day for each uranium isotope (0.6–1.0 pCi/day [0.9–1.5 µg/day] total uranium) (EPA 1985j; Welford and Baird 1967). Based on consumption rates, root crops such as potatoes, parsnips, turnips, and sweet potatoes contribute approximately 38% of total dietary intake of uranium (EPA 1985j).

Ingestion of food grown in the vicinity of a uranium mill may lead to an intake up to 3 pCi/day uranium (Rayno 1983). Other investigators have estimated a dietary intake of 2.86–4.55 mg/day for individuals living near a uranium mine (Yamamoto et al. 1971).

An alternate method for estimating uranium intake is to measure the daily excretion of uranium in urine and feces. Using this method in a study of 12 subjects in Utah, it was estimated that the average dietary intake for the Salt Lake City population was 4.4±0.6 µg, an intake that is higher than that reported for New York City, Chicago, and San Francisco residents (1.3–1.4 µg) (Singh et al. 1990).

Intakes of uranium in food may also increase when certain ceramic glazed dishes are used for serving or storing food (Landa and Councell 1992). Leaching occurs on contact with acidic foods or beverages. Experiments show that when a ceramic glazed plate was kept in contact with a 4% acetic acid solution for 24 hours, the concentration of uranium in the leachate was 31.8 mg/L (Landa and Councell 1992).

Uranium glazed commercial ceramic dinnerware is no longer made and sold because it was determined that the uranium is leachable by acidic foods and beverages (Landa and Councell 1992). Experiments show that when a Fiesta tableware plate was kept in contact with 20 mL of 4% acetic acid solution for 24 hours, the quantity of uranium in the leachate was 600 µg (400 pCi). Other liquids were much less effective at leaching uranium, with water giving a value over three orders of magnitude lower, and other uranium glazed ceramics were much less leachable (Landa and Councell 1992).

Uranium intakes from food in Japanese diets from two control areas ranged from 0.86 to 1.02 µg/day (Yamamoto et al. 1971). A more recent study reported a mean value of 0.71 µg/day for Japanese males from 31 prefectures (Shiraishi et al. 1992). Worldwide intake values for uranium have been reported at an average of 1 pCi/day (1.5 µg/day) (range 0.6–3.2 pCi/day [0.9–4.8 µg/day]) (Linsalata 1994).

Concentrations of uranium from selected drinking water supplies in the United States were analyzed by the EPA laboratories and found to be generally <1 pCi/L (EPA 1985j). Based on data obtained from the NURE program plus data prepared for the EPA (Drury 1981), a population-weighted average of 0.8 pCi/L uranium was determined. In another study, Ohanian (1989) reported population-weighted average concentrations of uranium in U.S. community drinking water ranging from 0.3 to 2.0 pCi/L. Considering an individual water intake of approximately 1.7 L/day, and an average intake of uranium from drinking water of 0.8 pCi/L as reported in the EPA study, the total intake of uranium for an individual from drinking water each day is approximately 1.4 pCi.

Uranium is also taken into the body by the inhalation route. The average daily intake of uranium from inhalation of air has been estimated to range from 0.007 pCi/day (0.010 µg/day) (Cothern 1987) to 0.0007 pCi/day (0.0010 µg/day) (UNSCEAR 1988). This value may be somewhat higher for persons living near sources of uranium emission. Glass makers and potters who use uranium-containing enamels may be exposed to small amounts of uranium from handling the powder or from fuming operations in glass making (Rossol 1997). In general, however, exposure to uranium from inhalation is small compared to exposure from food and drinking water.

Measurements of concentrations of uranium have been made in human tissues and body fluids resulting from consumption of food and water and from natural background sources. These are non-occupationally exposed populations. Two longtime residents of Los Alamos, New Mexico (one a smoker and one not) were shown to have uranium tissue concentrations for the skeleton (average 5.8 µg/g wet weight) and liver (average 0.08 µg/kg) in closer agreement with the Reference Man (Kathren 1997; ICRP 1975) than those reported in New York City residents (Fisenne and Welford 1986). Values of uranium in whole blood measured in New York City residents and Illinois residents averaged 0.14 µg/kg (0.09 pCi/kg) and 0.1 µg/kg (0.07 pCi/kg), respectively, compared to a mean value worldwide of 0.58 µg/kg (Fisenne 1988). Mean concentrations of uranium were measured in the organs of persons representing all age groups from different parts of the United States. The uranium values for lungs, liver, kidney, and bone (vertebrae, rib, and skeleton) were 0.5–1.17 µg/kg (0.34–0.78 pCi/kg), 0.12–0.33 µg/kg (0.08–0.22 pCi/kg), 0.39–1.00 µg/kg (0.26–0.67 pCi/kg), and 0.25–1.9 µg/kg (0.17–1.3 pCi/kg), respectively (Fisenne et al. 1988; Fisenne and Welford 1986; Singh et al. 1986b). These differences reflect dietary variations.

Workers engaged in the extraction and processing of uranium are occupationally exposed to uranium. Industries where uranium exposures are known to have occurred are uranium mining and milling, uranium conversion and enrichment, uranium fuel fabrication, and nuclear weapons production. Epidemiologic surveys were initiated in the United States as early as 1950 to study the effects of uranium exposure on uranium millers, and similar studies were performed of workers at the Oak Ridge Gaseous Diffusion Plant in Oak Ridge, Tennessee, where uranium conversion and enrichment were performed. Those studies attributed the health decrement to radon progeny and other toxicants and not directly to the uranium (BEIR IV 1988).

5.6   EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in Section 2.6, 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, and 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; they put things in their mouths; they may ingest inappropriate things such as dirt or paint chips; they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

Specific information on the exposure of children to uranium is not available. As for adults in the general population, small exposures occur from normal ingestion of food and drinking water and inhaling air. These exposures may be higher in areas with naturally high uranium soil levels or near uranium processing sites and hazardous waste sites containing uranium. A study of uranium content in bone from three age groups (<13, 13–20, 20–25 years old) reported somewhat higher uranium content in the youngest compared to the oldest age group (approximately 1.5–3-fold); however, there were only 2–4 subjects in each group and the results were not statistically significant (Broadway and Strong 1983). No information on uranium levels in amniotic fluid, meconium, cord blood, neonatal blood, or breast milk was located.

At hazardous waste sites, uranium that is found in excess of natural background levels is most likely to be in soil and presents a special hazard for young children. Hand-to-mouth activity and eating contaminated dirt will result in oral exposure to uranium. The hazard in this case depends on the form of uranium present at the waste site. Soluble uranium compounds (e.g., uranyl nitrate) are absorbed by the gastrointestinal tract to a much greater degree than insoluble uranium compounds (e.g., insoluble oxides of uranium), and a large toxicity database in animals supports the higher toxicity of the soluble forms (see Chapter 2). Uranium in soil at non-hazardous waste sites is almost entirely (>99%) in the form of insoluble oxides of uranium which have very low bioavailability.

As for adults, the potential for uranium exposure is greater for children who consume foods grown in areas with elevated concentrations of uranium in the soil and for children with elevated concentrations of uranium in their drinking water (EPA 1985; NCRP 1984a). Other home exposures are unlikely since no household products or products used in crafts, hobbies or cottage industries contain significant amounts of uranium, except in cases where uranium-bearing rocks are used in and around the home for decorative, collection, or construction purposes (ATSDR 1997)

No information is available on whether children differ from adults in their weight-adjusted intake of uranium. The fractional absorption of uranium (as uranyl nitrate and uranyl citrate) by the oral route was higher in neonatal than in adult rats and swine (Sullivan 1980b; Sullivan and Gorham 1982). In a mathematical model developed by the International Commission for Radiological Protection (ICRP) for risk assessment, one of the assumptions is that the fractional absorption of ingested uranium is twice as high in children under the age of 1 year compared to adults.

Uranium exposure to children from parents' work clothes, skin, hair, tools, or other objects from the workplace is possible if the parent uses uranium at work. However, in a comprehensive review of incidents of home contamination by workers (NIOSH 1997), no cases of uranium contamination were described.

As a radionuclide, uranium is potentially genotoxic and thus it is important to know if parental exposure to uranium could affect the developing fetus or germ cells. However, epidemiological studies of workers exposed to uranium show no evidence of genotoxic effects. This is most likely due to the very low specific activity, the low systemic absorption of uranium, and the lack of concentration of uranium in the germ cells. Genotoxic effects to parental germ cells or to a developing fetus are not likely at probable levels of exposure to uranium from the environment or at hazardous waste sites. Some uranium is stored in bone, but it is not known if this uranium is released during pregnancy and lactation, when it could result in exposure to the fetus or infant.

5.7   POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Higher rates of uranium exposure have been reported for some populations. The potential for uranium exposure is greater for individuals who consume foods grown in areas with elevated concentrations of uranium in the soil, and for individuals with elevated concentrations of uranium in their drinking water (EPA 1985; NCRP 1984a). Industries where higher exposures to uranium are known to occur include uranium mining and milling, uranium conversion and enrichment, uranium fuel fabrication, and nuclear weapons production (BEIR IV 1988; Miller 1977; NCRP 1984a; West et al. 1979). Other groups with the potentially higher exposures include persons involved in producing and using phosphate fertilizers and individuals living and working near fossil fuel plants (Jaworowski and Grzybowska 1977; NCRP 1984a; Tadmor 1986; Weissman et al. 1983). Uranium compounds were previously used in dental appliances, and individuals with dental work of this kind have potentially higher exposures (Sairenji et al. 1980).

5.8   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 uranium 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
uranium.

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 prepared.

5.8.1   Identification of Data Needs

Physical and Chemical Properties.   Pertinent data on the physical and chemical properties of
uranium and uranium compounds are available in the literature.

Production, Import/Export, Use, Release, and Disposal.   Data regarding the past and present
production (ABMS 1994; EPA 1985a) and import/export volumes (USDOC 1995) for uranium are
available. The uses of uranium and uranium compounds are well known (EPA 1985j; Stokinger 1981;
USDI 1980). Other than glazed ceramic foodware and decorative items (Landa and Councell 1992) and
dental appliances (Sairenji et al. 1980), consumer contact with uranium products is negligible. Since
uranium is not covered under SARA, Title III, manufacturers and users are not required to report releases to
the EPA. There is a lack of data on the release and disposal of uranium during mining, milling, and
chemical processing and its use during fuel cycle operations. The disposal of uranium is governed by the
U.S. Nuclear Regulatory Commission (NRC) regulations (10 CFR 61), and releases of uranium to the
environment are governed by NRC and EPA regulations (10 CFR 20, Appendix B; 40 CFR 190; 40 CFR
192). Since significant amounts of depleted uranium are used on modern battlefields, it would be useful to
have more information on the export of depleted uranium to other nations, the disposal of related wastes in

the United States, and the mass of depleted uranium released to long-distance air transport when projectiles are used against different target types.

Environmental Fate.   For solids, there is a need to determine uptake factors into edible portions of plants and not just adherance to the root structure. For the solid-liquid interface, a method is needed to determine method by which ^{234}U to ^{238}U ratio deviates from unity such that the EPA ERAMS water sample results indicate disequilibrium. Uranium enters the atmosphere in particulate form from natural sources and from uranium mining, milling, and processing. Dry or wet deposition from the atmosphere to soil and water can occur (Essien et al. 1985). Little experimental data on the particle size and residence time of uranium and uranium compounds present in ambient atmospheres are available. Additional data regarding the measured particle size of uranium compounds in ambient air, settling velocity, and knowledge of the chemical forms and lifetime of the particles in air would be useful. Although recent studies have characterized the oxidation states and chemical forms of some uranium compounds (UO_2 and UO_3) (Dodge and Francis 1994; Wersin et al. 1994), more data identifying the chemical forms of uranium in the environment are needed to better understand the fate and transport of uranium. Since significant amounts of depleted uranium are used on modern battlefields, it would be useful to have more information on the export of depleted uranium to other nations and the disposal of related wastes in the United States, as well as estimates of projectile quantities that aerosolize to a significant extent and associated downwind air contamination levels.

Bioavailability from Environmental Media.   The absorption and distribution of uranium as a result of inhalation and ingestion exposures have been discussed in Sections 2.3.1 and 2.3.2. However, quantitative data relating to physical/chemical properties such as particle size, chemical form, and degree of absorption with the bioavailability of uranium from inhaled air particles and inhaled and/or ingested soil particles, are lacking. Such studies would be useful in assessing potential public health impact of uranium to people living near a hazardous waste site.

Food Chain Bioaccumulation.   Information about uranium bioaccumulation in fish (Mahon 1982; Poston 1982; Swanson 1983; Waite et al. 1988) is available. Also data concerning levels of uranium in various foods (EPA 1985j) are available. These data indicate that uranium does not biomagnify in the food chain (Ahsanullah and Williams 1989; Morishima et al. 1977; Swanson 1983, 1985). Data on the levels of

uranium in food grown in contaminated areas are limited. Additional data are needed on whether the uptake of uranium in fish is restricted to the gills and how much actually distributes to the meat.

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

The levels of uranium in airborne particles and precipitation have been monitored since 1973 (EPA 1986, 1994). Data from several large studies of uranium in domestic water supplies are available (Cothern and Lappenbusch 1983; Drury 1981), as are data from studies of groundwater and surface water (NCRP 1984a). The primary source of recent information on the occurrence of uranium in drinking water is the National Inorganics and Radionuclides Survey (NIRS) conducted by EPA (EPA 1991). Some monitoring data are available for uranium-contaminated soils and sediments associated with the nuclear fuel cycle. Better information on background levels in the environment and speciation of uranium in soils and sediments would be useful for determining which species lead to actual public exposure.

Exposure Levels in Humans.   Although some data on the levels of uranium in human tissues exposed to natural background levels (food, water, and air) are available, few measurements have been made on the uranium content in human tissues. The principal source of information about occupationally exposed individuals is the U.S. Transuranium and Uranium Registries (USTUR) Tissue Program and database, established to document uranium levels and distribution in human tissues for occupationally exposed workers (PNL 1981). Several major database files are available. The Radiochemical file contains information about radiochemical analysis of tissue donations from occupationally exposed individuals. The Health Physics file contains bioassay and other health physics data. These two databases are regularly updated. The Medical file contains abstracted personal, medical, and clinical data; the Pathology file contains autopsy and pathology information; and the Skeletal Estimate file contains estimated actinide concentrations for unanalyzed half skeletons from donors (USTUR 1999).

Exposures of Children.   Children will be exposed to uranium in the same manner as adults in the general population (i.e. ingestion of food and water and inhalation of air). A study of uranium content in bone from three age groups (<13, 13–20, 20–25 years old) reported somewhat higher uranium content in the

youngest compared to the oldest age group (approximately 1.5–3 fold); however, there were only 2–4 subjects in each group and the results were not statistically significant (Broadway and Strong 1983). Since the skeletons of children are growing (higher rate of bone formation), it is possible that a higher fraction of circulating uranium will be deposited in bone than in adults. Further information is needed on bone levels of uranium in children to determine if this is the case. Uranium is found in all soil, and at potentially higher levels at some hazardous waste sites. Since children may have oral exposure to soil through hand-to-mouth activity, bioavailability studies of uranium in soil may be useful to assess the risk of this type of exposure. There is some evidence that neonatal animals absorb uranium in the gastrointestinal tract to a greater extent than adults. Experiments to confirm this finding and to determine how long into maturation a difference exists would help refine risk assessment for uranium exposure in children.

Exposure Registries.   A voluntary exposure registry, the U.S. Transuranium and Uranium Registry (USTUR) for occupationally exposed individuals, was established at Richland, Washington, in 1968 as the National Plutonium Registry for investigation of the potential hazards for occupational exposure to uranium. In 1971, additional radiochemistry support was provided by Los Alamos National Laboratory. The United States Uranium Registry was created as a separate entity in 1978, and the two registries operated in parallel until 1987, when a single director was given responsibility for both registries. In 1992, the management and operation of the registries was combined at Washington State University under a grant from the U.S. Department of Energy. The primary goals are to develop information on the distribution and dose of uranium and transuranic elements in humans, providing data for verification or development of radiation protection standards, and to determine and evaluate health effects due to exposure to these radioactive elements.

5.8.2 Ongoing Studies

The Federal Research in Progress database lists ongoing studies about environmental effects of uranium (FEDRIP 1999). These are shown in Table 5-6.

Table 5-6. Ongoing Studies on Environmental Effects of Uranium

Investigat	Affiliation	Study	Sponsor
Lioy P	New Jersey University of Environmental and Occupational Health Sciences Institute, Piscataway NJ	Refinement of exposure/dose models. Comparison of bioavailability of elemental waste laden soils using *in vivo* and *in vitro* analytical methodology	DOE
Davidson P	Stanford University Palo Alto CA	Sorption of heavy metals and radio-nuclides on mineral surfaces in the presence of organic co-contaminants	DOE
Gilliland F	Univ of New Mexico Albuquerque,NM	Improved exposure assessment using ^{210}Pb measurements for epidemiological study	NIH, Natl Center For Res Resources
Chaney RL	Beltsville Agr Res Center Beltsville, MD	Phytoremediation technology for cleanup of radionuclide contaminated sites	U.S. Department of Agriculture, Agricultural Research Service
Harsh JB	Washington State U, Agriculture and Soils, Pullman, WA	Physical chemical state and plant availability of uranium in contaminated mine soil	U.S. Departmentt of Agriculture Cooperative State Res Service
Huang JW	Phytotech, Monmouth Junction, NJ	Phytiremediation of uranium contaminated soils	DOD, Army
Gibson DK	Australian Nuclear Science and Technology Organisation, Palmerston, N Territory, Australia	Water pollution by a uranium mine	DOE
Jeffree RA	Australian Nuclear Science and Technology Organisation, Menai, New South Wales, Australia	Biological impacts of uranium mining	DOE
USTUR	Washington State University	Various studies including determining relationships between uranium concentrations of body organs and between organs and body burdens in healthy and non-healthy individuals	DOE
Beasley T	Oregon State U College of Oceanography	Cycling of transuranic and other long-lived radionuclides in Columbia River	USDOE Energy Research
Barton L	U of New Mexico Albuquerque NM	Mechanisms of metal transformation in bacteria	NIH, Natl Inst of Gen Med Science
Faison B	Oak Ridge National Laboratory	Crada: biosorption of uranium.	USDOE Environmental Restoration and Waste Management

DOD = Department of Defense; DOE = Department of Energy; USTUR = United StatesTransuranium Uranium Registry

Source: FEDRIP 1999; USTUR 1999

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring uranium in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify uranium. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect uranium in environmental samples are the methods approved by federal agencies such as EPA, DOE, and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by a trade association such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to lower detection limits, and/or to improve accuracy and precision.

Most of the equipment and analytical methods described in this chapter for field measurements and, to a lesser extent, laboratory sample analysis are summarized in the Multi-Agency Radiation Survey and Site Investigation Manual (MARSSIM 1997). It is anticipated that its companion manual, the Draft Multi-Agency Radiological Laboratory Analytical Protocols (MARLAP) manual, will robustly describe relevant analytical equipment and methods, and be available for public comment in 2000.

6.1 BIOLOGICAL MATERIALS

Uranium can enter the human body through inhalation, ingestion, or penetration through the skin. Measurement of the quantities of uranium in the body can be performed by two primary methods, *in vivo* measurements and *in vitro* measurements. These types of measurements are called bioassays. *In vivo* techniques measure the quantities of internally deposited uranium directly using a whole body counter while *in vitro* techniques permit estimation of internally deposited uranium by analysis of body fluids, excreta, or (in rare instances) tissues obtained through biopsy or postmortem tissue sectioning (NCRP 1987) (USUTR 1999). Some of these analytical methods are summarized in Table 6-1.

6.1.1 Internal Uranium Measurements

In vivo or direct measurements of uranium in the body are made with radiation detector systems and associated electronics called whole body counters that measure radiation as it leaves the body from internally deposited uranium. *In vivo* assays are the most direct method of quantifying internally deposited

radioactive materials. However, not all radionuclides emit radiations than may be detected outside the body (^{234}U and ^{238}U, for example) (NCRP 1978). The most commonly used detectors for uranium *in vivo* counting are sodium iodide, phoswich (NaI and CsI sandwich), and hyperpure germanium which measure the gamma rays emitted during uranium decay (DOE 1988). Since the gamma radiations emitted from uranium and a number of its progeny are the same as those emitted by uranium in the environment, shielded rooms are normally used to house the uranium internal monitoring equipment to ensure that background radiation is as low as possible (DOE 1999; Parrington et al. 1996) . Although whole body counters may be made in many configurations, a chest counter is usually used for inhaled uranium. *In vivo* analysis is widely used throughout the nuclear industry, both commercial and government, for quantifying levels of insoluble uranium in the body. *In vitro* analysis (see Section 6.1.2) is often used in conjunction with whole body counting for monitoring workers handling uranium (DOE 1988).

In vivo counting systems are calibrated using tissue-equivalent phantoms. These phantoms have shapes similar to the human torso and are made of polystyrene or other tissue equivalent material. Standard uranium sources of known activity are inserted into the phantom at locations where uranium would be expected to accumulate in a human body (DOE 1988). Relationships are determined between the uranium activity measured by the detection system and the known activity in the phantom (DOE 1988; HPS 1996).

There are limitations associated with *in vivo* counting uranium measurements. First, soluble uranium is readily excreted, with fractions retained for varying periods in the bone and kidney, so detectability depends on factors such as intake quantity, chemical and physical form, biodistribution fraction, time since intake, background uranium contribution, analysis time, and detection system efficiency. Second, only the ^{235}U isotope can be detected using the sodium iodide or hyperpure germanium detectors, since ^{234}U and ^{238}U decay does not result in emission of gamma rays, which are required for detection by sodium iodide and hyperpure germanium detectors (NCRP 1987). In such cases, indirect *in vitro* methods can be used for measuring uranium in urine or feces (DOE 1988; HPS 1996). Analytical equipment and procedures vary widely among laboratories and often require individual-specific input (NCRP 1987). The Minimum Testing Level (MTL) of 0.81 nCi ^{235}U (lung) has been established as a performance level to which laboratories are expected to adhere for *in vivo* detection (HPS 1996).

6.1.2   *In Vivo* and *In Vitro* Uranium Measurements

In vitro uranium analyses are routinely performed in support of a personnel monitoring program, or in cases where the size of an operation does not justify the cost of whole body counter facilities. These analyses are usually done on urine samples, but other types of body materials may also be used (e.g., feces or blood).

Urinalysis is effective for analysis of transportable or soluble uranium. A fraction of insoluble uranium also appears in the urine (DOE 1988).

The excretion of uranium in fecal material results primarily from intakes by ingestion, and includes uranium swallowed after inhalation. Usually, uranium will appear in feces within hours after intake thus providing a rapid means of determining whether an intake has occurred. Fecal analysis requires prechemistry preparation that includes ashing of the sample, cleaning by co-precipitation, and solvent extraction followed by electrodeposition. Alpha spectroscopy is then performed (Singh and Wrenn 1988). Urinalysis is typically favored over both fecal and blood analysis because it is generally more sensitive and less costly, and because fecal analysis provides no uptake or retention information and blood analyses is invasive.

Several methods that do not require chemical separation are available for measuring uranium in urine (in units of total mass or total activity). These methods include spectrophotometric (total mass), fluorometric (total mass), kinetic phosphorescence analysis (KPA) (total mass), and gross alpha (total activity) analyses (Wessman 1984). The most widely used methods for routine uranium analysis are α-spectrometry and liquid scintillation spectrometry. These methods utilize the natural radioactivity of uranium and are sensitive and require little sample preparation. Photometric techniques such as fluorometry and phosphor-ometry are less widely used, but kinetic phosphorescence analysis is becoming more widely used. Measure-ments of total uranium do not provide the relative isotopic abundance of the uranium isotopes, but this may only be important when converting between activity and mass when the isotopic ratios are uncertain.

If quantification of an individual uranium isotope is needed (e.g., ^{234}U, ^{235}U, or ^{238}U), the most commonly used methods require chemical separation followed by α-spectrometry, or chemical separation and electrodeposition followed by α-spectrometry (see Table 6-1). Mass spectrometric methods have emerged as sensitive, reliable techniques for determining uranium isotopes at low concentrations. Inductively coupled plasma-mass spectrometry (ICP-MS) requires sample preparation, but is rapid and is becoming less expensive (Twiss et al. 1994).

Uranium may also be measured in fecal material using the same methods identified above for urinalyses, except that this matrix requires extensive preparation. For α-spectroscopy, this includes ashing of the sample, cleaning by co-precipitation, and solvent extraction followed by electrodeposition and α-spectro-scopy (Singh and Wren 1988). In the other methods, electrodeposition is replaced with an equipment-specific step, such as direct injection for ICP-MS and mixing with a scintillation cocktail for liquid scintillation.

Table 6-1

Table 6-1. Analytical Methods for Determining Uranium in Biological Samples

Sample matrix	Sample preparation	Analytical method	Detection limit	Accuracy	Reference
Urine	Enrichment on an anion exchange column, solvent extraction	α-Counting (total uranium)	Not given	92% at 0.9 dpm spike	Hinton 1983
	Spiked urine wet ashed; sample clean-up by coprecipitation, solvent extraction and electro-deposition	α-Spectrometry (total uranium)	0.02 dpm/L for ^{238}U [a]	78%	Singh and Wrenn 1988
	Sample treated with HCl and H_2O_2, clean-up on anion exchange resin column	Spectrophotometric (total uranium)	5 µg/L	87% at 11 µg/L	Kressin 1984
	Sample wet ashed, enrichment on anion exchange column, purification by solvent extraction	Fluorometric (total uranium)	0.1 µg/L	75% at 0.1–100 µg/L	Dupzyk and Dupzyk 1979
	Sample digestion with $K_2S_2O_8$ and dissolution in water	Laser-induced fluorometry (total uranium)	1 µg/L	86% at 7 µg/L	Hinton and White 1981
	Wet-ashed; solubilized	KPA	~0.050 µg/L	90–110	Birkenfeld et al. 1995
	Acid digestion, purification by coprecipitation and column chromatography	NAA (isotopic quantification)	<6 µg/L	80% at 2 µg added uranium	Pleskach 1985
	Sample with ^{232}U spike wet ashed, clean-up by anion exchange chromatography	Isotope dilution-MS (isotopic quantification)	5 pg (10^{-6} µg) uranium (total chemical blank)	No data	Kelly et al. 1987
	Acidification; dilution	ICP-MS	3 ng/L	No data	Karpas et al. 1996
Soft tissue	Spiked tissues wet ashed; clean-up by coprecipitation, solvent extraction and electrodeposition	α-Spectrometry (total uranium)	0.03 µg/ sample	85–92%	Singh and Wrenn 1988

Table 6-1. Analytical Methods for Determining Uranium in Biological Samples (continued)

Sample matrix	Sample preparation	Analytical method	Detection limit	Accuracy	Reference
Soft tissue	Spiked sample wet digested; purification by anion exchange; loaded into a single ion-exchange bead as a point source for MS	Isotope dilution-MS (isotopic quantification)	<5 pg/L	77%	Kelley and Fassett 1983
Bones	Spiked sample dry ashed; clean-up by coprecipitation, solvent extraction and electrodeposition	α-Spectrometry (isotopic quantification)	0.03 μg/ sample	60–93%	Singh and Wrenn 1988; Singh et al. 1984
Bone ash	Spiked sample wet ashed; clean-up by solvent extraction and electrodeposition	α-Spectrometry (isotopic quantification)	0.4 μg/kg for ^{238}U	>95%	Fisenne et al. 1980
Feces	Spiked sample dry and wet ashed; clean-up by coprecipita-tion, solvent extraction and electrodeposition	α-Spectrometry (isotopic quantification)	0.03 μg/ sample	58%	Singh and Wrenn 1988
	Sampled dried; wet-ashed; homogenization; dissolution in acid	ICP-MS	3 ng/g	No data	Twiss et al. 1994
Lung, liver, kidney, thyroid, bone	Sample wet or dry ashed, irradiation	^{3}He neutron analyzer	0.04 ng/ sample	No data	Gonzales et al. 1988

[a] This detection limit was reported by Melgard 1988.

ICP = inductively coupled plasma spectrometry; KPA = kinetic phosphorescence analysis; MS = mass spectrometry; NAA = neutron activation analysis

The MTL for ^{234}U, ^{235}U, and ^{238}U using α-spectroscopy is 0.54 pCi/L in urine. An acceptable minimum detection activity of 20 µg/L of urine has also been established for natural uranium based on mass determination (HPS Standard N13.30 1996). Determining the accuracy and precision of the quantification methods for biological materials by either *in vivo* or *in vitro* methodologies requires that standard, certified sources with known concentrations of appropriate radionuclides be available for calibrations. The primary source of certified standards is the National Institute of Standards and Technology (NIST) (Inn 1987). An aqueous solution of uranium containing 10 mg/mL (SRM 3164) standard stock solution is available, as are solutions of ^{232}U (1.1 nCi/g [40 Bq/g]) (SRM 4324) and ^{238}U, "natural uranium," (6.7 nCi/g [250 Bq/g]) (SRM 4321B) (NIST 1995). Standard Reference Materials of human lung (SRM 4351) and human liver (SRM 4352) are also available from NIST.

6.2   ENVIRONMENTAL SAMPLES

Two types of methods are commonly used for measurement of uranium in environmental samples. The first are field surveys using portable survey instruments, and the second is analysis of samples procured in the field that are returned to the laboratory for quantification.

6.2.1   Field Measurements of Uranium

Uranium measurements in the field are typically qualitative in nature in that the instruments simply respond to alpha emissions, regardless of their isotopic origin. However, the levels can be measured quantitatively if key parameters are known, such as relative abundances of all alpha-emitting isotopes present, the thickness of the layer being assessed, and the detection efficiency of the instrument for the type of surface being assessed. Measurements in the past have typically been made using a portable, hand-held alpha scintillation detector (e.g. ZnS) equipped with a count rate meter, which detects alpha radiation while discriminating against beta-emitters in the same area. However, the need for low detection limits in radiological remediation efforts has found a more suitable and sensitive instrument in the large-area gas-flow proportional counter. These instruments can be carried by an individual or attached to a holder for maintaining a selected surface-to-detector distance. The latter method can be integrated into a system which moves along a surface at a predetermined velocity recording spatially-related real-time data for later graphical imaging of absolute surface activity distributions (DOE 1988). These surveys can also be performed on people whose skin or clothing is contaminated. Survey instruments can provide a quick

estimate or a measure of the level of activity that might be present. However, more accurate measurement
of uranium activity may require that samples be taken for laboratory analyses. Under normal usage, the
lowest level of uranium that can be reliably detected using an alpha scintillation survey meter is
200–500 disintegrations per minute/100 cm^2 (0.09–0.23 nCi/100 cm^2) (DOE 1988); however, detection of
levels several time lower is practical with gas flow proportional counters, especially when used in the
integrate mode. Detection capability varies with the type of detector used, the active area of the probe, the
electronics, etc.

Several limitations are associated with the measurement of uranium by portable survey instruments. First,
the uranium must be present on the surface of the material being surveyed. Since uranium decays by
emission of α particles, which travel only short distances in materials, any uranium that is imbedded in the
surface being surveyed will be partially or completely masked . Secondly, when performing surveys, it
must be possible to place the detector very close to the surface being surveyed (i.e., approximately one-
quarter of an inch) (DOE 1988, 1994), and uneven surfaces that are unintentionally touched can tear the
detector window, disabling the instrument. Additional information is available in MARSSIM (1997) on the
use and usefulness of field survey instruments.

6.2.2 Laboratory Analysis of Environmental Samples

Analytical methods for measuring uranium in environmental samples are summarized in Table 6-2. The
available methods can be divided into two groups: chemical methods to determine the total mass of uranium
in a sample, and radiological methods to determine amounts of individual isotopes. Environmental media
that have been tested for uranium include air filters, swipes, biota, water, soil, and others; a full range of
laboratory analysis methods has been used to quantify the total uranium or its individual isotopes. The
equipment and methods tend to improve over time. The radiological analysis methods primarily use high
resolution α-spectroscopy, although gamma spectroscopy is usable with great care. The chemical methods
which are often used include spectrophotometry, fluorometry, and kinetic phosphorescence, with the recent
addition of various mass spectrometer applications (ICP-MS, AES-MS, and accelerator-MS). If
conversions between mass and activity are to be made accurately, prior knowledge of the relative abun-
dance of the various uranium isotopes must be available or measured radiologically. A few media-specific
methods which have been used successfully for measuring uranium concentrations in environmental
samples are described below. The current trend, however, is away from prescriptive methods and toward

Table 6-2. Analytical Methods for Determining Uranium in Environmental Samples

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Accuracy	Reference
Air	Air particulate collection on glass fiber filter; digestion in HNO_3	ICP-MS (total uranium)	0.1 µg/L in final solution	No data	Boomer and Powell 1987
Air	Spiked air particulate dry and wet ashed; dissolution; coprecipitation with iron hydroxide and Ca oxalate, purification by solvent extraction and electrodeposition onto platinum	α-Spectrometry (isotope quantification)	0.02 dpm/L[b] for ^{238}U in solution	No data	Singh and Wrenn 1988
Air	Sample collection on cellulose filters; ashing; extraction with triisooctylamine; purification by anion exchange chromatography and coprecipitation.	α-Spectroscopy	0.015 pCi	No data	EPA 1984b
Air	Collection on cellulose filters	INAA	0.03 µg per filter	No data	Querol et al. 1997
Rainwater	Coprecipitation with iron hydroxide, radiochemical, ion-exchange and solvent extractive purification, and electrodeposition on steel	α-Spectrometry (isotope quantification)	0.02 dpm/L for ^{238}U in solution[a]	68%	Jiang et al. 1986
Drinking water	Direct analysis or concentration by co-precipitation and solvent extraction; fusion	Fluorometry (total uranium)	<20 µg/L (direct); 0.1 µg/L (cleaned)	104% (cleaned)	Krieger and Whittaker 1980 (EPA Method 908.1)
Drinking water	Concentrated by co-precipitation; separation; clean-up by ion-exchange	Gross α-counting (total uranium)	1 pCi/L	92.6%	Krieger and Whittaker 1980 (EPA Method 908.0)

Table 6-2. Analytical Methods for Determining Uranium in Environmental Samples (continued)

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Accuracy	Reference
Drinking water	Sample chelation in EDTA; addition of Fluron	Laser-induced fluorometry	0.08 µg/L	100% at 1 µg/L	Velten and Jacobs 1984 (EPA Method 908.2)
Natural waters	Sample concentration by cation-exchange resin, separation by ion-exchange resin and complexation with Arsenazo III	Spectrophotometry (total uranium)	0.1 µg/L	80%	Paunescu 1986
Water	Sample fusion with NaF and LiF	Fluorometry (total uranium)	5 µg/L	117.5% at 6.3 µg/L	ASTM 1986 (ASTM Method D2907-83)
Water	Coprecipitation with iron hydroxide; purification by ion-exchange chromatography and electrodeposition	α-Spectrometry (isotope quantification)	0.02 dpm/L	97.7–108% at 0.028–0.044 Bq/L	ASTM 1986 (EPA Method D3972-82)
Water	Solvent extraction; coprecipitation with $BaSO_4$; dissolution in $HClO_4$; reprecipitation with TiF_3; filtration	α-Spectrometry (isotope quantification)	0.02 dpm/L[b] for ^{238}U	No data	Stewart et al. 1988
Water	Preconcentration by complexation with oxine and adsorption on activated carbon	NAA (total uranium)	3 µg/L	>80%	Holzbecher and Ryan 1980
Water	Preconcentration by ion-exchange chromatography; purification by ion-exchange and solvent extraction	NAA (^{235}U and ^{238}U)	No data	No data	Gladney et al. 1983
Water	Extraction by ion-exchange; dissolution in low oxygen solvent; irradiation	Delayed neutron analysis (total uranium)	0.4 µg/L	No data	Zielinski and McKown 1984

Table 6-2. Analytical Methods for Determining Uranium in Environmental Samples (continued)

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Accuracy	Reference
Water	Wet-ashed; reaction with complexant	Pulsed-laser phosphorimetry	0.05 ppb	103 (average)	ASTM 1994 (Method 5174-91)
Water (uranyl nitrate)	Solvent extraction	Fluorescence spectroscopy	6.1-10.5 ppm	No data	ASTM 1994 (Method D4763-88)
Groundwater	Separaration on resin; automated	FI-ICP-MS (isotope quantification)	0.3 ng/L for ^{238}U	±1.8%	Aldstadt et al. 1996
Groundwater	Separation and concentration on two HPLC columns; complexation with Arsenazo III	Spectrophotometry (total uranium)	1–2 µg/L	No data	Kerr et al. 1988
Water and wastes	Acid digestion; filtration (dissolved); acid digestion (total recoverable)	ICP-MS (total uranium)	0.1 µg/L	105–110%	Long and Martin 1991 (EPA Method 200.8)
Seawater	Uranium enriched by chelation with APDC in the presence of Fe^{+2}, complexation with APDC followed by adsorption on activated carbon	X-ray fluorescence (total uranium)	0.56–0.64 µg/L	No data	Nagj et al. 1986
Seawater	Oxine addition	Cathodic stripping voltametry (total uranium)	0.02–0.2 nM	No data	Van den Berg and Nimmo 1987
Sediment	Sediment dried and well-mixed; dissolution in HCl-HClO$_4$-HF; purification by coprecipitation, ion exchange and electrodeposition	α-Spectrometry (isotope quantification)	No data	No data	Anderson and Fleer 1982
Soil	Soil leached with HCl-HNO$_3$-HF; purification by ion-exchange, and solvent extraction, and electrodeposition	α-Spectrometry (isotope quantification)	No data	No data	Golchert et al. 1980

Table 6-2. Analytical Methods for Determining Uranium in Environmental Samples (continued)

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Accuracy	Reference
Soil	Dissolution in HCl-HNO$_3$-HF; purification by coprecipitation, solvent extraction and electrodeposition	α-Spectrometry (isotope quantification)	0.03 μg/sample	67%	Singh and Wrenn 1988
Soil, sediment, and biota	Ashing; fusion with KF and K$_2$S$_2$O$_7$; purification by extraction with triisooctylamine, anion exchange chromatography and coprecipitation.	α-Spectroscopy	No data	No data	EPA 1984b
Soil, sediment, and biota	Ashing; extraction into triisooctylamine, strip from triisooctylamine with HNO$_3$ and coprecipitation with lanthanum.	gross α-Spectroscopy or α-Spectroscopy	No data	No data	EPA 1984b
Minerals	Dissolution in HNO$_3$-HF-HClO$_4$; purification by solvent extraction	Laser fluorometry (total uranium)	No data	No data	Veselsky et al. 1988
Low level radioactive waste	Dissolution; purification by coprecipitation, ion-exchange and electrodeposition	α-Spectrometry (isotope quantification)	0.03 dpm	No data	Wessman 1984
Building materials and lichen	Wet ashing with HNO$_3$-H$_2$O-HF; purification by coprecipitation, solvent extraction and electrodeposition	α-Spectrometry (isotope quantification)	0.03 μg/sample	54–73%	Singh and Wrenn 1988
Vegetation	Sample dried and homogenized; dry and wet ashing	ICP-MS (total uranium)	0.1 μg/L in final solution	No data	Boomer and Powell 1987
Vegetation	Sample dried and homogenized; wet ashing and purification by solvent extraction	Laser fluorometry (total uranium)	0.05 mg/kg in plant ash	No data	Harms et al. 1981
Process water	Dilution and filtration water	Laser fluorometry (total soluble uranium)	0.01 μg/L[b]	No data	Hinton and White 1981

Table 6-2. Analytical Methods for Determining Uranium in Environmental Samples (continued)

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Accuracy	Reference
Process water	Direct analysis	Ion chromatography spectrophotometric detection (U^+6)	0.04 mg/L	No data	Byerley et al. 1988
Field survey	None	Scintillation detector and count rate meter	200–500 dpm/ 100 cm^2 (scintillation detector)	No data	ANSI 1978 (ANSI Standard N323)

[a] This detection limit was reported by Melgard 1988.
[b] This detection limit was reported by Wessman 1984.

APDC = ammonium pyrrolidine dithiocarbamate; Bq = Bequerel and 1 pCi = 0.37 Bq; dpm = disintegration per minute and 1 pCi = 2.22 dpm; EDTA = ethylenediaminetetraacetic acid; FI = flow injection; HPLC=high performance liquid chromatography; ICP = inductively coupled plasma spectrometry; INAA = instrumental neutron activation and analysis; MS = mass spectrometry; NAA = neutron activation analysis; nM = nanomole or 10^{-9} of a mol

performance-based methods which enable the user to optimize their available analytical tools. A corner-stone of this method is the development of Data Quality Objectives and the use of Data Quality Assessment to ensure that the selected method is properly developed and the results are of the appropriate quality (DOE 1997; EPA 1994b, 1996).

DOE's method for analyzing environmental materials is based on a method of Welford et al. (1960) and involves preparing triplicate air, water, and soils samples by concentrating or isolating uranium from the media prior to separation in an anion exchange column, followed by fluorometric analysis (DOE 1997).

In one analytical method for air filters, the air filters are ashed, silica content is volatilized with hydrogen fluoride, uranium is extracted with triisooctylamine, purified by anion exchange chromatography and co-precipitated with lanthanum as fluoride. The precipitated uranium is collected by filtration, dried, and α-spectroscopy is performed (EPA 1984b). The activities of ^{234}U, ^{235}U, and ^{238}U are determined based on the number of counts that appear in the α energy region unique to each isotope. This method is used by the EPA National Air and Radiation Environmental Laboratory for measurement of uranium in air as part of the Environmental Radiation Ambient Monitoring System (see Chapter 5).

Singh and Wrenn (1988) describe a method for uranium isotopic analysis of air filters. Air filters are ashed, redissolved, and co-precipitated with iron hydroxide and calcium oxalate. The uranium is further purified by solvent extraction and electrodeposition. An alpha spectroscopy detection level of 0.02 dpm/L for ^{238}U in solution was reported (Singh and Wrenn 1988).

Considerable work has been done to develop methods for analysis of uranium in water. In 1980, the EPA published standardized procedures for measurement of radioactivity in drinking water which included uranium analysis by both radiochemical and fluorometric methods (Krieger and Whittaker 1980), and more recently developed an ICP-MS method. An example of each is provided below.

The radiochemical method quantifies gross α activity utilizing either a gas flow proportional counter or a scintillation detection system following chemical separation. In the EPA radiochemical method, the uranium is co-precipitated with ferric hydroxide, purified through anion exchange chromatography, and converted to a nitrate salt. The residue is transferred to a stainless steel planchet, dried, flamed, and counted for α particle activity (Krieger and Whittaker 1980).

For the fluorometric method, uranium is concentrated by co-precipitation with aluminum phosphate, dissolved in diluted nitric acid containing magnesium nitrate as a salting agent, and the co-precipitated uranium is extracted into ethyl acetate and dried. The uranium is dissolved in nitric acid, sodium fluoride flux is added, and the samples fused over a heat source (EPA 1980).

The ICP-MS method was developed for measuring total uranium in water and wastes. The sample preparation is minimal—filtration for dissolved uranium, acid digestion for total recoverable uranium. Recovery is quantitative (near 100%) for a variety of aqueous and solid matrices and detection limits are low, 0.1 µg/L for aqueous samples and 0.05 mg/kg for solid samples (Long and Martin 1991).

The EPA developed two methods for the radiochemical analysis of uranium in soils, vegetation, ores, and biota, using the equipment described above. The first is a fusion method in which the sample is ashed, the silica volatilized, the sample fused with potassium fluoride and pyrosulphate, a ^{236}U tracer is added, and the uranium extracted with triisooctylamine, purified on an anion exchange column, coprecipitated with lanthanum, filtered, and prepared in a planchet. Individual uranium isotopes are separately quantified by high resolution alpha spectroscopy and the sample concentration calculated using the ^{236}U yield. The second is a nonfusion method in which the sample is ashed, the silica volatilized, a ^{236}U tracer added, and the uranium extracted with triisooctylamine, stripped with nitric acid, co-precipitated with lanthanum, transferred to a planchet, and analyzed in the same way by high resolution α-spectroscopy (EPA 1984).

The detection capability of any measurement process is an important performance characteristics, along with precision and accuracy. The Lower Limit of Detection (LLD) has been adopted to refer to the intrinsic detection capability of the measurement process (sampling through data reduction and reporting) (USNRC 1984). Factors that influence the LLD include background count rate, sensitivity of detector, and, particularly, the length of time a sample and background are counted. Because of these variables, LLDs between laboratories, employing the same or similar chemical separation procedures, will vary. Additional examples of the techniques for quantification of uranium (as described above) are available, as well as examples of less frequently used techniques. These are identified in Table 6-3.

Determining the accuracy of the analytical methods for environmental samples and for calibrating radiation instrumentation requires that standard, certified radioactive sources with known concentrations of uranium,

Table 6-3. Additional Analytical Methods for Determining Uranium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Rocks, minerals, nuclear fission products, biological material	Solvent extraction as MHFA complex; optional purification by back-extraction	Spectro-photometric	0.0062 mg/L (with back-extraction)	99–103	Abassi 1989
Ore leachates	Separation as arsenazo III complex	Flow injection; spectro-photometric	6.6 µg/L	No data	Perez et al. 1990
Aqueous solutions	Complexation with o-hydroxy-propiophenone isonicotinoyl-hydrazone	Spectro-photometric	No data	No data	Ramachandraiah et al. 1993
Natural waters	Co-precipitation with Fe(OH)$_3$; selective separation by precipitation; determined as dibenzoyl methane complex	Laser fluorometry	5 ppb	No data	Eral 1989
Rocks, minerals, nuclear fission products and biological material	Solvent extraction as MHFA complex; optional purification by back-extraction	Atomic absorption spectrometry	<0.08 mg/L	No data	Abassi 1989
Phosphate rock and phosphoric acid	Wet digestion; separation by extraction with trioctylphosphine oxide; destruction of complex prior to analysis	Argon plasma emission spectrometry	No data	98–100	Woodis et al. 1980
Uranium tailings (U$_3$O$_8$)	Wet digestion; solvent extraction	ICP-OES	No data	101	Feeney et al. 1983
Phosphate rock	Wet digestion; extraction with trioctylphosphine oxide; back-extraction with stripping solution	dc argon ICP	<1 ppm	99–106	Norman et al. 1983
Ground, mine waters	Direct analysis	ICP	low ppm	No data	Greene et al. 1985
Coal ash	Acid digestion; separation with s-thenoyltrifluoric acetone; back-extraction	ICP	29 µg/L	98	Kamata et al. 1987
Seawater	Separation on chelate fiber	ICP-OES	5 µg/L	No data	Chang et al. 1990

Table 6-3. Additional Analytical Methods for Determining Uranium in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Apatite minerals	Extraction with 3-phenyl-4-benzoyl-s-isoxazolone	ICP-AES	0.02 mg/L	No data	Fujino et al. 1994
Natural waters	Extraction with s-thenoyltrifluoric acetone and tri-n-butyl phosphate	Stripping voltametry	10^{-10} mol/dm^3	≈90	Mlakar and Branica 1989
Groundwater, soil	Separation as propyl gallate complex	Stripping voltametry	subnanomolar	No data	Wang et al. 1994
Surface soils	in situ	Gamma spectrometry	0.1 Bq/g	No data	Miller et al. 1994
Ceramic and plastic semiconductor packaging material	None	NAA with fission track counting	0.02 ppb	No data	Riley 1982
River sediments	None	Instrumental NAA	No data	≈70 (certified materials)	Labrecque et al. 1986
Air samples	Sample collection on filters	Instrumental NAA	2 ng/sample	95	Landsberger and Wu 1993
Sediment, pore water	Dilution	ICP-MS	40 pg/mL	99	Toole et al. 1991
Soil	None	Proton induced fluorescent X-rays	No data	No data	Lazo et al. 1991
		Isotope dilution MS			Wessman 1984
Biological and environmental samples	Complexation with phosphoric acid	Laser phosphorimetry	Sensitivity 10^{-12} g	No data	Bushaw 1984

AES = atomic emission spectrometry; Bq = Bequerel; ICP = inductively coupled plasma (spectrometry); MHFA = N-p-methoxyphenyl-2-furylacrylohydroxamic acid; MS = mass spectrometry; NAA = neutron activation analysis; OES = optical emission spectrometry

or other appropriate radionuclides, be available for use. The primary source of such certified standards is
NIST (Inn 1987). An aqueous solution of uranium containing 10 mg/mL (SRM 3164) standard stock
solution is available, as are solutions of ^{232}U (1.1 nCi/g [40 Bq/g]) (SRM 4324) and ^{238}U, "natural uranium"
(6.7 nCi/g [250 Bq/g]) (SRM 4321B) (NIST 1995). Standard Reference Materials of human lung (SRM
4351) and human liver (SRM 4352) are also available from NIST.

6.3   ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 uranium is available. Where adequate information is not available, ATSDR, in
conjunction with the NTP, is required to assure the initiation of a program of research designed to deter-
mine the health effects (and techniques for developing methods to determine such health effects) of
uranium.

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 or eliminate the uncertainties of human health assessment. In the future, the identified data needs
will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1   Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.   Analytical methods with
satisfactory sensitivity and precision are available to determine the levels of uranium in human tissues and
body fluids. However, improved methods are needed to assess the biological effects of uranium in tissues.

Uranium is in essentially all food, water, and air, so everyone is exposed to some levels. In a study reported
by NIOSH (Thun et al. 1981, 1985), enhanced levels of β_2-microglobulin levels were observed in the urine
of uranium workers. It was postulated that enhanced excretion of β_2-microglobulin might be used as an
indication of uranium exposure; however, Thun et al. (1981, 1985) were unable to establish a dose response
correlation between level of exposure and excretion of the β_2-microglobulin. Limson-Zamora et al. (1996)
identified changes in several potential biomarkers of effect following exposure to uranium, in which each

individual biomarker could be affected by a range of chemicals, but the results suggested that it may be possible to identify a series of biomarkers whose combined responses could serve as a single uranium-specific biomarker of effect. Development of new or combination biomarkers for high uranium exposures would be useful.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media.   Analytical methods with the required sensitivity and accuracy are available for quantification of uranium, both total and isotopic, in environmental matrices (Table 6-2). Knowledge of the levels of uranium in various environmental media, along with the appropriate modeling (see Chapters 2 and 4), can be used to evaluate potential human exposures through inhalation and ingestion pathways.

Whether in the environment or in the human body, uranium will undergo radioactive decay to form a series of radioactive nuclides that end in a stable isotope of lead (see Chapter 3). Examples of these include radioactive isotopes of the elements thorium, radium, radon, polonium, and lead. Analytical methods with the required sensitivity and accuracy are also available for quantification of these elements in the environment where large sample are normally available (EPA 1980, 1984), but not necessarily for the levels from the decay of uranium in the body. More sensitive analytical methods are needed for accurately measuring very low levels of these radionuclides.

6.3.2   Ongoing Studies

The Federal Research in Progress (FEDRIP) database lists ongoing studies investigating new methods for detection and speciation of uranium (FEDRIP 1999). These are shown in Table 6-4.

Table 6-4. Ongoing Studies on Analytical Methods for Uranium

Investigator	Affiliation	Subject	Sponsor
Wang J	New Mexico State University, Dept of Chemistry and Biochemistry Las Cruces, NM	Development of *in situ* microsensor for the measurement of chromium and uranium in groundwater at DOE sites.	DOE
Blancett, A	Aiken SC	Fiber optic sensor for measurement of uranium in solution.	DOE
Hainfeld JF	Brookhaven National Laboratory Upton, NY	Site specific labels for biomolecules; electron microscopy and X-rays.	DOE
Lieser KH	Technische Hochschule Darmstadt, Germany	In-line measurement of U, Pu, and Np in process currents using energy-dispersive X-ray fluorescence analysis.	National Ministry for Research and Technology Bonn, Germany
John A	Los Alamos Nat Lab, Los Alamos NM	P-electron spectroscopy of transuranics.	DOE
Metzger R	Radiation Safety Engineering, Chandler, AZ	A portable gamma spectrometer with a high resolution cdte array detector	DOD, Defense Special Weapons Agency

DOE = Department of Energy; DOD = Department of Defense

Source: FEDRIP 1999

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding uranium in air, water, and other media are summarized in Table 7-1.

ATSDR has derived an MRL of $8.0x10^{-3}$ mg U/m^3 for intermediate-duration inhalation exposure to insoluble compounds of uranium based on a NOAEL of 1.1 mg U/m^3 for renal effects in dogs (Rothstein 1949b).

ATSDR has derived an MRL of $4.0x10^{-4}$ mg U/m^3 for intermediate-duration inhalation exposure to soluble compounds of uranium based on a LOAEL of 0.15 mg U/m^3 for renal effects in dogs (Rothstein 1949a).

ATSDR has derived an MRL of $3.0x10^{-4}$ mg U/m^3 for chronic-duration inhalation exposure (365 days or more) to soluble compounds of uranium based on a NOAEL of 0.05 mg U/m^3 for renal effects in dogs (Stokinger et al. 1953).

ATSDR has derived an MRL of $2.0x10^{-3}$ mg/kg/day has been derived for intermediate-duration oral exposure (and is protective for chronic-duration oral exposure) to soluble compounds of uranium based on a LOAEL of 0.05 mg U/kg/day d for renal effects in rabbits (Gilman et al. 1998b).

According to the EPA's Integrated Risk Information System (IRIS), neither a reference dose (RfD) nor a reference concentration (RfC) are available for uranium (IRIS 1997).

The International Agency for Research on Cancer, the U.S. Department of Human and Health Services, and the National Toxicology Program have not classified uranium as to its carcinogenicity. According to the Integrated Risk Information System (IRIS) database, the U.S. Environmental Protection Agency (EPA) withdrew its carcinogenic assessment of uranium in 1993 and has not completed its evaluation and determination of the evidence of uranium's human carcinogenicity potential (IRIS 1997).

Radiation protection recommendations for radiation workers and members of the public are provided by the International Commission on Radiological Protection (ICRP) (ICRP 1977, 1991) and the National Council on Radiation Protection and Measurements (NCRP) (NCRP 1987, 1993). These recommendations are not

regulations, but they provide the scientific basis for the development of regulations by federal agencies, such as EPA, the U.S. Nuclear Regulatory Commission (USNRC), and the U.S. Department of Energy (DOE), as well as by individual states.

The EPA is responsible for federal radiation protection guidance (EPA 1988c), "generally applicable" environmental radiation standards (40 CFR 190), and regulations to implement specific statutory requirements, such as Safe Drinking Water Act (40 CFR 141). The USNRC's regulations apply to source materials and special nuclear material, such as enriched uranium and plutonium; the utilization of special nuclear material, such as the operation of nuclear reactors; and the use of by-product materials, which include wastes produced in the processing of uranium or thorium and materials made radioactive in the utilization of special nuclear material (USNRC 1997a). The DOE has issued regulations applicable to its facilities (DOE 1993a).

States are free to regulate radioactive materials and other sources of radiation that the Atomic Energy Act does not give the USNRC authority to regulate. This includes sources of natural radioactivity, such as, uranium and radium, and radiation producing machines, such as x ray machines. Section 274 of the Atomic Energy Act (AEA) of 1954, as amended provides that states (and U.S. territories) may enter into an agreement with the USNRC to regulate by-product materials, source materials, and special nuclear materials (USNRC 1969). The relinquishes to these "agreement states" the majority of its regulatory authority over source, by-product, and special nuclear material in quantities not sufficient to form a critical mass. However, the USNRC retains its authority to regulate the construction and operation of production facilities (nuclear reactors used for production and separation of plutonium or ^{233}U or fuel reprocess plants) and utilization facilities (nuclear reactors used for production of power, medical therapy, research and testing); the import of by-product, source, or special nuclear materials; and the disposal of regulated materials into the ocean or otherwise (USNRC 1969). Currently there are 30 "agreements states" and 17 "non-agreement states." The governors of five states (Minnesota, Ohio, Oklahoma, Pennsylvania, and Wisconsin) have submitted letters of intent for their states to become agreement states (ORNL 1998). The regulations established by agreement states must be "compatible" with the USNRC's regulations, which require that the states' regulations be at least as strict as the USNRC's regulations. The responsibilities of agreement states also include the regulation of low-level radioactive wastes, which contain by-product materials. In non-agreement states, the USNRC still handles all of the inspection, enforcement, and licensing responsibilities. Figure 7-1 shows the agreement, non-agreement, and intending states.

Current federal and state regulations limit radiation workers' doses to a total effective dose equivalent (TEDE) of 5 rem/year and a committed dose equivalent to any organ, other than the lens of the eye, of 50 rem/year (EPA 1988c; USNRC 1995a). These limits apply to the sum of external and internal doses. The limits are upper limits, and an important philosophy in radiation protection is to keep radiation doses as low as reasonably achievable (ALARA).

For the control of internal doses, annual limits of intake (ALI) and derived air concentrations (DAC) have been determined. ALIs and DACs in EPA guidance and the USNRC and DOE regulations are based on the recommendations of the ICRP (ICRP 1979). Values of the ALIs and DACs for uranium isotopes are presented in Table 7-1. These values are for soluble, Class D (Days) material, which has a half-time for clearance from the pulmonary region of the lung of less than 10 days. Values of ALIs and DACs for Class W (Weeks) and Class Y (Years) uranium are available in Appendix B to 10 CFR 20 (USNRC 1993f).

The ALI is the activity of a radionuclide that can be taken into the body in a year, by inhalation or ingestion, without exceeding a committed effective dose equivalent (CEDE) of 5 rem/year or a committed dose equivalent to any organ of 50 rem/year, whichever is more limiting. The total effective dose equivalent TEDE is the sum of the CEDE and any penetrating external dose (10 CFR 20). If any external dose is present the ALI must be reduced by a proportional amount to ensure that the dose limits are not exceeded. For example, if a worker received an external dose of 1 rem/year, the ALI would have to be reduced by 20% to ensure that the TEDE did not exceed 5 rem/year.

The DAC is simply the inhalation ALI divided by the volume of air that a worker is assumed to breathe in a year (2,400 m^3). Thus, if the average air concentration is controlled so as not to exceed the DAC, a worker will not take in more than an ALI, and the worker's dose will not exceed 5 rem CEDE or 50 rem committed dose equivalent to any organ (ICRP 1977).

Uranium is unusual among the elements because it presents both chemical and radiological hazards. For soluble uranium, with an ^{235}U enrichment no greater than 5%, limits on intakes and air concentrations for radiation workers are based on the chemical toxicity of uranium since it is more limiting than the radiological hazard. For this case, the USNRC's limit for a 40-hour workweek is 0.2 mg uranium per cubic meter of air average (USNRC 1993f).

Between June 27, 1974 and January 18, 1989, the Occupational Safety and Health Administration (OSHA) promulgated protective, permissible exposure limits (PELs) for more than 400 toxic substances (OSHA 1993). The OSHA PELs were established to protect employees against adverse health effects which could result from exposure to hazardous substances found in the workplace. An employer must ensure that an employee's exposure to a toxic substance in any 8-hour work shift of a 40-hour week does not exceed the 8-hour time-weighted average (TWA) established for the substance (OSHA 1993). On January 18, 1989 OSHA promulgated more protective PELs for approximately 376 toxic substances. In July 1992, the 11th Circuit Court Appeals rescinded the 1989 promulgation. On March 23, 1993, OSHA resumed enforcing the air contaminant exposure limits that were in effect prior to the issuance of the new 1989 limits (i.e., OSHA 1974 PELs). On June 30, 1993 OSHA published in the Federal Register a final rule announcing the revocation of the 1989 exposure limits. Current OSHA general industry standards specify that an employer must use engineering and work practice controls, if feasible, to reduce exposures to or below an 8-hour TWA of 0.05 mg per cubic meter of soluble uranium and 0.25 mg/m^3 for insoluble uranium (OSHA 1993, 1997c). OSHA standards for construction workers indicate that exposures to uranium in gases, vapors, fumes, dust, and mist, through inhalation, ingestion, skin absorption, or contact at concentrations above those specified in the ACGIH "Threshold Limit Values of Airborne Contaminants for 1970" should be avoided. The "Threshold Limit Values of Airborne Contaminants for Construction" are codified at 29 CFR 1926, and indicate a limit of exposure at 0.2 mg/m^3 for soluble and insoluble uranium (OSHA 1997a). The same limits of exposure are codified at 29 CFR 1915 for shipyard personnel (OSHA 1997b).

Recent reports of the ICRP (ICRP 1991) and the NCRP (NCRP 1993) contain recommendations for lower worker dose limits. The ICRP recommends a limit on total effective dose of 2 rem/year averaged over 5 years, with the additional provision that the dose not exceed 5 rem in any single year. The NCRP's recommendations are that a worker's total accumulated dose should not exceed his or her age in years time 1 rem, and that the dose should not exceed 5 rem in any single year. These recommendations have not yet been incorporated into U.S. regulations.

Regulations for the general public are based on an annual TEDE of 0.1 rem/year, with provisions for a limit of 0.5 rem/year under special circumstances (USNRC 1997b). Considering the lower limit for members of the public and their potential continuous exposure, the limits on air concentrations of radionuclides for the public are two orders of magnitude lower than the DACs for radiation workers. Regulations for specific applications limit the dose to the public to values <0.1 rem/year. Under its responsibility for generally

applicable environmental radiation standards, the EPA has issued regulations for the nuclear fuel cycle that limit the total-body annual dose equivalent for members of the public to 0.025 rem/year. Except for the thyroid, which has a dose equivalent of 0.075 rem/year, the regulations also specify a 0.025 rem/year dose equivalent for a single organ (EPA 1988c). Also, based on the Clean Water Act, EPA proposed, but subsequently withdrew in 1998, a drinking water standard of 30 pCi/L for naturally occurring uranium (EPA 1991, 1995c). Analytical results for uranium are reported in units of activity with radiochemical and alpha spectrometry methods and in mass units with flurometric and laser phosphorimetry methods (EPA 1997c). A conversion factor is required when converting the fluorometric or laser phosporimetric results from micrograms to picocuries. EPA selected the larger of two proposed values (1.38 pCi/μg and 0.67 pCi/μg) as the conversion factor (EPA 1997c). Using this conversion factor, the proposed drinking water standard would have been converted to 20 μg/L.

The Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) requires that persons in charge of vessels or facilities from which a hazardous substance has been released in a 24-hour period in a quantity equal to or greater than its reportable quantity (RQ) immediately notify the National Response Center of the release. Values of RQs for isotopes of uranium are shown in Table 7-1 (EPA 1989f). These values are estimates, made using conservative assumptions, of the smallest activity of the radionuclides that, if released over a 24-hour period, could result in a person located 30 meters from the release point receiving an effective dose equivalent of 0.5 rem (0.005 Sv). Other regulations, including ones specific to uranium mining and milling, are cited in Table 7-1.

Table 7-1. Regulations and Guidelines Applicable to Uranium

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
WHO	Listed as an inorganic constituent requiring no action with respect to potential health significance	Yes	WHO 1984
ICRP	Occupational - whole body exposure	5 rem/yr (50 mSv)	ICRP 1977
	Individual - short-term, to critical populations	0.5 rem/yr (5 mSv)	
	Individual - chronic exposure	0.1 rem/yr (1 mSv)	
NATIONAL			
Regulations:			
a. Air:			
EPA OAR	New Source Performance Standards:		
	General Provisions Priority List	Yes	40 CFR 60, Subpart A EPA 1982a
	Metalic Mineral Processing Plants	Yes	40 CFR 60, Subpart LL EPA 1984a
	National Emission Standards for Hazardous Air Pollutants:		
	Radon from Underground Uranium Mines	Yes	40 CFR 61, Subpart B EPA 1989a
	Radionuclide Emissions from Facilities Licensed by Nuclear Regulatory Commission and federal facilities not covered by Subpart H: Applicability	Yes	40 CFR 61, Subpart I EPA 1989b
	Radon Emissions from DOE Facilities	Yes	40 CFR 61, Subpart Q EPA 1989c
	Radon Emissions from Disposal of Uranium Mill Tailings	Yes	40 CFR 61, Subpart T EPA 1989d
	Radon Emissions from Operating Mill Tailing	Yes	40 CFR 61, Subpart W EPA 1989e
	Environmental Standards for Uranium Fuel Cycle: Standards for Normal Operation Annual dose not to exceed:		40 CFR 190, Subpart B EPA 1977b
	-whole body	$\leq$ 25 mrems	
	-thyroid	$\leq$ 75 mrems	
	-any other organ	$\leq$ 25 mrems	
	Quantity of radioisotopes material entering environment per gigawatt -year	< 50,000 Ci krypton-85 < 5 mCi plutonium 239 and other alpha-emissions with half-lives greater than 1 year	
	Effective Date for Implementation Standards	Yes	40 CFR 190, Subpart B EPA 1977b
	Environmental standards for disposal	Yes	40 CFR 191.12 EPA 1985i

Table 7-1. Regulations and Guidelines Applicable to Uranium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Standards for Control of Residual Radioactive Material from Inactive Uranium Processing Sites	Yes	40 CFR 192, Subpart A EPA 1995c
	Definitions	Yes	
	Standards (for control of residual radioactive materials and their listed constituents)	Yes	
	Maximum concentration of constituents for ground-water protection	30 pCi/L	
	Standards for Cleanup of Land and building Contaminated with Residual Radioactive Materials from Inactive Uranium Processing Sites	Yes	40 CFR 192, Subpart B EPA 1995a
	Guidance for Implementation	Yes	40 CFR 192, Subpart C EPA 1995b
	Additional Listed Constituents (replacement list of constituents for screening purposes)	Combined uranium-234 and uranium-238	
	Standards for Management of Uranium Byproduct Materials Pursuant to Section 84 of the Atomic Energy Act of 1954, as Amended	Yes	40 CFR 192, Subpart D EPA 1993b
	Standards (for application during processing operations and prior to the endo of the closure period— Concentration limits	5 pCi/L	
USNRC and DOE	Occupational Annual Limits on Intake (ALI's) for Inhalation	U-230 4×10^{-1} µCi U-231 8×10^3 µCi U-232 2×10^{-1} µCi U-233 1.0 µCi U-234 1.0 µCi U-235 1.0 µCi U-236 1.0 µCi U-237 3.0×10^3 µCi U-238 1.0 µCi U-239 2×10^5 µCi U-240 4.0×10^3 µCi $U_{natural}$ 5.0×10^{-10} µCi	10 CFR 20 Appendix B USNRC 1993f and 10 CFR 835, Subpart C DOE 1993a
	Occupational Derived Air Concentrations (DACs)	U-230 2.0×10^{-10} µCi/mL U-231 3.0×10^{-6} µCi/mL U-232 9.0×10^{-11} µCi/mL U-233 5.0×10^{-10} µCi/mL U-234 5.0×10^{-10} µCi/mL U-235 6.0×10^{-10} µCi/mL U-236 5.0×10^{-10} µCi/mL U-237 1.0×10^{-6} µCi/mL U-238 6.0×10^{-10} µCi/mL U-239 8.0×10^{-5} µCi/mL U-240 2.0×10^{-6} µCi/mL $U_{natural}$ 5.0×10^{-10} µCi/mL	10 CFR 20 Appendix B USNRC 1993f and 10 CFR 835, Subpart C DOE 1993a

Table 7-1. Regulations and Guidelines Applicable to Uranium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	40-hour workweek average air concentration limit for soluble uranium with ^{235}U enrichment ≤5%	0.2 mg/m^3	10 CFR 20 Appendix B USNRC 1993f
	Effluent Concentrations	U-230 4-8x10^{-13} µCi/mL U-231 6x10^{-9}–1x10^{-8} µCi/mL U-232 1x10^{-14}–6x10^{-13} µCi/mL U-233 5x10^{-14}–3x10^{-12} µCi/mL U-234 5x10^{-14}–3x10^{-12} µCi/mL U-235 6x10^{-14}–3x10^{-12} µCi/mL U-236 2-4x10^{-9} µCi/mL U-237 6x10^{-7}–1x10^{-6} µCi/mL U-238 6x10^{-14}–3x10^{-12} µCi/mL U-239 2-3x10^{-7} µgCi/mL U-240 3-5x10^{-9} µCi/mL U-natural 9x10^{-14}–3x10^{-12} µCi/mL	10 CFR 20 Appendix B USNRC 1993f

OSHA	PEL TWA (corrected rule)
	  soluble
	  insoluble
		
		0.05 mg/m^3
		0.25 mg/m^3
			62 FR 42018 (29 CFR 1910) OSHA 1997c

	STEL	0.6 mg/m^3 insoluble	

	Occupational Safety and Health Standards for Shipyard Employment—TWA for Air Contaminants
	  soluble
	  insoluble
		
		0.2 mg/m^3
		0.2 mg/m^3
			29 CFR 1915.1000 OSHA 1997b

	Safety Regulations for Construction —TWA for Air Contaminants
	  soluble
	  insoluble
		
		0.2 mg/m^3
		0.2 mg/m^3
			29 CFR 1926.55, Appendix A OSHA 1997a

b. Water:			
EPA OW	National Primary Drinking Water Regulations		
	Monitoring Analytical Requirements	ASTM D-2907	40 CFR 141.25 EPA 1980a
	Maximum Contaminant Level (proposed)	30 pCi/L (20 µg/L)	62 FR 52194 EPA 1997a
	NPDES Permit Application Requirements: Hazardous Substances	Yes	40 CFR 122, App. D EPA 1983a
	Criteria and standards for NPDES	Yes	40 CFR 125 EPA 1979
	Underground Injection Control Program		
	Classification of Class III Injection Wells for the Underground Injection Control Program	Yes	40 CFR 146.5 EPA 1980c
	Class III Classification of Underground Injection Wells for in-situ Production of Uranium	Yes	40 CFR 146.6 EPA 1987b
	State Underground Injection Control Programs		
	Aquifer Exemptions	Yes	40 CFR 147.3003 EPA 1984d

Table 7-1. Regulations and Guidelines Applicable to Uranium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Plugging and Abandonment of Class III Wells	Yes	40 CFR 147.3011 EPA 1984c
	National Oil and Hazardous Substances Pollution Contingency Plan - National Priority List	Yes	40 CFR 300, Appendix B EPA 1994c
	Definition for Designation, Reportable Quantities and Notificatoin of Hazardous Substances	Yes	40 CFR 302.3 EPA 1985a
	Definitions for Reimbursement to Local Government for Emergency Response to Hazardous Substance Release	Yes	40 CFR 310.11 EPA 1993a
	Nonferrous Metals Manufacturing Effluent Guideline and Standards		
	Secondary Uranium Subcategory	Yes	40 CFR 421, Subpart AD EPA 1985b
	Secondary Uranium Subcategory: Effluent Limitations Attainable by Best Practicable Control Technology	Yes	
	Secondary Uranium Subcategory: Effluent Limitations Attainable by Best Available Technology	Yes	
	Secondary Uranium Subcategory: Standards of Performance for New Source	Yes	
	Secondary Uranium Subcategory: Pretreatment Standards for New Sources	Yes	
	Uranium, Radium and Vanadium Ores Effluent Guidelines and Standards		40 CFR 440, Subpart C EPA 1982b
	Description of Uranium Ore Subcategory	Yes	
	Effluent Limits Attainable by Applicability of Best Practicable Control Technology (BPT)	4.0 mg/L (1 day) 2.0 mg/L (30 days)	
	Subpart C - Uranium Effluent Limit Attainable by Applicability of Best Achievable Technology (BAT)	4.0 mg/L - max. for 1 day 2.0 mg/L - avg. for 30 consec. days	
	New Source Performance Standards (NSPS)	Yes	
	Ore Mining and Dressing Effluent Guidelines and Standards		
	Vanadium Ore Subcategory: Effluent Limit Attainable from BPT	Yes	40 CFR 440, Subpart H EPA 1982c
	Nonferrous Metals Forming and Metals Powder Effluent Guidelines and Standards		
	Uranium Forming Subcategory:	Yes	40 CFR 471, Subpart G EPA 1985c
	Effluent Limits by Applicability of BPT	Yes	40 CFR 471.71 EPA 1985d

Table 7-1. Regulations and Guidelines Applicable to Uranium (continued)

Agency	Description	Information		References
NATIONAL (cont.)				
	Effluent Limits by Applicability of BAT	Yes		40 CFR 471.72 EPA 1985e
	NSPS	Yes		40 CFR 471.73 EPA 1985f
	PSNS	Yes		40 CFR 471.75 EPA 1985g
USNRC	Occupational Annual Limits on Intake (ALI's) for Oral Ingestion	U-230	4.0 µCi	10 CFR 20, App. B USNRC 1993f
		U-231	5.0×10^3 µCi	
		U-232	2.0 µCi	
		U-233	1.051 µCi	
		U-234	1.0×10^1 µCi	
		U-235	1.0×10^1 µCi	
		U-236	1.0×10^1 µCi	
		U-237	2.0×10^3 µCi	
		U-238	1.0×10^1 µCi	
		U-239	7.054 µCi	
		U-240	1.0×10^3 µCi	
		$U_{natural}$	$1.0 \times 10^{+1}$ µCi	
	Effluent Concentrations	U-230	8×10^{-8} µCi/mL	10 CFR 20 Appendix B USNRC 1993f
		U-231	6×10^{-5} µCi/mL	
		U-232	6×10^{-8} µCi/mL	
		U-233	3×10^{-7} µCi/mL	
		U-234	3×10^{-7} µCi/mL	
		U-235	3×10^{-7} µCi/mL	
		U-236	3×10^{-7} µCi/mL	
		U-237	3×10^{-5} µCi/mL	
		U-238	3×10^{-7} µCi/mL	
		U-239	9×10^{-4} µCi/mL	
		U-240	2×10^{-5} µCi/mL	
		$U_{natural}$	3×10^{-7} µCi/mL	
c. Other:				
DOI	Endangered and Threatened Wildlife and Plants: Proposed Rule to Reclassify the Plant *Pediocactus sileri* from Endangered to Threatened (proposed)	Yes		50 CFR 17 (58 FR 13244) DOI 1993a
	Endangered and Threatened Wildlife and Plants; Proposal to Determine the Plant *Pediocactus winkler* to be an Endangered Species (proposed)	Yes		50 CFR 17 (58 FR 52059) DOI 1993b
DOI Mining Recl. and Enforcement	Exclusion of Certain Non-coal Reclamation Sites	Yes		30 CFR 875.16 DOI 1994
	Approval of Amendment to State Regulatory Programs - Montana	Yes		30 CFR 926.15 DOI 1984
EPA OSWER	Exclusion from Identification and Listing of Uranium as a Hazardous Waste	Yes		40 CFR 261.4 EPA 1980d
	Land Disposal Restriction Phase IV: Final Rule Promulgating Treatment Standards for Metal Wastes and Mineral Processing Wastes	Yes		63 FR 28556 EPA 1998b

Table 7-1. Regulations and Guidelines Applicable to Uranium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Uncontrolled Hazardous Waste Site Ranking System: Def. of Uranium Mill Tailings Radiation Control Act Standards	Benchmark Screening Concentration Corresponding to 10^{-6} Individual Cancer Risk for Inhalation Exposure, Oral Exposure, Food Chain Soil Exposure	40 CFR 300 Appendix A EPA 1990a
	Definition for National Oil and Hazardous Substance Pollution Contingency Plan	Yes	40 CFR 300.5 EPA 1990b
	National Priorities List for Uncontrolled Hazardous Waste Sites, Proposed Rule No. 15 (proposed)	Yes	58 FR 34018 (40 CFR 300) EPA 1993c
	National Oil and Hazardous Substances Pollution Contingency Plan (proposed)	Yes	58 FR 54702 (40 CFR 300) EPA 1993d
	Barium Sulfate; Toxic Chemical Release Reporting; Community Right-to-know (proposed)	Yes	59 FR 32622 (40 CFR 372) EPA 1993e
EPA	Timing of Administration Act under Uranium Mill Tailing Radiation Control Act of 1978	Yes	40 CFR 23.8 EPA 1985h
USNRC	Standards for Protection Against Radiation		
	Definitions	Yes	10 CFR 20.1003 USNRC 1997a
	Dose limits for individual members of the public—total effective dose equivalent	<0.1 rem	10 CFR 20.1301 USNRC 1997b
	Maximum limit of operation requiring prior authorization	0.5 rem	
	Occupational dose limits for adults Annual limit Total weekly limit	Yes 10 mg	10 CFR 20, Subpart C USNRC 1995a 10 CFR 20.1206 USNRC 1993f
	Radiological criteria for License termination—applicability	10 CFR 40, Appendix A uranium recovery facilities-not applicalbe	10 CFR 20, Subpart E USNRC 1997c
	Requirements for transfers of low-level radioactive waste intended for disposal at licensed land disposal facilities and manifests	Yes	10 CFR 20, Appendix G USNRC 1995b
Guidelines:			
a. Air:			
ACGIH	Soluble and Insoluble TWA STEL	0.2 mg/m³ 0.6 mg/m³	ACGIH 1998
NIOSH	Insoluble REL-TWA (insoluble) REL-STEL Soluble REL-TWA (soluble)	0.2 mg/m³ 0.6 mg/m³ 0.05 mg/m³	NIOSH 1997

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Uranium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
b. Water:			
EPA OW	Maximum Contaminant Level Goal (proposed)	Zero	62 FR 52194 EPA 1997a
	Analytical Methods: Radio Chem (EPA Method 908.0), Fluoremetric (EPA Mehtod 980.1); final rule	Yes	62 FR 10168 EPA 1997c
c. Other			
EPA-OSWER	Use of Soil Cleanup Criteria in 40 CFR Part 192 as Remediation goals for CERCLA Cleanup	OSWER Directive 9200.4-25	EPA 1998
	Establishment of Cleanup levels for CERCLA Site with Radioactive Contamination	OSWER Directive 92004.18	EPA 1997b
ACGIH	Cancer classification	A1[a]	ACGIH 1998
EPA	Cancer classification	Withdrawn	IRIS 1997
NIOSH	Cancer classification	Ca[b]	NIOSH 1997
EPA OSWER	Reportable Quantity for Accidental Release	U-230 1 Ci U-231 1000 Ci U-232 0.01 Ci U-233 0.1 Ci U-234 0.1 Ci U-235 0.1 Ci U-236 0.1 Ci U-237 100 Ci U-238 0.1 Ci U-239 1000 Ci U-240 1000 Ci	40 CFR 302.4, App. B EPA 1989f
STATE			
Guidelines:			
a. Water Quality Standards			EPA 1990c
AZ		35 µg/L	
CA	Standard Guideline	20 µg/L 30 µg/L	
MA		10 µg/L	
	Water Quality Criteria: Human Health		CELDs 1994
AZ	Domestic water source Alpha particle activity	≤15 pCi/L	
	Criteria for domestic water source	35 µm/L	
CA	Average Maximum Contaminant Level	≤20 pCi/L	
	Groundwater Quality Standards		CELDs 1994
NM	Human health standards	5.0 mg/L	

## Table 7-1. Regulations and Guidelines Applicable to Uranium (continued)

Agency	Description	Information	References
STATE (cont.)			
WY	For fish and aquatic life in special A1 waters	0.03–1.4 mg/L	
	Underground Injection Wells		CELDs 1994
	Class III well requirements		
GA		Yes	
MO		Yes	
SD		Yes	
	Water Monitoring		CELDs 1994
CA	Average MCL	$\leq$ 20 pCi/L	
b. Air:			NATICH 1992
AZ		1.5 µg/m^3 (1 hr) 4.0x10^{-1} µg/m^3 (24 hr)	
CT		4.0 µg/m^3 (8 hr)	
FL-Pinellas		5.0x10^{-1} µg/m^3 (8 hr) 1.20x10^{-1} µg/m^3 (24 hr)	
ND		2.0x10^{-3} mg/m^3 (8hr) 6.0x10^{-3} mg/m^3 (1 hr)	
NV		5.0x10^{-3} mg/m^3 (8 hr)	
TX		5.0x10^{-1} µg/m^3 (30 min) 5.0x10^{-2} µg/m^3 (Annual) 2.0 µg/m^3 (30 min) 2.0x10^{-1} µg/m^3 (Annual)	
VA		3.3 µg/m^3 (24 hr)	
WA-BFW		2.0x10^{+2} ppm	
WA-SWEST		7.0x10^{-1} µg/m^3 (24 hr)	
c. Other:			
	Hazardous Waste Constituent		CELDs 1994
CA		Yes	
NJ		Yes	
SD		Yes	

[a] A1 cancer classification. ACGIH defers to the NIOSH classification

[b] Ca cancer classification indicates that the agent is a potential occupational carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; ALI = Annual Limits on Intake; ASTM = American Society for Testing and Materials; BAT = Best Available Technology; BPT = Best Practicable Technology; DAC = Derived Air Concentration; DHHS = Dept. Of Health and Human Services; DOE = Department of Energy; DOI = Department of Interior; EPA = Environmental Protection Agency; HAPs = Hazardous Air Pollutants; IDLH = Immediately Dangerous to Life and Health; IRIS = Integrated Risk Information System; MCL = Maximum Contaminant Level; NATICH = National Air Toxics Information Clearinghouse; NESHAP = National Emission Standards for Hazardous Air Pollutants; NIOSH = National Institute for Occupational Safety and Health; NOAA = National Oceanographic and Atmospheric Association; NPDES = National Pollutant Discharge Elimination System; NSPS = New Source Performance Standard; OAQPS = Office of Air Quality Planning and Standards; OAR = Office of Air and Radiation; OGWDW = Office of Ground Water and Drinking Water; OPPTS = Office of Pollution Prevention and Toxic Substances; OSHA = Occupational Safety and Health Administration; OSWER = Office of Solid Waste and Emergency Response; OW = Office of Water; PEL = Permissible Exposure Limit; PQL = Practical Quantitation Limit; PSNS = Pretreatment Standards for New Sources; REL = Recommended Exposure Limit; STEL = Short-term Exposure Limit; TWA = Time Weighted Average; USNRC = U.S. Nuclear Regulatory Commission; WHO = World Health Organization

Figure 7-1. Nuclear Regulatory Commission Agreement States

| Agreement States (30) | Non-Agreement States (20) | * Letter of intent to become an agreement state |
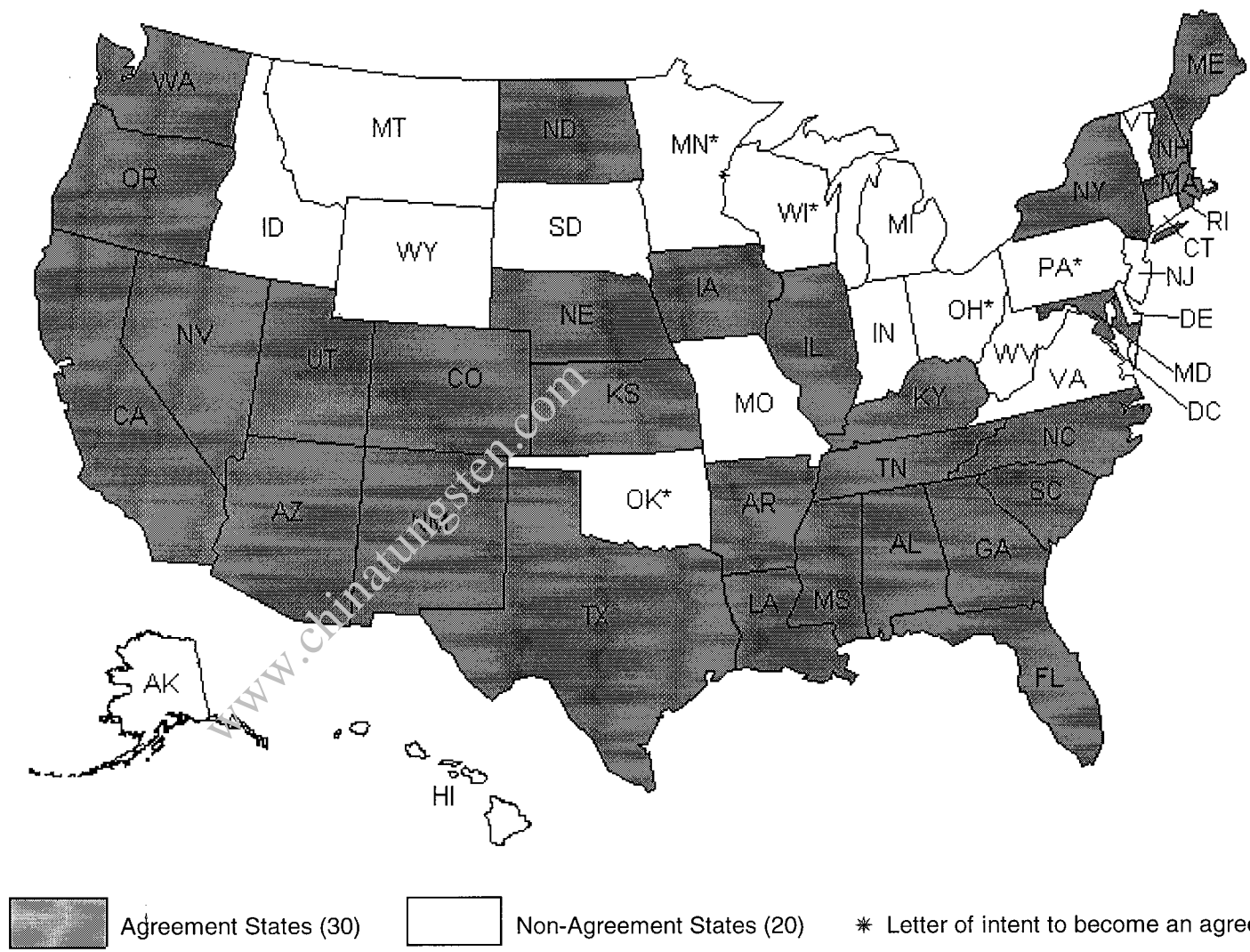
Source: USNRC 1999

8. REFERENCES

*Abbasi SA. 1989. Atomic absorption spectrometric and spectrophotometric trace analysis of uranium in environmental samples with N-p-methoxyphenyl-2-furylacrylohydroxamic acid and 4-(2-pyridylazo) resorcinol. Intern J Environ Anal Chem 36:163-172.

*ABMS. 1994. American Bureau of Metal Statistics. Non-ferrous metal data.

*ACGIH. 1998. Threshold limit values for chemical substances and physical agents. Biological exposure Indices. 1998 TLVs and BEIs. American Conference of Governmental Industrial Hygienists. March 1, 1998.

*Acquavella JP, Wiggs LD, Waxweiler RJ, et al. 1985. Mortality among workers at the Pantex Weapons Facility. Health Phys 48:735-746.

*Adachi S, Takemoto K. 1987. Occupational lung cancer: A comparison between humans and experimental animals. Jpn J Ind Health 29:345-357.

*Adams N, Spoor NL. 1974. Kidney and bone retention functions in the human metabolism of uranium. Phys Med Biol 19:460-471.

*Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. Developmental Medicine & Child Neurology 27:532-537.

*AEC. 1974. U.S. Atomic Energy Commission. Environmental survey of the uranium fuel cycle. USAEC Report WASH-1248.

*Ahsanullah M, Williams AR. 1989. Kinetics of uranium uptake by the crab *Pachygrapsus laevimanus* and the zebra winkle *Austrocochlea constricta*. Marine Biology 101:323-327.

*Aldstadt JH, Kuo JM, Smith LL, et al. 1996. Determination of uranium by flow injection inductively coupled plasma mass spectrometry. Analytica Chimica Acta 319(1-2):135-143.

*Allard B, Kipatsi H, Torstenfelt B, et al. 1979. Nuclide transport by groundwater in Swedish bedrock. Mater Res Soc Symp Proc 403-410.

*Allard B, Olofsson U, Torstenfelt B, et al. 1982. Sorption of actinides in well-defined oxidation states on geologic media. Mater Res Soc Symp Proc 11:775-782.

*Altman PK, Dittmer DS. 1974. In: Biological handbooks: Biology data book, Volume III, second edition. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

*Ames LL, McGarrah JE, Walker BA. 1982. Sorption of uranium and cesium by Hanford basalts and associated secondary smectite. Chem Geol 35:205-225.

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*Cited in text

8. REFERENCES

*Amethyst Galleries. 1995. The mineral tyuyamunite. Amethyst Galleries, Inc.
http://mineral.galleries.com/minerals/phosphat/tyuyamun/tyuyamun.htm.

*Andersen ME, MacNaughton MG, Clewell HJ, et al. 1987. Adjusting exposure limits for long and short
exposure periods using a physiological pharmacokinetic model. Am Ind Hyg Assoc J 48(4):335-343.

*Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically-based tissue
dosimetry and tissue response models.   In: H. Salem, ed. Animal test alternatives. U.S. Army Chemical
Research Development and Engineering Center, Aberdeen Proving Ground, Maryland.

*Anderson RF. 1984. A method for determining the oxidation state of uranium in natural waters. Nucl
Instrum Methods Phys Res, Sect A 223:213- 217.

*Anderson RF, Fleer AP. 1982. Determination of natural actinides and plutonium in marine particulate
material. Anal Chem 54:1142-1147.

*Andre S, Metivier H, Auget D, et al. 1989. Lung dissolution of uranium tetrafluoride in rats and baboons.
Comparison with dissolution by alveolar macrophages in culture and chemical dissolution. Human Toxicol
8:111-119.

*Anonymous. 1984. Annual environmental monitoring report, January-December 1983. Govt Rep
Announce Ind, Issue 18.

*ANSI. 1978. American national standard radiation protection instrumentation test and calibration.
American National Standard Institute, ANSI N323. New York, NY: Institute of Electrical and Electronics
Engineers, Inc.

*Anthony ML, Gartland KPR, Beddell CR, et al. 1994. Studies of the biochemical toxicology of uranyl
nitrate in the rat. Archives of Toxicology 68(1):43-53.

*Archer VE. 1977. Occupational exposure to radiation as a cancer hazard. Cancer Suppl 39:1802-1806.

*Archer VE. 1981. Health concerns in uranium mining and milling. J Occup Med 23:501-505.

*Archer VE. 1985. Enhancement of lung cancer by cigarette smoking in uranium and other miners.
Carcinog Compr Surv 8:23-37.

*Archer VE, Gillman JD, Wagoner JK. 1976. Respiratory disease mortality among uranium miners. Ann
NY Acad Sci 271:280-293.

*Archer VE, Wagoner JK, Lundin FE. 1973a. Lung cancer among uranium miners in the United States.
Health Phys 25:351-371.

*Archer VE, Wagoner JK, Lundin FE Jr. 1973b. Cancer mortality among uranium mill workers. J Occup
Med 15:11-14.

*ASTM. 1986. American Society for Testing of Materials. Annual books of ASTM standards. Water and
environmental technology, Section 11, Vol. 11.02 (water 11). Philadelphia, PA: ASTM, 511-515; 516-521;
523-528.

8. REFERENCES

*ASTM. 1994. American Society for Testing of Materials. Annual books of ASTM standards.Water and environmental technology, Philadelphia, PA: ASTM, 449-452.

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicologicol profiles. Agency for Toxic Substances and Disease Registry, Division of Toxicology, Atlanta, GA.

*ATSDR. 1990a. Toxicological profile for thorium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*ATSDR. 1990b. Toxicological profile for radium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*ATSDR. 1990c. Toxicological profile for radon. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*ATSDR. 1997. Public health assessment. Monticello Mill Tailings (DOE) [CERCLIS no. UT3890090035] and Monticello Radioactively Contaminated Properties (aka Monticello Vicinity Properties) [CERCLIS no. UTD980667208]. Atlanta, GA: Energy Section, Federal Facilities Assessment Branch, Division of Health Assessment and Consultation, Agency for Toxic Substances and Disease Registry, Sept 30, 1997, http://www.atsdr.cdc.gov/HAC/PHA/monticel/mon_toc.html

*ATSDR/CDC. 1990. Subcommittee report on biological indicators of organ damage. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA.

*Au WW, Lane RG, Legator MS, et al. 1995. Biomarker monitoring of a population residing near uranium mining activities. Environ Health Perspect 103(5):466-70.

*Aub JC, Evans RD, Hempelmann LH. 1952. The late effects of internally deposited radioactive materials in man. Medicine 31: 221-329.

*Auerbach O, Saccomanno G, Kuschner M, et al. 1978. Histologic findings in the tracheobronchial tree of uranium miners and non-miners with lung cancer. Cancer (Phila) 42:483-489.

*Avasthi PS, Evan AP, Hay D. 1980. Glomerular endothelial cells in uranyl nitrate-induced acute renal failure in rats. J Clin Invest 65:121-127.

*Bailey EH, Kemp AJ, Ragnarsdottir KV. 1993. Determination of uranium and thorium in basalts and uranium in aqueous solution by inductively coupled plasma mass spectrometry. 551-556.

*Bains ME, Rowbury PW. 1969. The biological excretion pattern from a person involved in the inhalation of a mixture of enriched uranium oxide and lead metal powders. Health Phys 16:449-453.

*Bakhtiar N, Lee SC, Kuroda PK. 1985. Uranium-235 fallout from the nuclear-powered satellite Cosmos-1402. J Radioanal Nucl Chem 91:403-409.

*Ballou JE, Gies RA, Case AC, et al. 1986. Deposition and early disposition of inhaled uranium-233 uranyl nitrate and uranium-232 uranyl nitrate in the rat. Health Phys 51:755-772.

*Baltschukat K, Horneck G, Buecker H, et al. 1986. Genetic response of bacterial spores to very heavy ions. Adv Space Res 6:109-115.

8. REFERENCES

*Band P, Feldstein M, Saccomanno G, et al. 1980. Potentiation of cigarette smoking and radiation: Evidence from a sputum cytology survey among uranium miners and controls. Cancer 45:1273-1277.

*Band P, Feldstein M, Watson L, King G, et al. 1982. Lung cancer screening programs in Canadian uranium mines. Recent Results Cancer Res 82:153-158.

*Barnes CE, Cochran JK. 1993. Uranium geochemistry in estuarine sediments controls on removal and release processes. Geochimica et Cosmochimica Acta 57:555-569.

*Barnes D, Bellin J, DeRosa C, et al. 1987. Reference dose (RfD): description and use in health risk assessments. Volume I, Appendix A: Integrated risk information system supportive documentation. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-86/032a.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. U.S. Environmental Protection Agency. Regul Toxicol Pharmacol 8:471-486.

*Bassett SH, Frenkel A, Cedars N, et al. 1948. The excretion of hexavalent uranium following intravenous administration. II. Studies on human subjects. USAEC Report UR-37.

*Bearman PJ. 1979. A review of the environmental problems associated with the disposal of uranium tailings. Miner Environ 1:64-74.

*Bechtel National, Inc. 1984. Environment monitoring report for the former Middlesex Sampling Plant and Middlesex Municipal Landfill sites, calendar year 1984. Report: ISS DOE/OR/20722-56. DE85017886.

*BEIR III. 1980. The effects on populations of exposure to low levels of ionizing radiation. Committee on the Biological Effects of Ionizing Radiations, National Research Council. Washington, DC: National Academy Press.

*BEIR IV. 1988. Health risks of radon and other internally deposited alpha-emitters. Committee on the Biological Effects of Ionizing Radiations, National Research Council. Washington, DC: National Academy Press.

*BEIR V. 1990. Health effects of exposure to low levels of ionizing radiation. Committee on the Biological Effects of Ionizing Radiations, National Research Council. Washington, DC: National Academy Press.

*Beiter H, Gibb FR, Morrow PE. 1975. Intramuscular retention of UO_3 and UO_2. Health Phys 29:273-277.

*Bender MA. 1964. Chromosome aberrations in irradiated human subjects. Annals of the New York Academy of Science. 114:249-251.

*Bentley KW, Stockwell DR, Britt KA, et al. 1985. Transient proteinuria and aminoaciduria in rodents following uranium intoxication. Bull Environ Contam Toxicol 34:407-416.

*Bentley KW, Wyatt JH, Wilson DJ, et al. 1982. Uranium and plutonium in hair as an indicator of body burden in mice of different age and sex. Bull Environ Contam Toxicol 28:691-696.

8. REFERENCES

*Berard P, Quesne B, Auriol B, et al. 1994. Cutaneous contamination after a uranyl nitrate skin burn: incident report. Radiat Prot Dosim 53(1-4):269-272.

*Berdnikova AV. 1964. [Of the uranium content in the external environment and the human excreta]. Vopr Pitaniya 23:17-20. (Russian).

*Berlin M, Rudell B. 1986. Uranium. In: Friberg L, Nordberg GF, Voulc V, eds. Handbook on the toxicology of metals, Vol. II, 2nd ed. New York, NY: Elsevier Science Publishers.

*Bernard SR, Struxness EC. 1957. A study of the distribution and excretion of uranium in man. Oak Ridge National Laboratory, Oak Ridge, TN. Union Carbide Nuclear Company 1-57.

*Beverly CR, Ernstberger EG. 1986. Method for monitoring stack gases for uranium activity. Govt Rep Announce Ind, Issue 25. NTIS/DE86013703.

*Bhattacharyya RP, Larsen P, Cohen N, et al. 1989. Gastrointestinal absorption of plutonium and uranium in fed and fasted adult baboons and mice: Application to humans. Radiation Protection Dosimetry 26:159-165.

*Bibler JP, Marson DB. 1992. Behavior of mercury, lead, cesium, and uranyl ions on four SRS soils (U). Westinghouse Savannah River Company Savannah River Site. WSR-RP--92-326.

*Bigu J. 1988. Relationship of 220Rn and 222Rn progeny levels in Canadian underground U mines. Health Phys 55:525-532.

*Bigu J, Duport P. 1992. Characterization of long-lived radioactive dust in uranium mill operations. Am Ind Hyg Assoc 53:588-595.

*Bigu J, Grenier NK, Dave TP, et al. 1984. Study of radon gas concentration surface radon flux and other radiation variables from uranium mine tailings areas. Uranium 1:257-277.

*Birkenfeld HP, Kathren RL, Hedaya MA. 1995. A sensitive method for the determination of uranium in biological samples utilizing kinetic phosphorescence analysis (KPA). Pharmaceutical Research (New York) 12(9 Suppl.):S48.

*Blanchard RL, Fowler TW, Horton TR, et al. 1982. Potential health effects of radioactive emissions from active surface and underground uranium mines. Nucl Saf 23:439-450.

*Blanchard RL, Hahne RMA, Kahn B, et al. 1985. Radiological sampling and analytical methods for national primary drinking water regulations. Health Phys 48:587-600.

*Blantz RC. 1975. The mechanism of acute renal failure after uranyl nitrate. J Clin Invest 55:621-635.

*Boniforti R. 1987. Lanthanides, uranium, and thorium as possible simulators of the behavior of transuranics in the aquatic environment. Sci Total Environ 64:181-189.

*Boomer DW, Powell MJ. 1987. Determination of uranium in environmental samples using inductively coupled plasma mass spectrometry. Anal Chem 59:2810-2813.

*Boothe GF. 1977. The need for radiation controls in the phosphate and related industries. Health Phys 32:285.

*Bosque MA, Domingo JL, Llobet JM, et al. 1993. Embryotoxicity and teratogenicity of uranium in mice following subcutaneous administration of uranyl acetate. Biol Trace Elem Res 36(2):109-18.

*Bostick WD, McCulla WH, Pickrell PW. 1985. Sampling, characterization, and remote sensing of aerosols formed in the atmospheric hydrolysis of uranium hexafluoride. J Environ Sci Health, Part A A20:369-393.

*Bradford GR, Bakhtar D, Westcot D. 1990. Uranium vanadium and molybdenum in saline waters of California. J Environ Qual 19:105-108.

*Brady HR, Kone CB, Brenner RM et al. 1989. Early effects of uranyl nitrate on respiration and K transport in rabbit proximal tuble. Kidney International 36:27-34.

*Brandom WF, Saccomanno G, Archer VE, et al. 1978. Chromosome aberrations as a biological dose-response indicator of radiation exposure in uranium miners. Radiat Res 76:159-171.

*Brandvold LL, Brandvold DK, Popp CJ. 1981. Effects of uranium mining and milling on surface water in New Mexico. In: 7th National Conference: Energy Environ, 467-476.

*Braunlich H, Fleck C. 1981. Urinary enzyme excretion as a indicator of nephrotoxicity in dependence on age. Exp Pathol 20(3):182-7.

*Broadway JA, Strong AB. 1983. Radionuclides in human bone samples. Health Phys 45:765-768.

*Brodsky A. 1996. Radiation risks and uranium toxicity. RSA Publications, Hebron, Connecticut.

*Brookins DG, Thomson BM, Longmire PA, et al. 1993. Geochemical behavior or uranium mill tailings leachate in the subsurface. Radioactive Waste Management and the Nuclear Fuel Cycle 17(3-4):269-287.

*Brown DP, Bloom T. 1987. Mortality among uranium enrichment workers. Report to National Institute for Occupational Safety and Health, Cincinnati, OH. NTIS PB87-188991.

*Brown RM, Long SE, Pickford CJ. 1988. The measurement of long lived radionuclides by non-radiometric methods. In: 5th Symposium: Environmental Radiochemical Analysis, Part B, Harwell, England, UK, October 1-3, 1986. Sci Tot Environ 70:265-274.

*Brunskill GJ, Wilkinson P. 1987. Annual supply of uranium-238, uranium- 234, thorium-230, radium-226, lead-210, polonium-210 and thorium-232 to lake 239 (Experimental Lakes Area, Ontario, (Canada) from terrestrial and atmospheric sources. Can J Fish Aquat Sci 44(Suppl 1):215-230.

*Bureau of Radiological Health. 1970. Radiological health handbook, revised ed. Rockville MD: U.S. Department of Health, Education and Welfare, January 1970.

*Bushaw BA. 1984. Advanced analytical techniques. In: Biokinetics and analysis of uranium in man. Proceedings of a colloquium held at Richland, WA, August 8-9, 1984. Prepared by the Hanford Environmental Health Foundation for the Department of Energy, K-1 to K-36.

*Butler C, Samet JM, Black WC, et al. 1986. Histopathologic findings of lung cancer in Navajo men: Relationship to U mining. Health Phys 51:365-368.

*Butler FE. 1968. Rapid bioassay methods for plutonium, neptunium, and uranium. Health Phys 15:19-24.

*Butterworth A. 1955. The significance and value of uranium in urine analysis. Trans Assoc Ind Med Offrs 5:30-43.

*Butterworth A, McLean AS. 1955. Observation on the metabolism of soluble uranium in humans. UKAEA Report IGO-R/R. 8.

*Byerley JJ, Scharer JM, Atkinson GF. 1987. Determination of uranium(VI) in process liquors by ion chromatography. Analyst 112:41-44.

*Carpenter AV, Flanders WD, Frome EL, et al. 1987. Radiation exposure and central nervous system cancers: A case-control study among workers at two nuclear facilities. Govt Reports Announce Ind, Issue 19. NTIS/DE87007922.

*Carpenter AV, Flanders WD, Frome EL, et al. 1988. Chemical exposures and central nervous system cancers: A case-control study among workers at two nuclear facilities. Am J Ind Med 13:351-362.

*Carten CT, Jr., 1978. A review of parameter values used to assess the transport of plutonium, uranium, and thorium in terrestrial food chains. Environ Research 17:437-452.

CELDs. 1994. Computer-assisted Environmental Legislative Database. University of Illinois at Urbana.

*Chang X, Luo X, Zhan G, et al. 1990. Performance for PAN-3 Chelate fiber for adsorbing and separating trace uranium. Mikrochim Acta 101-105.

*Chase GR. 1989. Correlation between airborne uranium exposure and uranium urinalysis results at Bear Creek Uranium. Health Phys 56(2):195-199.

*Checkoway H, Crawford-Brown D. 1987. Metabolic modeling of organ-specific doses to carcinogens as illustrated with alpha-radiation emitting radionuclides. In: Symposium: Time-related factors in cancer epidemiology, Bethesda MD, April 15-16. J Chronic Dis 40(2):191S-200S.

*Checkoway H, Mathew RM, Shy CM, et al. 1985. Radiation, work experience, and cause specific mortality among workers at an energy research laboratory. Br J Ind Med 42:525-533.

*Checkoway H, Pearce N, Crawford-Brown DJ, et al. 1988. Radiation doses and cause-specific mortality among workers at a nuclear materials fabrication plant. Am J Epidemiol 127(2):255-266.

*Chemelevsky D, Kellerer AM, Spiess H. 1986. A proportional hazards analysis of bone sarcoma rates in German radium 224 patients. In: Gossener W, Gerber GB, et al. eds. The radiobiolgy of radium and thorotrast. Munich, West Germany: Urban and Schwarzenberg.

*Chovil A, Chir B. 1981. The epidemiology of primary lung cancer in uranium miners in Ontario. J Occup Med 23(6):417-421.

*Clark R. 1999. Control of low-level radiation exposure: time for a change? J Radiol Prot 19(2):107-115.

*Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1:111-113.

*Cohen BL. 1982a. Radon daughter exposure to uranium miners. Health Phys 42:449-457.

*Cohen BL. 1982b. Failures and critique of the BEIR III lung cancer risk estimates. Health Phys 42:267-284.

*Cohen BL. 1982c. Effects of ICRP Publication 30. Health Phys 42:133-143.

*Cohen BL. 1987. Tests of the linear, no-threshold dose-response relationship for high-LET radiation. Health Phys 52:629- 636.

*Cookfair DL, Beck WL, Shy C, et al. 1983. Lung cancer among workers at a uranium processing plant. In: Proceedings of the Health Physics Society 398-406.

*Cooper JR, Stradling GN, Smith H, et al. 1982. The behavior of uranium-233 oxide and uranyl-233 nitrate in rats. Int J Radiat Biol Relat Stud Phys, Chem Med 41(4):421-433.

*Cothern CR. 1987. Development of regulations for radionuclides in drinking water. In: Graves B, ed. Radon in ground water, radon, radium and other radioactivity in ground water: Hydrogeologic impact and application to indoor airborne contamination. Proc National Water Well Association conference, Somerset, NJ, April 7-9, 1987. Chelsea, MI: Lewis Publishers, Inc. 1-11.

*Cothern CR, Lappenbusch WL. 1983. Occurrence of uranium in drinking water in the U.S. Health Phys 45:89-99.

*Cothern CR, Lappenbusch WL, Cotruvo J. 1983. Health effects guidance for uranium in drinking water. Health Phys 44(Suppl 1):377-384.

*Cotton FA, Wilkinson. 1980. Advanced inorganic chemistry. A comprehensive text. 4th ed. New York, NY: John Wiley & Sons, 1028-1036.

*Cottrell WD, Haywood FF, Witt DA, et al. 1981. Radiological survey of the Shpack Landfill, Norton, Massachusetts. Report: ISS DOE/EV-0005/31. DE82004939.

*Cowart JB, Burnett WC. 1994. The distribution of uranium and thorium decay-series radionuclides in the environment- A Review. J Environ Qual 23:651-662.

*Cragle DL, McLain RW, Qualters JR, et al. 1988. Mortality among workers at a nuclear fuels production facility. Am J Ind Med 14:379-401.

*Cross FT. 1979. Exposure standards for uranium mining. Health Phys 37:765-772.

*Cross FT, Filipy RE, Loscutoff SM, et al. 1981a. Histopathologic, morphometric and physiologic investigation of lungs of dogs exposed to uranium ore dust. In: International Conference: Hazards Min Control. Meas, Med, Aspects 228-235.

*Cross FT, Palmer RF, Busch RH, et al. 1981b. Development of lesions in Syrian golden hamsters following exposure to radon daughters and uranium ore dust. Health Phys 41:135-153.

8. REFERENCES

*Cross FT, Palmer RF, Filipy RE, et al. 1982. Carcinogenic effects of radon daughters, uranium ore dust and cigarette smoke in Beagle dogs. Health Phys 42(1):33-52.

*Damon EG, Eidson AF, Hahn FF, et al. 1984. Comparison of early lung clearance of yellowcake aerosols in rats with *in vitro* dissolution and IR analysis. Health Phys 46:859-866.

*Davis MW. 1985. Correlation analysis of first phase monitoring results for uranium mill workers. Govt Rep Announce Ind, Issue 26. NTIS DE85701970.

*De Rey BM, Lanfranchi HE, Cabrini RL. 1983. Percutaneous absorption of uranium compounds. Environ Res 30:480-491.

*De Rey BM, Lanfranchi HE, Cabrini RL. 1984. Deposition pattern and toxicity of subcutaneously implanted uranium dioxide in rats. Health Phys 46:688-692.

*de Siloniz MI, Lorenzo P, Perera J. 1991. Distribution of oxidizing bacterial activities and characterization of bioleaching-related microorganisms in a uranium mineral heap. Microbiologia 7(2):82-89.

*Dehos A, Hinz G, Schwarz ER. 1986. Changes in number and function of the lyphocyte populations as a biological indicator for ionizing radiation. In: Biological indicators for radiation dose assessment. Munchen: MMV Medizin Verlag, 298-301.

*Diamond GL. 1988. Biological monitoring of urine for exposure to toxic metals. In: Clarkson TW, Friberg L, Nordberg GF, et al., eds. Biological monitoring of toxic metals. New York, NY: Plenum Press, 515-529.

*Diamond GL, Morrow PE, Panner BJ, et al. 1989. Reversible uranyl nephrotoxicity in the Long Evans rat. Govt Rep Announce Ind, Issue 01. NTIS/NUREG/CR-4951.

*Diel JH, Lundgren DL. 1982. Repeated inhalation exposure of Beagle dogs to 239PUO2: Retention and translocation. Health Phys 43:655-662.

*Dockery DW, Arden P, Xu X. 1993. An association between air pollution and mortality in six US cities. The New England Journal of Medicine. 329(24):1753-1759.

*Dodge CJ, Francis AJ. 1994. Photodegradation of uranium-citrate complex with uranium recovery. Envion Sci Technol 28:1300-1306.

*Dodge CJ, Francis AJ. 1997. Biotransformation of binary and ternary citric acid complexes of iron and uranium. Environ Sci Technol 31(11):3062-3067.

*DOE. 1988. Health physics manual of good practices for uranium facilities. U.S. Department of Energy, Idaho National Engineering Laboratory, EGG-2530 UC-41.

*DOE. 1993a. U.S. Department of Energy. Code of Federal Regulations 10 CFR 835.

*DOE. 1993b. Occupational radiation protection, final rule. U.S. Department of Energy. Federal Register, Vol 58, No 238, December 1993.

*DOE. 1994a. Radiological control manual. U.S. Department of Energy, DOE/EH-0256T, Revision 1, April 1994.

*DOE. 1994b. U.S. Department of Energy. Alternative strategies for the long-term management of depleted uranium hexafluoride resources at several geographic locations. Federal Register 56324, Washington, D.C., November 1994.

*DOE. 1995. Uranium Industry Annual 1994. Energy Information Administration, Office of Coal, Nuclear, Electric and Alternate Fuels, U. S. Department of Energy. Washington DC.

*DOE. 1996a. Uranium industry annual 1995. Energy Information Administration, Office of Coal, Nuclear, Electric and Alternate Fuels, U. S. Department of Energy. Washington DC.

*DOE. 1996b. Uranium industry annual 1996. Energy Information Administration, Office of Coal, Nuclear, Electric and Alternate Fuels; U.S. Department of Energy, Washington, DC, April 1997, DOE/EIA-0478(96), Distribution Category UC-950.

*DOE. 1996c. Annual limits on intake (ALIs) and derived air concentrations (DACs) of radionuclides for occupational exposure; effluent concentrations; concentrations for release to sewerage. 10CFR20 Appendix B. U. S. Department of Energy, Washington, D.C.

*DOE. 1997. EML procedures manual, HASL-300, 28th edition. Environmental Measurements Laboratory, U. S. Department of Energy, New York.

*DOE. 1998. Location of laboratories and national laboratories. U.S. Department of Energy, http://www.doe.gov/people/labsmap.htm

*DOE. 1999a. Total production of uranium concentrate in the United States. U. S. Department of Energy. http://www.eia.doe.gov/cneaf/nuclear/page/at_a_glance/qtr_upd/qupd.html

*DOE. 1999b. Uranium industry annual 1998. Energy Information Administration, Office of Coal, Nuclear, and Alternate Fuels, U.S. Department of Energy. Washington, D.C. DOE/EIA0478(98).

*DOE. 1999c. Location of U.S. Department of Energy laboratories, offices, and facilities. U.S. Department of Energy. http://home.doe.gov/people/labsmap

DOI. 1980. Depleted uranium. U.S. Department of the Interior. Washington DC, Bureau of Mines Bulletin 671.

*DOI. 1993a. U.S. Department of Interior. Federal Register. 58 FR 13244 (proposed).

*DOI. 1993b. U.S. Department of Interior. Federal Register. 58 FR 52059 (proposed).

*DOI. 1994. U.S. Department of Interior. Code of Federal Regulations. 30 CFR 875.16.

*Doll R. 1977. Strategy for detection of cancer hazards to man. Nature 265:589-596.

*Domingo JL, Colomina MT, Llobet JM, et al. 1992. The action of chelating agents in experimental uranuim intoication in mice: Variations with structure and time of administration. Fundamental and Applied Toxicology, 350-357

8. REFERENCES

*Domingo JL, de la Torre A, Belles M, et al. 1997. Comparative effects of the chelators sodium 4,5-dihydroxybenzene-1,3-disulfonate (tiron) and diethylenetriaminepentaacetic acid (dtpa) on acute uranium nephrotoxicity in rats. Toxicology 118(1):49-59.

*Domingo JL, Llobet JM, Tomas JM, et al. 1987. Acute toxicity of uranium in rats and mice. Bull Environ Contam Toxicol 39:168-174.

*Domingo JL, Ortega A, Llobet JM, et al. 1989a. The effects of repeated parenteral administration of chelating agents on the distribution and excretion of uranium. Research Communications Chemical Pathology and Pharmacology 64(1):161.

*Domingo JL, Ortega A, Paternain JL, et al. 1989b. Evaluation of the perinatal and postnatal effects of uranium in mice upon oral administration. Arch Environ Health 44(6):395-8.

*Domingo JL, Paternain JL, Llobet JM, et al. 1989c. The developmental toxicity of uranium in mice. Toxicology 55(1-2):143-52.

*Donaldson AW. 1969. The epidemiology of lung cancer among uranium miners. Health Phys 16:563-569.

*Dounce AL, Flagg JF. 1949. The chemistry of uranium compounds. In: Voegtlin, Hodge, eds. Pharmacology and toxicology of uranium compounds, 82-84.

*Downs WL, Wilson HB, Sylvester GE, et al. 1967. Excretion of uranium by rats following inhalation of uranium dioxide. Health Phys 13:445-453.

*Dreesen DR, Williams MJ, Marple ML, et al. 1982. Mobility and bioavailability of uranium mill tailings contaminants. Environ Sci Technol 16:702-709.

*Drury JS. 1981. Uranium in U. S. surface, ground, and domestic waters. Volume 1. U. S Department of Commerce. National Technical Information Services.

*Drury JS, Reynolds S, Owen PT, et al. 1982. Uranium in U.S. surface, ground, and domestic waters. Volume 1. Govt Rep Announce Ind, Issue 24. NTIS/PB82-258740.

*du Preez JGH. 1989. A review of the industrial process involving uranium from the ore to the reactor. Radiation Protection Dosimetry 26:7-13.

*Dungworth DL. 1989. Noncarcinogenic responses of the respiratory tract to inhaled toxicants. In: McClellan RO, Henderson RF, eds. Concepts in inhalation toxicology. New York. NY: Hemisphere Publishing Corporation.

*Dunning DE, Leggett RW, Sullivan RE. 1984. An assessment of health risk from radiation exposures. Health Phys 46:1035-1051.

*Dunning DE, Leggett RW, Yalcintas MG. 1980. A combined methodology for estimating dose rates and health effects for exposure to radioactive pollutants. Oak Ridge, TN: Oak Ridge National Laboratory. ORNL/RM-7105.

*Dupree EA, Cragle DL, McLain RW, et al. 1987. Mortality among workers at a uranium processing facility, the Linde Air Products Company Ceramics Plant, 1943-1949. Scand J Work Environ Health (Finland) 13(2):100-107.

*Dupzyk IA, Dupzyk RJ. 1979. Separation of uranium from urine for measurement by fluorimetry of isotope-dilution mass spectrometry. Health Phys 36:526-529.

*Durbin PW, Wrenn ME. 1975. Metabolism and effects of uranium in animals. In: Wrenn ME, ed. Conference: Occupational health experience with uranium. Arlington, VA, April, 1975. U.S. Energy Research and Development Administration, Washington, DC. ERDA-93, 67-129.

*Dygert HP. 1949a. Pharmacology and toxicology of uranium compounds. New York, NY: McGraw-Hill Book Inc., 603-613.

*Dygert HP. 1949b. Pharmacology and toxicology of uranium compounds. New York, NY: McGraw-Hill Book Inc., 666-672.

*Dygert HP. 1949c. Pharmacology and toxicology of uranium compounds. New York, NY: McGraw-Hill Book Inc., 673-675.

*Dygert HP. 1949d. Pharmacology and toxicology of uranium compounds. New York, NY: McGraw-Hill Book Inc., 647-652.

*Dygert HP. 1949e. Pharmacology and toxicology of uranium compounds. New York, NY: McGraw-Hill Book Inc., 676-700.

*Eadie GG, Fort CW, Beard ML. 1979. Ambient airborne radioactivity measurements in the vicinity of the jackpile open pit uranium mine New Mexico. Report: ISS ORP/LV-79/2. NTIS PB292379.

*Eadie GG, Kaufmann RF. 1977. Radiological evaluation of the effects of uranium mining and milling operations on selected ground water supplies in the Grants Mineral Belt, New Mexico. Health Phys 32:231-241.

*Early P, Razzak M, Sodee D. 1979. Nuclear medicine technology. 2nd ed. St. Louis MO: C.V. Mosby Company.

*Edling C. 1982. Lung cancer and smoking in a group of iron ore miners. Am J Ind Med 3:191-200.

*Eichholz G. 1982. Environmental aspects of nuclear power. Ann Arbor, MI: Ann Arbor Science.

*Eidson AF, Griffith WC, Jr., Hahn FF, et al. 1989. A model for scaling the results of U excretion rate studies in Beagle dogs to man. Health Physics 57:199-210.

*Eidson AF. 1994. The effect of solubility on inhaled uranium compound clearance. Health Phys 67(1):1-14.

*Eisenbud M. 1959. Discussion of apparent anomalies in lung retention of uranium. USEAC Report HAS-58, 212-213.

*Eisenbud M, Quigley JA. 1955. Industrial hygiene of uranium processing. AMA Archives of Industrial Health, 12-22.

*Eisenbud M, Quigley JA. 1956. Industrial hygiene of uranium processing. Arch Ind Health 14:12-22.

*Ellender M. 1987. The clearance of uranium after deposition of the nitrate and bicarbonate in different regions of the rat lung. Human Toxicol 6:479-482.

*Ellender M, Haines JW, Harrison JD. 1995. The distribution and retention of plutonium, americium and uranium in cba/h mice. Hum Exp Toxicol 14(1):38-48.

*EPA. 1977a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.15.

*EPA. 1977b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 190, Subpart B.

*EPA. 1979. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 125.

*EPA. 1980a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.25.

*EPA. 1980b. U. S. Environmental Protection Agency.   Prescribed procedures for measurement of radioactivity in drinking water. Environmental monitoring and support laboratory, Cincinnati, OH. EPA-600-4-0-032. 96-111.

*EPA. 1980c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 146.5.

*EPA. 1980d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.4.

*EPA. 1981. Radioactivity in drinking water. Office of Drinking Water, U.S. Environmental Protection Agency, Washington, DC. NTIS PB81-192833.

*EPA. 1982a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60, Subpart A.

*EPA. 1982b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 440, Subpart C.

*EPA. 1982c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 440, Subpart H.

*EPA. 1982d. U.S. Environmental Protection Agency. 1982. Ore mining and dressing point source category effluent limitations guidelines and new source performance standards. Fed Reg 47:54598-545621. Final rule.

*EPA. 1983a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 122, Appendix D.

*EPA. 1983b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 192, Subpart A.

*EPA. 1983c. U.S. Environmental Protection Agency. Reportable quantity document for uranyl nitrate. Prepared by the Office of Health and Environmental Assessment, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC.

*EPA. 1984a. U. S. Environmental Protection Agency Code of Federal Regulations. 40 CFR 60 Subpart LL.

*EPA. 1984b. U.S. Environmental Protection Agency. Radionuclides: Background information document for final rules. Vol 1. U.S. Environmental Protection Agency, Office of Radiation Program, Washington, DC. EPA 520/1- 84-022-1. NTIS PB85-165751.

*EPA. 1984c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 147.3011.

*EPA. 1984d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 147.3003.

*EPA. 1985a. U. S. Environmental Protection Agency Code of Federal Regulations. 40 CFR 302.3.

*EPA. 1985b. U. S. Environmental Protection Agency Code of Federal Regulation CFR 421, Subpart AD.

*EPA. 1985c. U.S. Environmental Protection Agency. Code of Federal Regulations.   40 CFR 471, Subpart G.

*EPA. 1985d. U.S. Environmental Protection Agency. Code of Federal Regulations.   40 CFR 471.71.

*EPA. 1985e. U.S. Environmental Protection Agency. Code of Federal Regulations.   40 CFR 471.72.

*EPA. 1985f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 471.73.

*EPA. 1985g. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 471.75.

*EPA. 1985h. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 23.8.

*EPA. 1985i. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 191.12.

*EPA. 1985j. U.S. Environmental Protection Agency. Drinking water criteria document for uranium. Washington, DC, April 1985, PB86-241049.

*EPA. 1986a. U.S. Environmental Protection Agency. Reference values for risk assessment. Prepared by Environmental Criteria and Assessment Office, Office of Solid Waste, Washington, DC.

*EPA. 1986b. U.S. Environmental Protection Agency. Final rule for radon- 222 emissions from licensed uranium mill tailings. Background information document. Report. EPA 520/1-86-009. NTIS PB87-207569.

*EPA. 1986c. U.S. Environmental Protection Agency. Proposed rules: Water pollution control; natural primary drinking water regulations; radionuclides. 40 CFR 141. Federal Register 34836.

8. REFERENCES

*EPA. 1987a. U.S. Environmental Protection Agency. Reportable quantity adjustments for radionuclides. Federal Register 52(50):8176.

*EPA. 1987b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 146.6.

*EPA. 1988a. U.S. Environmental Protection Agency. Analysis of clean water act effluent guidelines pollutants: Summary of the chemicals regulated by industrial point source category.   Prepared by the Industrial technology Division (WH 552), Office of Water Regulations and Standards, Office of Water, Washington, DC. 40 CFR Parts 400-475.

*EPA. 1988b. U.S. Environmental Protection Agency. Limiting values of radionuclide intake and air concentration and dose conversion factors for inhalation, submersion, and ingestion. EPA-520/1-88-020. U.S. Environmental Protection Agency. Washington, DC.

*EPA. 1988c. U.S. Environmental Protection Agency.   Environmental radiation protection standards for nuclear power operations. 40 CFR 190.

*EPA. 1989a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart B.

*EPA. 1989b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart I.

*EPA. 1989c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart Q.

*EPA. 1989d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart T.

*EPA. 1989e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 61, Subpart W.

*EPA. 1989f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

*EPA. 1989g. U.S. Environmental Protection Agency.   Interim methods for development of inhalation references doses. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. Washington, DC. EPA 600/8-88-066F.

*EPA. 1990a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 300, Appendix A.

*EPA. 1990b. U.S. Environmental Protection Agency. Code of Federal Regulations.   40 CFR 300.5.

*EPA. 1990c. U.S. Environmental Protection Agency. Summary of state and federal drinking water standards and guidelines.

*EPA. 1990d. U.S. Environmental Protection Agency.   Interim methods for development of inhalation reference doses. EPA-600/8-90/066A.

*EPA. 1991. U.S. Environmental Protection Agency. Radionuclides in drinking water fact sheet.
National Primary Drinking Water Regulations for Radionuclides, Proposed Rule, June, 1991.
EPA-570/9-91-700. Washington, DC.

*EPA. 1993a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 310.11.

*EPA. 1993b. U.S. Environmental Protection Agency. Standards for management of uranium byproduct
material pursuant to section 84 of the Atomic Energy act of 1954, as amended. Code of Federal
Regulations. 40 CFR 192, Subpart D.

*EPA. 1993c. U.S. Environmental Protection Agency. Federal Register. 58 FR 34018 (proposed).

*EPA. 1993d. U.S. Environmental Protection Agency. Federal Register. 58 FR 54072 (proposed).

*EPA. 1993e. U.S. Environmental Protection Agency. Federal Register. 59 FR 32622 (proposed).

*EPA. 1994a. U.S. Environmental Protection Agency. Environmental radiation data report 74, April-June
1993. National Air and Radiation Environmental Laboratory. EPA 402-R-93-093, August 1994.

*EPA. 1994b. U.S. Environmental Protection Agency. EPA requirements for quality assurance project
plans for environmental data operations. EPA QA/R-5, draft interim final, Quality Assurance Management
Staff, Washington, D.C.

*EPA. 1994c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 300,
Appendix B.

*EPA. 1995a. U.S. Environmental Protection Agency. Standards for cleanup of land and buildings
contaminated with residual radioactive materials from inactive uranium processing sites. Code of Federal
Regulations. 40 CFR 192, Subpart B.

*EPA. 1995b. Implementation. U.S. Environmental Protection Agency. Code of Federal Regulations.
40 CFR 192, Subpart C.

*EPA. 1995c. U.S. Environmental Protection Agency. Standards for the control of residual radioactive
materials from inactive uranium processing sites. Code of Federal Regulations. 40 CFR 192, Subpart A.

*EPA. 1995d. U.S. Environmental Protection Agency. Technical resource document, extraction and
beneficiation of ores and minerals. EPA 530-R-94-032, NTIS PB94-2008987.

*EPA. 1996. U.S. Environmental Protection Agency. Guidance for Data Quality Assessment: Practical
Methods for Data Analysis. EPA QA/G-9 QA96 Version, EPA/600/R-96/084, Quality Assurance
Management Staff, Washington, D.C.

*EPA 1997a. U.S. Environmental Protection Agency. Announcement of draft drinking water contaminant
candidate list; Notice. Federal Register. 62 FR 52194. October 6, 1997.

8. REFERENCES

*EPA. 1997b. U.S. Environmental Protection Agency. Establishment of cleanup levels for CERCLA sites with radioactive contamination (memorandum and attachments). OSWER No. 9200.4-18. Office of Solid Waste and Emergency Response. Office of Emergency and Remedial Response. http://www.epa.gov/superfund/

*EPA. 1997c. U.S. Environmental Protection Agency. National primary drinking water regulations: Analytical methods for radionuclides; final rule and proposed rule. Federal Register. 62 FR 10168. March 5, 1997.

*EPA. 1998. U.S. Environmental Protection Agency. Use of soil cleanup criteria in 40 CFR 192 as remediation goals for CERCLA sites. Directive No. 9200.4-25. Office of Solid Waste and Emergency Response. Office of Emergency and Remedial Response. http://www.epa.gov/superfund/resources/soil/cleanup.htm.

*EPA. 1998b. U.S. Environmental Protection Agency. Land disposal restrictions phase IV: Final rule promulgating treatment standards for metal wastes and mineral processing wastes; mineral processing secondary materials and bevill exclusion issues; treatment standards for hazardous soils, and exclusion of recycled wood preserving wastewaters; final rule. Federal Register. 63 FR 28556. May 26, 1998.

*Eral M. 1989. Chemical determination of uranium in natural waters with DBM by the adsorption of U(VI) on Fe(OH)3. Spectroscopy Letters 22(4):431-440.

*Erdal BR, Daniels WR, Hoffman DC, et al. 1979. Sorption and migration of radionuclides in geologic media. Mater Res Sci Basis Nucl Waste Manage 423-426.

*Essien IO, Sandoval DN, Kuroda PK. 1985. Deposition of excess amount of natural U from the atmosphere. Health Physics 48(3):325-331.

*Evans RD, Keane AT, Kolenkow RJ. 1969. Radiogenic tumors in the radium cases studied at MIT. In: Mays CW, et al., eds. Delayed effects of bone seeking radionuclides. Salt Lake City, Utah: University of Utah Press, 157-194.

*Fabrikant JI. 1990. The health effects of radon and other alpha emitting radionuclides: The National Academy of Sciences BEIR IV report. Elsevier Science Publishers, 9-13.

*Fajgelj A, Horvat D, Pucelj B. 1992. Chromosome abberations induced in human lymphocytes by U-235 fission neutrons. Strahlentherapie and Onkologie 406-411.

*Feeney CM, Anderson JW, Tindall FM. 1983. Determination of uranium in tailings by inductively coupled plasma optical emission spectrometry. At Spectrosc 4:108-110.

*Filippova LG, Nifativ AP, Lyubchanskii ER. 1978. Some of the long-term sequelae of giving rats enriched uranium. Radiobiology 18:400-405.

*Finkel MP. 1953. Relative biological effectiveness of radium and other alpha emitters in CF no 1 female mice. Proc Soc Exp Biol Med 83:494-498.

*Fisenne I, Perry PM, Welford GA. 1980. Determination of uranium (isotopes) in human bone ash. Anal Chem 52:777-779.

*Fisenne IM. 1988. Uranium in humans. Radiation Protection Dosimetry 24:127-131.

*Fisenne IM, Perry PM. 1985. Isotopic U concentration in human blood from New York City donors. Health Phys 49:1272-1275.

*Fisenne IM, Perry PM, Decker KM, et al. 1987. The daily intake of the uranium, thorium, and radium isotopes 234, 235, 238U, 228, 230, 232Th, and 226, 228Ra by New York City residents. Health Phys 53:357-363.

*Fisenne IM, Welford GA. 1986. Natural uranium concentrations in soft tissues and bone of New York City residents. Health Phys 50:739-746.

*Fisher DR, Jackson PO. 1986. Reply to Singh and Wrenn regarding levels of uranium-234, -238 and thorium-230 in excreta of uranium mill crushermen. Health Phys 50:302-303.

*Fisher DR, Jackson PO, Brodaczynski GG, et al. 1983. Levels of 234U, 238U and 230th in excreta of uranium mill crushermen. Health Phys 45:617-629.

*Fisher Dr, Kathern RL, Swint MJ. 1991. Modified biokinetic model for uranium from analysis of acute exposure of UF6. Health Phys. 60(3):335-342.

*Fisher DR, Swint MJ, Kathren RL. 1990. Evaluation of health effects in Sequoyah Fuels Corporation workers from accidental exposure to uranium hexafluoride. U.S. Nuclear Regulatory Commission, Washington D.C. NUREG/CR-5566 PNL-7328

*Flamenbaum W, McNeil JS, Kotchen TA, et al. 1972. Experimental acute renal failure induced by uranyl nitrate in the dog. Circ Res 31:682-697.

*Foman SJ. 1966. Body composition of the infant (Part I: The male reference infant). In: Falkner F, ed. Human Development. Philadelphia, PA: WB Saunders, 239-246.

*Foman, SJ, Haschke F, Ziegler EE et al. 1982. Body composition of reference children from birth to age 10 years. American Journal of Clinical Nutrition 35:1169-1175.

*Fort CW, Jr., Douglas RL, Moore WE. 1980. Radioactive emissions from yellowcake processing stacks at uranium mills. Report: ISS ORP/LV-80-3. NTIS PB81-153389.

*Francis AJ, Dodge CJ, Gillow JB, et al. 1989. Microbial transformation of uranium in wastes. U. S. Department of Energy. Contract No. De-AC02-76CH00016.

*Fresquez PR, Armstrong DR. 1994. Radionuclide concentration in game (surface feeders) and non-game (bottom feeders) fish upstream and downstream of Los Alamos National Laboratory. New Mexico Conference on the Environment Albuqerque, NM.

*Friberg L, Nordberg GF, Vouk VB, eds. 1986. Handbook on the toxicology of metals. Vol. I: General aspects. 2nd ed. New York, NY: Elsevier Science Publishing Co., Inc.

*Frome EL, Cragle DL, McLain RW. 1990. Poison regression analysis of the mortality among a cohort of World War II. Radiation Research 123:138-152.

8. REFERENCES

*Fruchter JS, Robertson DE, Evans JC, et al. 1980. Reports - Mount St. Helens ash from the 18 May 1980 eruption: Chemical, physical, mineralogical, and biological properties. Science 209(5):1116-1125.

*FSTRAC. 1988. Federal State Toxicology and Regulatory Alliance Committee. Summary of state and federal drinking water standards and guidelines. Chemical Communication Subcommittee.

*Fujino O, Umetani S, Matsui M. 1994. Determination of uranium in apatite minerals by inductively coupled plasma atomic emission spectrometry after solvent extraction and separation with 3-phenyl-4-benzoyl-5-isoxazolone into diisobutyl ketone. Analytica Chimica Acta 296:63-68.

*Galibin GP, Pozdnyakov, Murav'eva LI. 1966. Biological effects of ammonium diuranate following prolonged inhalation. Gig Sanit Hyg Sanit 31(10-12):338-344.

*Galle P, Berry JP, Galle C. 1992. Role of alveolar macrophages in precipitation of mineral elements inhaled as soluble aerosols. Environ Health Perspect 97:145-147.

*Gallop RGC, Lawrenson WN, Lockyer, et al. 1988. Radionuclide levels in river sediment near to a treated effluent outfall. Sci Total Environ 780:237-251.

*Gilkeson RH, Cowart JB. 1987. Radium radon and uranium isotopes in groundwater from Cambrian-Ordovician sandstone aquifers in Illinois USA. In: Graves B, ed. Radon in ground water, radon, radium and other radioactivity in ground water: Hydrogeologic impact and application to indoor airborne contamination: Proc National Water Well Association conference, Somerset, NJ, April 7-9, 1987. Chelsea, MI: Lewis Publishers, Inc., 403-422.

*Gilman AP, Moss MA, Villeneuve DC, et al. 1998c. Uranyl nitrate: 91-day exposure and recovery studies in the male New Zealand white rabbit. Toxicol Sci 41(1):138-151.

*Gilman AP, Villeneuve DC, Secours VE, et al. 1998a. Uranyl nitrate: 28-day and 91-day toxicity studies in the Sprague-Dawley rat. Toxicol Sci 41(1):117-128.

*Gilman AP, Villeneuve DC, Secours VE, et al. 1998b. Uranyl nitrate: 91-day toxicity studies in the New Zealand white rabbit. Toxicol Sci 41(1):129-137.

*Gindler JE. 1973.   Physical and chemical properties of uranium. In: Hodge HC et al., eds. Uranium, plutonium transplutonic elements. New York, NY: Springer-Verlag, 69-164.

*Gladney ES, Peters RJ, Perrin DR. 1983. Determination of uranium- 235/uranium-238 ratio in natural waters by Chelex-100 ion exchange and neutron-activation analysis. Anal Chem 55:976-977.

*Gladney ES, Rook HL. 1975. Simultaneous determination of terrurium and uranium by neutron activation analysis. Anal Chem 47:1554-1557.

*Goel KA, Garg VK, Garg V. 1979. Histopathological alterations induced by uranyl nitrate in the liver of albino rat. Bull Environ Contam Toxicol 22:785-790.

*Goel KA, Garg VK, Garg V. 1980. Histopathology of kidney of albino rat poisoned with uranyl nitrate. Bull Environ Contam Toxicol 24:9-12.

*Gogolak CV. 1985. The radiological impact of atmospheric emissions from oil shale retorts. Environ Int 11:57-64.

*Golchert NW, Iwami FS, Sedlet J. 1980. Determination of actinides in soil. In: Lyon WS, ed. Radioelement analysis: Progress and problems. 23rd Conference: Analytical Chemistry in Energy Technology, Gatlinburg, TN, Oct. 9-11, 1979. Ann Arbor, MI: Ann Arbor Science Publishers, Inc., 215-222.

*Gonzales ER, Gladney ES, Boyd HA, et al. 1988. Determination of U in human tissues by delayed neutron activation analysis. Health Phys 55(6):927-932.

*Goode DJ, Wilder RJ. 1987. Ground-water contamination near a uranium tailings disposal site in Colorado. Ground Water 27:545-554.

*Goodman DR. 1985. Nephrotoxicity. Toxic effects in the kidneys. In: Williams PL, Burson JL, eds. Industrial toxicology safety and health applications in the workplace. New York. NY: Van Nostrand Reinhold Company.

*Gore DJ. 1983. The spatial and temporal distribution of inhaled UO2 particles in the respiratory tract of the rat. II. The relative concentration of UO2 between the intrapulmonary airways and the pulmonary tissue. Radiation Research 93:276-287.

*Gore DJ, Papworth DG. 1983. The spatial and temporal distribution of inhaled UO2 particles in the respiratory tract of the rat. I. Pulmonary tissue. Radiation Research 93:262-275.

*Gore DJ, Patrick G. 1978. The distribution and clearance of inhaled uranium dioxide particles on the first bifurcation and trachea of rats. Phys Med Biol 23:730-737.

*Gottlieb LS, Husen LA. 1982. Lung cancer among Navajo uranium miners. Chest 81:449-452.

*Grace M, Larson M, Hanson J. 1980. Bronchogenic carcinoma among former uranium mine workers at Port Radium, Canada. Health Phys 38:657-661.

*Grainger CR. 1994. Geochemistry and Environmental Health: Uranium in Cornwall. J Roy Soc Health 11.

*Greene B, Uranga A, Sneddon J. 1985. Observations on the determination of uranium in waters by direct current argon plasma emission spectrometry. Spectroscopy Letters 18(6):425-436.

*Grey C. 1993. Uranium: From ore to concentrate. The Nuclear Engineer 34(1):3-9.

*Guglielmotti MB, Ubios AM, Larumbe J, et al. 1989. Tetracycline in uranyl nitrate intoxication: Its action on renal damage and U retention in bone. Heath Physics 57:403-405.

*Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and differences between children and adults: implications for risk assessment. International Life Sciences Institute Press, Washington, D.C.

*Hadjimichael CC, Ostfeld AM, D'Atri DA, et al. 1983. Mortality and cancer incidence experience of employees in a nuclear fuels fabrication plant. J Occup Med 25:48-61.

*Hahn FF. 1989. Carcinogenic responses of the lung to inhaled materials. In: McClellan RO, Henderson RF, eds. Concepts in inhalation toxicology. New York, NY: Hemisphere Publishing Corporation.

*Haley DP. 1982. Morphologic changes in uranyl nitrate-induced acute renal failure in saline- and water-drinking rats. Lab Invest 46:196-208.

*Haley DP, Bulger RE, Dobyan DC. 1982. The long-term effects of uranyl nitrate on the structure and function of the rat kidney. Virchows Arch B 41:181-192.

*Hamilton EI. 1972. The concentration of uranium in man and his diet. Health Phys 2:149-153.

*Hans J Jr., Burris E, Gorsuch T. 1979. Radioactive waste management at the former Shiprock Uranium Mill Site New-Mexico ,USA. In: 24th Annual meeting of the Health Physics Society. Health Phys 37:811.

*Harduin JC, Cogema LH, Beaumont-Hague FP. 1994. Uptake and urinary excretion of uranium after oral administration in man. Radiation Protection Dosimetry 53(1-4):245-248.

*Harley NH, Fisenne IS. 1990. Distribution and radiation dose from naturally occuring U, Th and Ra in the human skeleton. Health Phys 58(4):515-518.

*Harley NH, Pasternack BS. 1979. Potential carcinogenic effects of actinides in the environment. Health Phys 37:291-300.

*Harley NH, Pasternack BS. 1981. A model for predicting lung cancer risks induced by environmental levels of radon daughters. Health Phys 40:307-316.

*Harms TF, Ward FN, Erdman JA. 1981. Laser fluorometric analysis of plants for uranium exploration. J Geochem Explor 15:617-623.

*Harrison JD, Stather JW. 1981. The gastrointestinal absorption of proactinium, uranium and neptunium in the hamster. Radiation Research 88:47-55.

*Hart DR, McKee PM, Burt AJ, et al. 1986. Benthic community and sediment quality assessment of Port Hope Harbour, Lake Ontario. J Great Lakes Res 12:206-220.

*Hawley GG. 1981. The condensed chemical dictionary. 10th ed. New York, NY: Van Nostrand Reinhold Co., 1071-1072.

*HazDat. 1998. Database. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*Heid KR, Fuqua PA. 1974. Review of uranium inhalation case. Health Phys 26:399-403.

*Hendee W. 1973. Radioactive isotopes in biological research. New York, NY: John Wiley and Sons.

*Henge-Napoli MH, Archimbaud M, Ansoborlo E, et al. 1995. Efficacy of 3,4,3-lihopo for reducing the retention of uranium in rat after acute administration. Int J Radiat Biol 68(4):389-93.

*Herczeg AL, Simpson HJ, Anderson RF, et al. 1988. Uranium and radium mobility in groundwaters and brines within the Delaware basin, southeastern New Mexico, U.S.A. Chem Geol 72:181-196.

*Hinton ER Jr. 1983. Development of a multi-purpose alpha-detection procedure for enriched uranium in urine. Anal Lett 16:367-380.

*Hinton ER Jr, White LE. 1981. Applications of laser-induced fluorimetry to analysis of ultra-trace levels of uranium in an industrial environment. Anal Lett 14:947-949.

*Ho CH, Doern DC. 1985. The sorption of uranyl species on a hematite sol. Can J Chem 63:1100-1104.

*Hobbs C, McClellan R. 1986. Radiation and radioactive materials. In: Doull J, et al., eds. Casarett and Doull's Toxicology. 3rd ed. New York, NY: Macmillan Publishing Co., Inc., 497-530.

*Hodge HC, Stannard JV, Hursh JB, eds. 1973. Uranium plutonium transplutonic elements. In: Handbook of experimental pharmacology XXXVI. New York, NY: Springer Verlag.

*Hodge HC, Stokinger HE, Neuman WF. 1949. Suggested maximum allowable concentration of soluble uranium compounds in air. USAEC Report AECD, 2785.

*Holmes C. 1982. Lung cancer rates and the heights of miners [letter]. J Occup Med 24:9-10.

*Holzbecher J, Ryan DE. 1980. Determination of uranium by thermal- and epithermal-neutron activation in natural waters and in human urine. Anal Chim Acta 119:405-408.

*Horikoshi T, Nakajima A, Sakaguchi T. 1981. Studies on the accumulation of heavy metal elements in biological systems. XIX. Accumulation of uranium by microorganisms. Eur J Appl Microbiol Biotechnol 12:90-96.

*Hornung RW, Meinhardt TJ. 1987. Quantitative risk assessment of lung cancer in USA uranium miners. Health Phys 52:417-430.

*Horvat DJ et al. 1981. Cytogenetic effect of uranyl nitrate and cadmium chloride on V79 Chinese hamster cells. Mutat Res 85:288.

*Howe GR, Nair RC, Newcombe HB, et al. 1986. Lung cancer mortality (1950-1980) in relation to radon daughter exposure in a cohort of workers at the Eldorado Beaverlodge Uranium Mine (Saskatchewan, Canada). N Natl Cancer Inst 77:357-362.

*Howe GR, Nair RC, Newcombe HB, et al. 1987. Lung cancer mortality (1950-1980) in relation to radon daughter exposure in a cohort of workers at the Eldorado Port Radium Uranium Mine: Possible modification of risk by exposure rate. J Natl Cancer Inst 79:1255-1260.

*HPS. 1996. Health Physics Society Standard no. N13.30-1996. Performance Criteria for Radiobioassay published by the Health Physics Society in 1996.

*HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Program (via TOXNET), Bethesda, MD. January 1995.

*Hsi CKD, Langmuir D. 1985. Adsorption of uranyl onto ferric oxyhydroxides: Application of the surface complexation site-binding model. Geochim Cosmochim Acta 49:1931-1942.

*Hu QY, Zhu SP. 1990. Detection of DNA damage in spermiogenic stages of mice and treated with enriched uranyl fluoride by alkaline elution. Radiat Environ Biophys 29(3):161-167.

*Hueper WC, Zuefle JH, Link AM et al. 1952. Experimental studies in metal carcinogenesis. II. Experimental uranium cancers in rats. Journal of the National Cancer Institute 13:291-305.

*Hursh JB. 1959. Urinary uranium as an indicator of dose to exposed personnel. USAEC Report HASL-58, 136-138.

*Hursh JB, Neuman WF, Toribara T, et al. 1969. Oral ingestion of uranium by man. Health Phys 17:619-621.

*Hursh JB, Spoor J. 1973. Data on man. Handbook Exp Pharmakol 36:197-239.

*Ibrahim SA, Wicker FW. 1988. Comparative uptake of U and Th by native plants at a U production site. Health Physics 54(4):413-419.

*ICRP. 1966. International Commission for Radiation Protection. Task group on lung dynamics, depositions and retention models for internal dosimetry of the human respiratory tract. Health Phys 21:173-207.

*ICRP. 1972. International Commission for Radiation Protection. The metabolism of compounds of plutonium and other actinides. ICRP Publication No. 19. New York Pergamon Press.

*ICRP. 1975. International Commission for Radiation Protection. Report of the task group on reference man. ICRP Publication No. 23. New York: Pergamon Press.

*ICRP. 1977. International Commission on Radiological Protection. Recommendations of the International Commission on Radiological Protection. ICRP Publication 26. Pergamon Press.

*ICRP. 1979. International Commission on Radiological Protection. Limits for Intakes of Radionuclides by Workers. Publication 30. Pergamon Press.

*ICRP. 1984. International Commission for Radiation Protection. A compilation of the major concepts and quantities in use by ICRP. ICRP Publication 42. Oxford: Pergamon Press.

*ICRP. 1991. International Commission on Radiological Protection. 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60 (Adopted 1978). Pergamon Press.

*ICRP. 1994. International Commission for Radiation Protection. Human respiratory tract model for radiological protection. ICRP Publication 66. Oxford: Pergamon Press.

*ICRP. 1995. International Commission for Radiation Protection. Age-dependent doses to members of the public from intake of radionuclides: Part 3, Ingestion dose coefficients. ICRP Publication 69. Oxford: Pergamon Press.

*ICRP. 1996. International Commission for Radiation Protection.   Age-dependent doses to members of the public from intake of radionuclides: Part 4, Inhalation dose coefficients. ICRP Publication 71. Oxford: Pergamon Press.

*ICRU. 1980. International Commission on Radiation Units and Measurements. ICRU Report No. 33. Washington, DC.

*Ingersoll JG. 1983. A survey of radionuclide contents and radon emanation rates in building materials used in the U.S. Health Phys 45:363-368.

*Inn KGW. 1987. The National Bureau of Standards fresh water lake sediment environmental-level radioactivity standard reference material. J Radioanal Nucl Chem 115:91-112.

*IRIS. 1997. Integrated risk information system. Uranium, natural. CASRN 7440-61-1. (03/01/97). U.S. Environmental Protection Agency. http://www.epa.gov/ngispgm3/iris/subst/0259.htm

*James A. 1987. A reconsideration of cells at risk and other key factors in radon daughter dosimetry. In: Hopke P, ed. Radon and its decay products: Occurrence, properties and health effects. ACS Symposium Series 331. Washington, DC: American Chemical Society, 400-418.

*James A, Roy M. 1987. Dosimetric lung models. In: Gerber G, et al., eds. Age-related factors in radionuclide metabolism and dosimetry. Boston: Martinus Nijhoff Publishers, 95-108.

*James RC. 1985. Hematotoxicity. Toxic effects in the blood. In: Williams PL, Burson JL, eds. Industrial toxicology safety and health applications in the workplace.   Van Nostrand Reinhold Company.

*Jaworowski Z, Grzybowska D. 1977. Natural radionuclides in industrial and rural soils. Sci Total Environ 7:45-52.

*Jiang FS, Lee SC, Bakhitiar SN, et al. 1986. Determination of thorium, uranium and plutonium isotopes in atmospheric samples. J Radioanal Nucl Chem 100:65-72.

*Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. Brain Research 190:3-16.

Kamata E, Nakashima R, Furukawa M. 1987. Determination of trace amounts of thorium and uranium in coal ash by inductively coupled plasma atomic emission spectrometry after extraction with 2-thenoyltrifluoroacetone and back-extraction with dilute nitric acid. J Anal At Spectrom 2:321-324.

*Kamboj VP, Kar AB. 1964. Antitesticular effect of metallic and rare earth salts. J Reprod Fertil 7:21.

*Karpas Z, Halicz L, Roiz J, et al. 1996. Inductively coupled plasma mass spectrometry as a simple, rapid, and inexpensive method for determination of uranium in urine and fresh water: Comparison with lif. Health Phys 71(6):879-85.

*Kathren RL. 1984. Radioactivity in the environment: Sources, distribution and surveillance. New York: Harwood Academic Publishers, 75.

*Kathren RL. 1987. Implications of human tissue studies. Govt Rep Announce Ind, Issue 11. NTIS/DE87002063.

8. REFERENCES

*Kathren RL. 1988. Implications of human tissue studies for radiation protection. Health Phys 55:315-319.

*Kathren RL. 1997. Uranium in the tissues of two whole body donations to the USTUR. United States Transuranium and Uranium Registries. Washington State University, Richland, WA. Annual report October 1, 1995-September 30, 1996. USTUR-0072-97.

*Kathren RL, McInroy JF, Moore RH, et al. 1989. Uranium in the tissues of an occupationally exposed individual. Health Phys 57:17-21.

*Kathren RL, Moore RH. 1986. Acute accidental inhalation of uranium: A 38-year follow-up. Health Phys 51:609-620.

*Kato H, Schull WJ. 1982. Studies of the mortality of A-bomb survivors. 7. Mortality, 1950-78: Part I, Cancer mortality. Radiation Research 90:395-432.

*Kauffman JW, Laughlin WC, Baldwin RA. 1986. Microbiological treatment of uranium mine waters. Environ Sci Technol 20:243-248.

*Keane AT, Polednak AP. 1983. Retention of uranium in the chest: Implications of findings in vivo and postmortem. Health Phys 44(Suppl 1):391-402.

*Kelly WR, Fassett JD. 1983. Determination of picogram quantities of uranium in biological tissues by isotope-dilution thermal-ionization mass spectrometry with ion-counting detection. Anal Chem 55:1040-1044.

*Kelly WR, Fassett JD, Hotes SA. 1987. Determining picogram quantities of uranium in human urine by thermal ionization mass spectrometry. Health Phys 52:331-336.

*Kerr A, Kupferschmidt W, Atlas M. 1988. Determination of uranium in natural groundwaters using high-performance liquid chromatography. Anal Chem 60:2729-2733.

*Kirk WS. 1980. Depleted uranium. U. S. Department of the Interior. Bureau on Mines bulletin no. 671.

*Klaasson CD. 1986. Biotransformation of xenobiotics. In: Cassarett & Doull's Toxicology. 5th edition, 113-120.

*Kobayashi S, Nagase M, Honda N, et al. 1984. Glomerular alterations in uranyl acetate-induced acute renal failure in rabbits. Kidney Int 26:808- 815.

*Komori M, Nishio K, Kitada M et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human liver. Biochemistry 29:4430-4433.

*Kressin IK. 1984. Spectrophotometric method for the determination of uranium in urine. Anal Chem 56:2269-2227.

*Krieger HL, Whittaker EL. 1980. Prescribed procedures for measurement of radioactivity in drinking water. Govt Rep Announce Ind, Issue 25. NTIS PB80-224744.

*Krishnan K, Andersen ME. 1994. Physiologically-based pharmacokinetic modeling in toxicology. In: Hayes W, ed. Principles and methods of toxicology. 3rd edition. New York, NY: Raven Press, Ltd.

8. REFERENCES

*Krishnan K, Andersen ME, Clewell HJ III, et al. 1994. Physiologically-based pharmacokinetic modeling of chemical mixtures. In: Yang RSA, ed. Toxicology of chemical mixtures. New York, NY.: Academic Press.

*Kuroda PK, Essien IO, Sandoval DN. 1984. Fallout of uranium isotopes from the 1980 eruption of Mount St. Helens. J Radioanal Nucl Chem 84:23-32.

*Kusiak RA, Ritchie AC, Muller J, et al. 1993. Mortality from lung cancer in Ontario uranium miners. British Journal of Industrial Medicine 50:920-928.

*Kvasnicka J. 1987. Assessing dose equivalent from intensive short-term uranium product inhalation. Health Phys 53:673-678.

*Labrecque JJ, Rosales PA, Mejias G. 1986. Instrumental neutron-activation analysis of river sediments from Rio Tigre (Venezuela) employing a planar germanium detector. Appl Spectrosc 40:1232-1235.

*Lal N, Sharma YP, Sharma PK, et al. 1982. Uranium assay in milk. Health Phys 43:425-428.

*Land CE, Shimosato Y, Saccomanno G, et al. 1993. Radiation-associated lung cancer. A comparison of the histology of lung: Cancers in uranium miners and survivors of the atomic bombings on Hiroshima and Nagasaki. Radiation Research 1:34 234-243.

*Landa ER, Councell TB. 1992. Leaching of uranium from glass and ceramic foodware and decorative items. Health Phys 343-348.

*Landsberger S, Wu D. 1993. Improvement of analytical sensitivities for the determination of antimony, arsenic, cadmium, indium, iodine, molybdenum, silicon and uranium in airborne particulate matter by epithermal neutron activation analysis. J Radioanalytical Nuclear Chemistry 167(2):291-225.

*Lang S, Kosma VM, Kumlin T, et al. 1994. Distribution and short-term effects of intratracheally instilled neutron-irradiation UO2 particles in the rat. Environmental Research 65:119-131.

*Lang S, Raunemaa T. 1991. Behavior of neutro-activated uranium dioxide dust particles in the gastrointestinal tract of the rat. Radiation Research 26:273-279.

*Lapham SC, Millard JB, Samet JM. 1989. Health implications of radionuclide levels in cattle raised near U mining and milling facilties in Ambrosia Lake, New Mexico. Health Physics 36(3):327-330.

*Larsen RP, Bhattachyaryya MH, Oldham RD, et al. 1984. Gastrointestinal absorption and retention of plutonium and uranium in the baboon. Division of Biological and Medical Research. Institute of Environmental Medicine, New York University Medical Center, Tuxedo, New York, 51-60.

*LaTouche YD, Willis DL, Dawydiak OI. 1987. Absorption and biokinetics of U in rats following an oral administration of uranyl nitrate solution. Govt Rep Announce Ind, Issue 12. NTIS PB88-170709.

*Laul JC. 1994. U-234/U-238 ratio: Qualitiative estimate of groundwater flow in Rocky Flats monitoring wells. Golden, CO: Environmental Technologies.

8. REFERENCES

*Lazo EN, Roessler GS, Berven BA. 1991. Determination of uranium and thorium concentrations in unprocessed soil samples. Health Physics 61(2):231-243.

*Leach LJ, Gelein RM, Panner BJ, et al. 1984. The acute toxicity of the hydrolysis products of uranium hexafluoride (UF6) when inhaled by the rat and guinea pig. Final report. ISS K/SUB-81-9039-3. NTIS DE84011539.

*Leach LJ, Maynard EA, Hodge CH, et al. 1970. A five-year inhalation study with natural uranium dioxide dust.   Health Phys 18:599-612.

*Leach LJ, Yuile CL, Hodge HC, et al. 1973. A five-year inhalation study with natural uranium dioxide (UO2) dust. II. Postexposure retention and biologic effects in the monkey, dog and rat. Health Phys 25:239-258.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: implications for practice. Pediatric Clinics of North America 44:55-77.

*Leggett RW. 1992. A generic age-specific biokinetic model for calcium-like elements. Radiat Protect Dosim 41:183-198.

*Leggett RW, Harrison JD. 1995. Fractional absorption of ingested uranium in humans.   Health Phys 68(4):484-498.

*Leggett RW, Warren BP. 1988. Age-specific models for evaluating dose and risk from internal exposures to radionuclides: Report of current work of the Metabolism and Dosimetry Research Group, July 1, 1985-June 30, 1987. Govt Rep Announce Ind, Issue 07. NTIS/DE88001528.

*Leifer R, Juzdan ZR, Kelly WR, et al. 1987. Detection of uranium from Cosmos-1402 in the stratosphere. Science 238:512-514.

*Leung H. 1993. Physiologically-based pharmacokinetic modeling. In: Ballantine B, Marro T, Turner T, eds. General and applied toxicology. Vol. I. New York, NY: Stockton Press, 153-164.

*Lide DR. 1994. Uranium. In: Handbook of chemistry and physics. 74th edition, CRC Press. 31-32.

*Lin RH, Wu LJ, Lee CH, et al. 1993. Cytogenetic toxicity of uranyl nitrate in Chinese hamster ovary cells. Mutation Research 319:197-203.

*Linsalata P. 1994. Uranium and thorium decay series radionuclides in human and animal foodchains. J Environ Qual 23:633-642.

*Lippmann M, Ong LDY, Harris WB. 1964. The significance of urine uranium excretion data. Ind Hyg J (January-February)43-54.

*Llobet JM, Sirvent JJ, Ortega A, et al. 1991. Influence of chronic exposure to uranium on male reporduction in mice. Fundamental and Applied Toxicology. 16:821-829.

*Long SE, Martin TD. 1991. Method 200.8: determination of trace elements in waters and wastes by inductively coupled plasma - mass spectrometry (revision 4.4). Environmental Monitoring Systems Laboratory, Office of Research and Development, US Environmental Protection Agency (Cincinnati, OH), April 1991.

*Longtin JP. 1988. Occurrence of radon, radium, and uranium in groundwater. Am Water Works Assoc J 80:84-93.

*Loomis DP, Shy CM, Allen JW, et al. 1990. Micronulei in epithelial cells from sputum of uranium workers. Scand J Work Environ Health. 16:355-362.

*Lowry JD, Hoxie DC, Moreau E. 1987. Extreme levels of radon-222 and uranium in a private water supply. In: Graves B, ed. Radon in ground water, radon, radium and other radioactivity in ground water: Hydrogeologic impact and application to indoor airborne contamination: Proc National Water Well Association conference, Somerset, NJ, April 7-9, 1987. Chelsea, MI: Lewis Publishers, Inc., 363-376.

*Lubin JH, Boice JD Jr., Edling C, et al. 1995. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. Journal of the National Cancer Institute 87(11):817-27.

*Luessenhop AJ, Gallimore JC, Sweet WH, et al. 1958. The toxicity in man of hexavalent uranium following intravenous administration. Am J Roentgenol 79:83-100.

*Lundin FE, Lloyd W, Smith EM, et al. 1969. Mortality of uranium miners in relation to radiation exposure, hard rock mining and cigarette smoking 1950 through September 1967. Health Phys 16:571-578.

*Mahon DC. 1982. Uptake and translocation of naturally-occurring radionuclides of the uranium series. Bull Environ Cont Toxicol 29:697-793.

*Malenchenko AF, Barkun NA, Guseva GF. 1978. Effect of uranium on the induction and course of experimental autoimmune orchitis and thyroiditis. J Hyg Epidemiol, Microbiol, Immunol 22:268-277.

*Mao Y, Desmeules M, Schaubel D, et al. 1995. Inorganic components of drinking water and microalbuminuria. Environ Res 71(2):135-40.

*MAORS. 1989. Written communication regarding Massachusetts guidelines for uranium in drinking water. Boston, MA: Massachusetts Office of Research and Standards.

*Martin F, Earl R, Tawn EJ. 1991. A cytogenetic study of men occupationally exposed to uranium. British J Industrial Medicine 48:98-102.

*Martland HS. 1931. The occurrence of maliganancy in radioactive person. Am J Cancer 15:2435-2516.

*Masuda K. 1971a. Intake and urinary excretion of uranium in non- occupationally exposed persons. I. Recovery of uranium in the daily diet and urine. Nippon Eiseigaku Zasshi (Japan) 26:434-437.

*Masuda K. 1971b. Intake and urinary excretion of uranium in non- occupationally exposed persons. II. Uranium in the daily diet. Nippon Eiseigaku Zasshi (Japan) 26:438-441.

8. REFERENCES

*Masuda K. 1971c. Intake and urinary excretion of uranium in non- occupationally exposed persons. III. Urinary excretion of uranium. Nippon Eiseigaku Zasshi (Japan) 26:442-446.

*Masuda K. 1971d. Intake and urinary excretion of uranium in non-occupationally exposed persons. IV. Discussions on dietary intake and urinary excretion of uranium. Nippon Eiseigaku Zasshi (Japan) 26:447-450.

*Maynard EA, Down WL, Hodge HC. 1953. Oral toxicity of uranium compounds. In: Voegtlin C, Hodge HC, eds. Pharmacology and toxicology of uranium compounds. New York, NY: McGraw-Hill.

*Maynard EA, Hodge HC. 1949. Studies of the toxicity of various uranium compounds when fed to experimental animals. In: Voegtlin IC, Hodge HC, eds. Pharmacology and toxicology of uranium compounds, National Nuclear Energy Series (VI). New York, NY: McGraw-Hill, 309-376.

*Mays CW. 1988. Alpha particle induced cancer in humans. Health Phys 55:637-652.

*Mays CW, Rowland RE, Stehaney AF et al. 1985. Cancer risk from the lifetime intake of Ra and U isotopes. Health Phys 48(5):635-647.

*McDiarmid MA, Keough JP, Hooper FJ et al. 1999a. Health effects of depleted uranium on exposed Gulf War veterans. J Int Neuropsychol Soc (in press).

*McDiarmid MA, Hooper FJ, Squibb K, et al. 1999b. The utility of spot collection for urinary uranium determinations in depleted uranium exposed Gulf War veterans. Health Phys (in press).

*McDonald-Taylor CK, Bhatnagar MK, Gilman A, et al. March 1992. Uranyl nitrate-induced glomerular basement membrane alterations in rabbits: A quantitative analysis. Bulletin of Environmental Contamination and Toxicology (March 1992) 48 (3):367-373.

*McDonald-Taylor et al. 1997. Uranyl nitrate-induced proximal tubule alterations in rabbits: A quantitive analysis. Toxicologic Pathology 25(4):381-389.

*McElroy N, Brodsky A. 1986. Training manual for uranium mill workers on health protection from uranium. Govt Rep Announce Ind, Issue 11. NTIS/NUREG-1159.

*McGuire SA. 1983. NRC's (Nuclear Regulatory Commission) limit on intake of uranium ore dust. Govt Rep Announce Ind, Issue 18. NTIS/NUREG-0941.

*Means JL, Crerar DA, Borcsik MP, et al. 1978. Adsorption of Co and selected actinides by Mn and Fe oxides in soils and sediments. Geochim Cosmochim Acta 42:1763.

*Meditext. 1998. Medical management (uranium). Micromedex Inc. Vol. 34 (expires 10-31-97), copyright 1987-1997.

*Melgard R. 1980. In: Kathren RL, Weber JR, eds. Ultrasensitive techniques for measurement of uranium in biological samples and the nephrotoxicity of uranium, Washington, DC, Dec. 4-5, 1985. Richland, WA: Pacific Northwest Laboratory, 1-9.

*Melville CM, Wai CM, Collopy M, et al. 1981. Uranium dispersion along roads paved with phosphate slag. Bull Environ Cont Toxicol 27:479-473.

*Meriwether JR, Beck JN, Keeley DF, et al. 1988. Radionuclides in Louisiana soils. J Environ Qual 17:563-568.

*Mettler F, Moseley R. 1985. Medical effects of ionizing radiation. New York, NY: Grune and Stratton.

*Metzger R, McKlveen JW, Jenkins, et al. 1980. Specific activity of uranium and thorium in marketable rock phosphate as a function of particle size. Health Phys 39:69-76.

*Mewhinney JA. 1983. Radiation dose estimates and hazard evaluations for inhaled airborne radionuclides. Annual Progress Report July 1982 - June 1983. Report to Nuclear Regulatory Commission, Office of Nuclear Regulatory Research, Washington, DC. NTIS NUREG/CR-3870.

*Michel J, Jordana MJ. 1987. Nationwide distribution of radium-228 radon- 222 and uranium in groundwater. In: Graves B, ed. Radon in ground water, radon, radium and other radioactivity in ground water: Hydrogeologic impact and application to indoor airborne contamination: Proc National Water Well Association conference, Somerset, NJ, April 7-9, 1987. Chelsea, MI: Lewis Publishers, Inc., 227-240.

*Miller AC, Blakely WF, Livengood D, et al. 1998b. Transformation of human osteoblast cells to the tumorigenic phenotype by depleted uranium-uranyl chloride. Environ Health Perspect 106:465-471.

*Miller AC, Fuciarelli AF, Jackson WE, et al. 1998a. Urinary and serum mutagenicity studies with rats implanted with depleted uranium or tantalum pellets. Mutagenesis 13:643-648.

*Miller HT. 1977. Radiation exposures associated with surface mining for uranium. Health Phys 32:523-528.

*Miller KM, Shebell P, Kemic A. 1994. *In situ* gamma-ray spectrometry for the measurement of uranium in surface soils. Health Phys 67(2):140-150.

*Mlakar M, Branica M. 1989. Stripping voltammetric determination of trace levels of uranium by synergic adsorption. Analytica Chimica Acta 221:279-287.

*MMES. 1985. United States Department of Energy Paducah Gaseous Diffusion Plant: Environmental monitoring report, 1984. Report ISS KY-747. Martin Marietta Energy Systems, Inc. DE85014027.

*Mnller C, Ruzicka-Jaroslav Bakstein L. 1967. The sex ratio in the offsprings of uranium miners. Acta Universitatis Carolinae Medica 13(7/8):599-603.

*Moffett D, Tellier M. 1977. Uptake of radioisotopes by vegetation growing on uranium tailings. Can J Soil Sci 57:417-424.

*Momeni MH, Kisieleski WE. 1980. Measured concentrations of radioactive particles in air in the vicinity of the Anaconda uranium mill [Bluewater, New Mexico]. Report: ISS NUREG/CR-1320, ANL/ES-89.

*Moolgavkar SH, Luebeck EG, Krewski D, et al. 1993. Radon, cigarette smoke, and lung cancer a re-analysis of the Colorado Plateau Uranium Miners Data. Epidemiology 4:204-217.

*Moore RH, Breitenstein BD Jr. 1983. The U.S. uranium registry tissue program. Health Phys 44(Suppl 1):373-376.

*Moore RH, Kathren RL. 1985. A World War II uranium hexafluoride inhalation event with pulmonary implications for today. J Occup Med 27:753-756.

*Morishima H, Koga T, Kawai H, et al. 1977. Studies on the movemnent of distribution of uranium in the environments-distribution of uranium in agricultural products. J Radiat Res 18:139-150.

*Morris KJ, Barker CL, Batchelor AL, et al. 1992. Dosimetric implications of pulmonary macrophage clusters observed within lungs of rats that have inhaled enriched UO2 particles. Environmental Health Perspectives 97:201-208.

*Morris KJ, Khanna P, Batchelor AL. 1990. Long-term clearance of inhaled UO2 particles from the pulmonary region of the rat. Health Phys 58(4):477-485.

*Morris KJ, Townsend KMS, Batchelor AL. 1989. Studies of alveolar cell morphometry and mass clearance in the rat lung following inhalation of an enriched uranium dioxide aerosol. Radiat Environ Biophys 28:141-154.

*Morrow PE, Gelein R, Beiter H. 1982a. Inhalation and intravenous studies of UF6/UO2F2 in dogs. Health Phys 43:859-873.

*Morrow PE, Gibb FR, Beiter HD. 1972. Inhalation studies of uranium trioxide. Health Phys 23:273-280.

*Morrow PE, Leach LJ, Smith FA, et al. 1982b. Metabolic fate and evaluation of injury in rats and dogs following exposure to the hydrolysis products of uranium hexafluoride. Implications for a bioassay program related to potential releases of uranium hexafluoride. Govt Rep Announce Ind, Issue 11. NTIS/NUREG/CR-2268.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants. Clinical Pharmacokinetics 5:485-527.

*Mortvedt JJ. 1994. Plant and soil relationships of uranium and thorium decay series radionuclides. J Environ Qual 23:643-650.

*Muller C, Rozicka L, Bakstein J. 1967. The sex ratio in the offsprings of uranium miners. Acta Univ Carol Med 13(7):599-603.

*Murray RL. 1994. Understanding radioactive waste, 4th edition. Batelle Pacific Northwest Laboratories, Batelle Press.

*Nagj M, Makjanic J, Orlic I, et al. 1986. Determination of uranium in sea-water by X-ray fluorescence spectroscopy. J Radioanal Nucl Chem 97:373-380.

*NAS. 1983. Drinking water and health. National Academy of Sciences. Washington, DC: National Academy Press, 5:90-117.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

*NATICH. 1987.   National Air Toxics Information Clearinghouse. Office of Air Quality Planning and Standards, Research Triangle Park, NC, State and Territorial Air Pollution Program Administrators, and Association of Local Air Pollution Control Officials.

*NATICH. 1992. National Air Toxics Information Clearinghouse, NATICH Data Base of Federal, State, and Local Air Toxics Activities.

*NCRP.   1971. National Council on Radiation Protection and Measurements. Basic radiation protection criteria. NCRP Report No. 39. Washington, DC.

*NCRP. 1975. National Council on Radiation Protection and Measurements. Natural background radiation in the United States. NCRP Report No. 45. Bethesda, MD, 4-6.

*NCRP. 1976. National Council on Radiation Protection and Measurements. Environmental radiation measurements. NCRP Report No. 50. Washington, DC.

*NCRP. 1978. National Council on Radiation Protection and Measurements. Instrumentation and monitoring methods for radiation protection. NCRP Report No. 57. Washington, DC.

*NCRP. 1984a. National Council on Radiation Protection and Measurements. Exposures from the uranium series with emphasis on radon and its daughter. NCRP Report No. 77. Bethesda, MD.

*NCRP. 1984b. National Council on Radiation Protection and Measurements. Radiological assessment: Predicting the transport, bioaccumulation and uptake by man of radionuclides released to the environment. NCRP Report No. 76.

*NCRP. 1985. National Council on Radiation Protection and Measurements. A handbook of radioactivity measurements procedures. 2nd ed. NCRP Report No. 58. Bethesda, MD.

*NCRP. 1987a. National Council on Radiation Protection and Measurements. Use of bioassay procedures for assessment of internal radionuclide deposition.   NCRP Report No. 87. Bethesda, MD.

*NCRP. 1987b. National Council on Radiation Protection and Measurements. Recommendations on limits of exposure to ionizing radiation. NCRP Report No. 91. Bethesda, MD.

*NCRP. 1991. National Council on Radiation Protection and Measurements. Calibration of survey instruments used in radiation protection for the assessment of ionizing radiation fields and radioactive surface contamination.   NCRP Report No. 112. Bethesda MD.

*NCRP. 1993. National Council on Radiation Protection and Measurements. Limitation of exposure to ionizing radiation. Report No. 116. Bethesda, MD.

*NCRP. 1997. Deposition, retention and dosimetry of inhaled radioactive substances. National Council on Radiation Protection and Measurement. NCRP Report No. 125. Bethesda, MD.

*NEDH. 1989. Nebraska Department of Health. Domestic well water sampling in Nebraska, 1987 laboratory findings and their implications. Division of Environmental Health and Housing Surveillance, Lincoln, NE.

*NIOSH. 1997. NIOSH pocket guide to chemical hazards. U.S. Department of Health and Human Services. Public Health Services. Centers for Disease Control and Prevention. National institute for occupational safety and health. June 1997.

*NIST. 1991. National Institute of Standards and Technology. NIST calibration services users guide, special publication 250. U.S. Department of Commerce, Washington DC: U.S. Government Printing Office.

*NIST. 1995. National Institute for Standards and Technology.   Standard reference materials catalog, special publication 260. U.S. Department of Commerce, Washington, DC: U.S. Government Printing Office.

*NMHED. 1989. New Mexico Health and Environment Department, Summary report on the Church Rock uranium mill tailings spill: A health and environment assessment. Santa Fe, NM.

*Norman JD, Stumpe LA, Trimm J, et al. 1983. Argon-plasma emission spectrometry of uranium in phosphatic materials (e.g., fertilizers). J Assoc Off Anal Chem 66:949-951.

*NRC. 1993. Pesticides in the diets of infants and children. National Research Council. Washington DC: National Academy Press.

*Ohanian EV. 1989. National primary drinking water regulations for radionuclides. Safe Drinking Water Act: Amendments, Regulations and Standards. Lewis Publishers, 45-55

*Orcutt JA. 1949. The toxicology of compounds of uranium following application to the skin. In: Voegtlin C, Hodge HC, eds. Pharmacology and toxicology of uranium compounds. Vols 3 and 4. New York, NY: McGraw Hill Book Co.

*ORNL. 1998. State program directory. Agreement states. Oak Ridge National Laboratory. Health Sciences Research Division. http://www.hsrd.ornl.gov/nrc/agstates.htm .

*Ortega A, Domingo JL, Gomez M, et al. 1989b. Treatment of experimental acute uranium poisoning by chelating agents. Pharmacol Toxicol 64:247-251.

*Ortega A, Domingo JL, Lloket JM, et al. 1989a. Evaluation of the oral toxicity of uranium in a 4-week drinking water study in rats. Bull Environ Contam Tox 42:935-941.

*Ortega JL, Domingo JL, Ortega A, et al. 1989c. The effects of uranium on reproduction, gestation, and postnatal survival in mice. Ecotox Environ Saf.

*OSHA. 1989. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

*OSHA. 1993. Air contaminants; final rule. U.S. Department of Labor. Occupational Safety and Health Administration. Federal Register. 58 FR 35338. June 30, 1993.

8. REFERENCES

*OSHA. 1997a. Occupational health and environmental controls. Threshold limit values of airborne contaminants for construction. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55, Appendix A.

*OSHA. 1997b. Toxic and hazardous substances. Air contaminants. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000.

*OSHA. 1997c. Air contaminants: corrections; rule. U.S. Department of Labor. Occupational Safety and Health Administration. Federal Register. 62 FR 42018. August 4, 1997.

*Otake M, Schull W. 1984. Mental retardation in children exposed *in utero* to the atomic bombs: A reassessment. Technical Report RERF TR 1-83, Radiation Effects Research Foundation, Japan.

*Owen GM, Brozek J. 1966. Influence of age, sex, and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: Saunders, 222-238.

*Paschoa AS, Cholewa M, Jones KW, et al. 1987. PIXE-RBS (Rutherford Back- Scattering) combination to measure uranium and thorium in environmental and biological samples. J Radioanal Nucl Chem 115:231-240.

*Paternain JL, et al. 1989. The effects of uranium on reproduction, gestation, and postnatal survival in mice. Ecotoxicology and Environmental Safety 17:291-296.

*Paunescu N. 1986. Determination of uranium and thorium concentration in natural waters. J Radioanal Nucl Chem 104:209-216.

*Pavlakis N, Pollock CA, McLean G, et al. 1996. Deliberate overdose of uranium: Toxicity and treatment. Nephron 72(2):313-7.

*Pelayo JC, Andrews PM, Coffey AK, et al. 1983. The influence of age on acute renal toxicity of uranyl nitrate in the dog. Pediatric Research 17(12):985-992.

*Pellmar TC, Fuciarelli AF, Ejnik JW et al. 1999a. Distribution of uranium in rats implanted with depleted uranium pellets. Toxicol Sci 49:29-39.

*Pellmar TC, Keyser DO, Emery C et al. 1999b. Electrophysiological changes in hippocampal slices isolated from rats embedded with depleted uranium fragments. Neurotoxicology (in press).

*Perez JL, Pavon B, Cordero M, et al. 1990. Determination of uranium using a flow system with reagent injection. Application to the determination of uranium in ore leachates. Analytica Chimica Acta 230:217-230.

*Petersen GR, Sever LE. 1982. Appraisal of selected epidemiologic issues from studies of lung cancer among uranium and hard rock miners. NTIS DE82015710.

*Pleskach SD. 1985. Determination of uranium and thorium in urine by neutron activation. Health Phys 48:303-308.

*PNL. 1981. Occupational exposures to uranium: Processes, hazards and regulations. Pacific Northwest Laboratory and Hanford Environmental Health Foundation, PNL-3341 USUR-01 UC-41.

*Polednak AP, Frome EL. 1981. Mortality among men employed between 1943 and 1947 at a uranium-processing plant. J Occup Med 23:168-178.

*Polednak AP, Keane AT, Beck WL. 1982. Estimation of radiation doses to the lungs of early uranium processing plant workers. Environ Res 28:313-328.

*Poston TM. 1982. The bioaccumulation potential of thorium and uranium in rainbow trout (*Salmo gairdneri*). Bull Environ Cont Toxicol 28:682-690.

*Pozzani, UC. 1949. Pharmacology and toxicology of uranium compounds. New York, NY: McGraw-Hill, Inc.

*Premuzie ET, Francis AJ, Lin M, et al. 1995. Induced formation of chelating agents by Pseudomonas aeruginosa grown in presence of thorium and uranium. Arch Environ Contam Toxicol 14:759-768.

*Price KR, Kinnison RR. 1982. Uranium and other heavy metals in soil and vegetation from the Hanford environs. Report: ISS PNL-4466. DE83003313.

*Priest ND, Howells GR, Green D, et al. 1982. Uranium in bone: Metabolic and autoradiographic studies in the rat. Hum Toxicol 1:97-114.

*Purtymun WD, Peters RJ, Buhl TE, et al. 1987. Background concentrations of radionuclides in soils and river sediments in northern New Mexico, 1974- 1986. Report: ISS LA-11134-MS. DE88001560.

*Purtymun WD, Peters RJ, Stoker AK. 1980. Radioactivity in soils and sediments in and adjacent to the Los Alamos area, 1974-1977. Report: ISS LA-8234-MS.

*Querol X, Alastuey A, Lopez-Soler A, et al. 1997. Trace element contents in atmospheric suspended particles: Inferences from instrumental neutron activation analysis. Fresenius' Journal of Analytical Chemistry 357(7):934-940.

*Ramachandraiah C, Vijayakumari D, Lakshminarayana K. 1993. A sensitive spectrophotometric method for the determination of trace amounts of uranium(VI) using o-hydroxypropiophenone isonicotinoyl hydrazone. J Radioanal Nucl Chem, Letters 175(3):185-190.

*Rayno DR. 1983. Estimated dose to man from uranium milling via the beef/milk food-chain pathway. Sci Total Environ 31:219-241.

*Reid DG, Sackett WM, Spaulding RF. 1977. Uranium and radium in livestock feed supplements. Health Phys 32:535.

*Reyes M, Wilkinson GS, Tietjen G, et al. 1984. Brain tumors at a nuclear facility. J Occup Med 26:721-724.

*Riley JE, Jr. 1982. Ultrahigh sensitivity uranium analyses using fission track counting: Further analyses of semiconductor packaging materials. J Radioanalytical Chem 72(1-2):89-99.

*Roberts E. 1949. Pharmacology and toxicology of uranium compounds. Mcgraw-Hill Book Company, Inc., 561-585.

Rossol M. 1997. Ceramic glazes, frit metal enamels, and glass; personal communication and supporting materials. Arts, Crafts and Theater Safety, New York.

*Rothermel JJ. 1949. Uranium tetrachloride. Pharmacology and toxicology of uranium compounds. McGraw-Hill Book Company, Inc., 588-602.

*Rothstein A. 1949a. Pharmacology and toxicology of uranium compounds. McGraw-Hill Book Company, Inc., 548-560.

*Rothstein A. 1949b. Pharmacology and toxicology of uranium compounds. McGraw-Hill Book Company, Inc., 614-621.

*Rothstein A. 1949c. Pharmacology and toxicology of uranium compounds. McGraw-Hill Book Company, Inc., 635-648.

*Rothstein A. 1949d. Pharmacology and toxicology of uranium compounds. McGraw-Hill Book Company, Inc., 588-607.

*Rowland RE, Stehney AF, Lucas HF. 1978. Dose-response relationships or female radium dial painters. Radiat. Res 76:368-383.

*Rubin P, Casarett G. 1968. Clinical radiation pathology. Philadelphia: W.B. Sanders Company, 33.

*Russel J, Kathren R, Dietert S. 1996. A histological kidney study of uranium and non-uranium workers. Health Physics 70(4):466-72.

*Saccomanno G, Archer VE, Saunders RP, et al. 1976. Early indices of cancer risk among uranium miners with reference to modifying factors. Ann NY Acad Sciences 271:377-383.

*Saccomanno G, Auerbach O, Kuschner M, et al. 1996. A comparison between the localization of lung tumors in uranium miners and in nonminers from 1947 to 1991. Cancer 77(7):1278-83.

*Saccomanno G et al. 1971. Histologic types of lung cancer among uranium miners. Cancer 27:515-523.

*Saccomanno G, Huth GC, Auerbach O, et al. 1988. Relationship of radioactive radon daughters and cigarette smoking in the genesis of lung cancer in uranium miners. Cancer 62:1402-1408.

*Saccomanno G, Thun MJ, Baker DB, et al. 1982. The contribution of uranium miners to lung cancer histogenesis renal toxicity in uranium mill workers. Cancer Research 82:43-52.

*Saccomanno G, Yale C, Dixon W, et al. 1986. An epidemiological analysis of the relationship between exposure to radon progeny, smoking and bronchogenic carcinoma in the uranium-mining population of the Colorado Plateau (USA): 1960-1980. Health Phys 50:605-618.

*Sairenji E, Moriwaki K, Shimizu M, et al. 1980. Estimation of radiation dose from porcelain teeth containing uranium compound. 59:1136-1140.

*Samet JM. 1993. The disease of uranium miners and others underground miners exposed to radon. In: Rom WN, ed. Environmental and occupational medicine. Boston, MA: Little Brown and Company.

8. REFERENCES

*Samet JM, Kutvirt DM, Waxweiler RJ, et al. 1984. Uranium mining and lung cancer in Navaho men. N Eng J Med 310:1481-1484.

*Samet JM, Morgan MV, Key CR, et al. 1986. Studies of uranium miners in New Mexico. Ann Am Conf Gov Ind Hyg 15:351-355.

*Sanders CL. 1986. Radiological health. Toxicological aspects of energy production. Columbus Ohio: Battelle Press, 253-284.

*Scharer JM, Ibbotson B. 1982. Bacterial oxidation of inorganic compounds in mining waste. Conserv Recycling 5:47:53.

*Schiefer HP, Gramain P, Kraeminger E. 1980. Improvement of the uranium determination in flame atomic emission spectrometry by addition of cobalt nitrate an interference agent. Fresenius Z. Anal Chem 303:29.

*Schieferdecker H, Dilger H, Doerfel H, et al. 1985. Inhalation of uranium aerosols from uranium dioxide fuel element fabrication. Health Phys 48:29-48.

*Scott LM. 1973. Environmental monitoring and personnel protection in uranium processing. In: Hodge et al. eds. Uranium, plutonium transplutonic elements. New York, NY: Springer-Verlag, 271-294.

*Scott LM, Bahler KW, De La Garza A, et al. 1972. Mortality experience of uranium and nonuranium workers. Health Phys 23:555-557.

*Seeley FG, Kelmers AD. 1985. Geochemical information for sites contaminated with low level radioactive wastes: 2. St. Louis Airport Storage Site. Govt Rep Announc Ind, Issue 11.

*Setchell BP, Waites GMH. 1975. The blood testis barrier (Chapter 6). In: Creep RO, Astwood EB eds, Geiger SR (executive ed.) Handbook of physiology: Endocrinology. V   American Physiological Society, Washington DC.

*Sharma PK, Lal N, Nagpaul KK. 1985. Estimation of uranium content in coffee samples by fission-track counting. Health Phys 48:809-810.

*Shaw TJ, Sholkovitz ER, Klinkhammer G. 1994. Redox dynamics in the Chesapeake Bay: The effect on sediment/water uranium exhange. Geochimica et Cosmochimica Acta 58(14):2985-2995.

*Shearer SD, Jr., Sill CW. 1969. Evaluation of atmospheric radon in the vicinity of uranium mill tailings. Health Phys 17:77.

*Sheppard MI, Thibault DH, Mitchell JH. 1987. Element leaching and capillary rise in sandy soil cores: Experimental results. J Env Qual 16:273-284.

*Sheppard MI, Vandergraaf TT, Thibault DH, et al. 1983. Technetium and uranium: Sorption by and plant uptake from peat and sand. Health Phys 44:635-644.

*Shiraishi K, Igarashi Y, Takaku Y, et al. 1992. Daily intakes of 232Th and 238U in Japanese males. Health Phys 63(2):187-191.

*Sikov MR, Mahlum DD. 1968. Cross-placental transfer of selected actinides in the rat. Health Phys 14(3):205-8.

*Sikov MR, Rommereim DN. 1986. Evaluation of the embryotoxicity of uranium in rats. In: 26th Annual meeting of the Teratology Society and the 10th annual meeting of the Behavioral Teratology Society, Boston, MA, July 6-10. Teratology 33:41C.

*Silva RJ, Benson LV, Apps JA. 1979. Studies of actinide sorption on selected geologic materials. ACS Symp Ser 100:215-240.

*Simpson HJ, Trier RM, Toggweiler JR, et al. 1982. Radionuclides in Mono Lake, California, USA. Science 216:512-514.

*Singh NP, Bennett DB, Wrenn ME. 1987b. Macro-distribution of naturally occurring d-emitting isotopes of U in the human skeleton. Health Phys 52:769-773.

*Singh NP, Bennett DD, Wrenn ME, et al. 1987a. Concentrations of alpha- emitting isotopes of U and Th in uranium miners' and millers' tissues. Health Phys 53:261-265.

*Singh NP, Burleigh DP, Ruth HM, et al. 1990. Daily U intake in Utah residents from food and drinking water. Health Phys 59(3):333-337.

*Singh NP, Lewis LL, Wrenn ME. 1986b. Uranium in human tissues of Colorado, Pennsylvania and Utah populations. Health Phys 550:583.

*Singh NP, Wrenn ME. 1986a. Levels of uranium-234, -238, and thorium-230 in excreta of uranium mill crushermen. Health Phys 50:300-302.

*Singh NP, Wrenn ME. 1987. Uptake of uranium from drinking water. In: Hemphill DD, ed. Trace substances in environmental health. Columbia, MO: University of Missouri, 203-212.

*Singh NP, Wrenn ME. 1988. 5th Symposium: Environmental Radiochemical Analysis, Part B, Harwell England, UK, October 1-3, 1986. Sci Total Environ 70:187-204.

*Singh NP, Wrenn ME. 1989. Is the Beagle dog an appropriate experimental animal for extrapolating data to humans on organ distribution patterns of U Th, and Pu? Health Phys 57:91-96.

*Singh NP, Wrenn ME, McInroy JF, et al. 1986a. Ratios of uranium-234, - 238, and thorium-230 in dog lungs exposed to uranium ore dust: An interlaboratory comparison. Health Phys 50:292-297.

*Singh NP, Zimmerman CJ, Lewis LL, et al. 1984. Nuclear instrumental methods. Physics Research 223:558-62.

*Smith DD, Black SC. 1975. Actinide concentrations in tissues from cattle grazing near the Rocky Flats Plant. Report: ISS NERC-LV-539-36.

*Smith MR, Laul JC, Johnson VG. 1988. Natural radionuclides in Hanford Site groundwaters. Mater Res Soc Symp Proc 112:249-257.

8. REFERENCES

*Sontag W. 1983. The early distribution of plutonium-239, americium-241 and uranium-233 in the soft tissues and skeleton of old rats. A comparative study. Hum Toxicol 2:91-100.

*Sontag W. 1986. Multicompartment kinetic models for the metabolism of americium, plutonium and uranium in rats. Hum Toxicol 5:163-173.

*Spencer H, Osis D, Isabel M, et al. 1990. Measured intake and excretion patterns of naturally occuring 234 U, 238 U, and calcium in humans. Radiation Research 124:90-95.

*Spiegl CJ. 1949. Pharmacology and toxicology of uranium compounds. McGraw-Hill Book Company, Inc. 532-547.

*Spiess FW, Mays CW. 1970. Bone cancers induced by Ra 224 in children and adults. Health Physics 19:713-729.

*Spiess FW, Mays CW. 1973. Protraction effect on bone sarcoma induction of Ra 224 in children and adults. In: Sanders CL, et al., ed. Radionuclide carcinogenesis. Springfield, VA: NTIS, 437-450.

*Spoor NL, Hursh JB. 1973. Protection criteria. In: Hodge HC, Stannard JN, Hursh JB, eds. Handbook of experimental pharmacology. Berlin: Springer- Verlag, 241-270,

*Sprague GF, Harrison WM. 1949. Pharmacology and toxicology of uranium compounds. McGraw-Hill Book Company, Inc., 525-531.

*Sram RJ, Binkova B, Dobias L, et al. 1993. Monitoring genotoxic exposure in uranium miners. Environ Health Perspect 99:303-305.

*SRI. 1988. 1988 Directory of Chemical Producers: United States of America. Menlo Park, CA: Stanford Research Institute, 1044.

*Stelling JHE. 1980. Source category survey: Uranium refining industry. Report. EPA-450/3-80-010. NITS PB80-192867.

*Stevens W, Bruenger FW, Atherton DR, et al. 1980. The distribution and retention of hexavalent uranium-233 in the Beagle. Radiat Res 83:109-126.

*Stevenson KA, Hardy EP. 1993. Estimate of excess uranium in surface soil surrounding the feed materials production center using a requalified data base. Health Phys 65(3):283-287.

*Stewart BD, McKlveen JW, Glinski RL. 1988. Determination of uranium and radium concentrations in the waters of the Grand Canyon by alpha spectrometry. J Radioanal Nucl Chem 123:121-132.

*Stokinger HE. 1981. Uranium, U. In: Clayton CD, Clayton FE, eds. Industrial hygiene and toxicology, Vol. 2A. 3rd ed. New York, NY: John Wiley & Sons, 1995-2013.

*Stokinger HE, Baxter RC, Dygent HP, et al. 1953. In: Voegtlin C, Hodge HC, eds. Toxicity following inhalation for 1 and 2 years.

*Stopps GJ, Todd M. 1982. The chemical toxicity of uranium with special reference to effects on the kidney and the use of urine for biological monitoring. Prepared for the Atomic Energy Control Board, Ottawa, Canada. CA 8306480. NTIS DE 84-701123.

*Strading GN, Stather JW, Gray SA, et al. 1988. The metabolism of ceramic and non-ceramic forms of uranium dioxide after deposition in the rat lung. Human Toxicol 7:133-139.

*Stradling GN, Gray SA, Moody JC, et al. 1991. Efficacy of tiron for enhancing the excretion of uranium from the rat. Human & Experimental Toxicology 10:195-198.

*Stradling GN, Smith H, Cooper JR, et al. 1984. Factors affecting the abundance of uranium isotopes in body tissues and excreta following the deposition of enriched uranium dioxide in the lungs - The radiological implications. Health Phys 46:434-438.

*Stradling GN, Stather JW, Gray SA, et al. 1987. Metabolism of uranium in the rat after inhalation of two industrial forms of ore concentrate: The implications for occupational exposure. Hum Toxicol 6:385-394.

*Stuart WI, Adams RB, Smith HE. 1979. Solubility and hemolytic activity of uranium trioxide. Environ Res 18:385-396.

*Sudo M, Honda N, Hishida A, et al. 1977. Renal hemodynamics in uranyl acetate-induced acute renal failure of rabbits. Kidney Int 11:35-43.

*Sullivan MF. 1980. Absorption of actinide elements from the gastrointestinal tract of neonatal animals. Health Phys 38(2):173-185.

*Sullivan MF. 1980a. Absorption of actinide elements from the gastrointestinal tract of rats, guinea pigs and dogs. Health Phys 38:159-171.

*Sullivan MF. 1980b. Absorption of actinide elements from the gastrointestinal tract of neonatal animals. Health Phys 38:173-185.

*Sullivan MF, Gorham LS. 1982. Further studies on the absorption of actinide elements from the gastrointestinal tract of neonatal animals. Health Phys 43(4):509-19.

*Sullivan MF, Ruemmler PS. 1988. Absorption of 233U, 237Np, 238Pu, 241Am and 244Cm from the gastrointestinal tracts of rats fed an iron-deficient diet. Health Phys 54:311-316.

*Sullivan MF, Ruemmler PS, Ryan JL, et al. 1986. Influence of oxidizing or reducing agents on gastrointestinal absorption of uranium, plutonium, americium, curium, and promethium by rats. Health Phys 50:233-232.

*Sullivan MR, Gorham L. 1982. Further studies on the absorption of actinide elements from the gastrointestinal tract of neonatal animals. Health Phys 43:509-519.

*Sullivan RE, Nelson NS, Ellett WH, et al. 1981. Estimates of health risk from exposure to radioactive pollutants. ORNL/TM-7745.

*Suzuki S, Hirai S. 1987. Instrumental neutron activation analysis of vehicle exhaust particulates as environmental reference material. Anal Sci 3:193-197.

*Swanson SM. 1983. Levels of 236Ra, 210Pb and total U in fish near a Saskatchewan uranium mine and mill. Health Phys 45(1):67-80.

*Swanson SM. 1985. Food chain transfer of U-Series radionuclides in northern Saskatchewan aquatic system. Health Phys 49:747-770.

*Szabo Z, Zapecza OS. 1987. Relation between natural radionuclide activities and chemical constituents in ground water in the Newark Basin New Jersey USA. In: Graves B, ed. Radon in ground water, radon, radium and other radioactivity in ground water: Hydrogeologic impact and application to indoor airborne contamination: Proc National Water Well Association conference, Somerset, NJ, April 7-9, 1987. Chelsea, MI: Lewis Publishers, Inc., 283-308.

*Tadmor J. 1986. Atmospheric release of volatilized species of radioelements from coal-fired plants. Health Phys 50:270-273.

*Tannenbaum A, Silverstone H, Koziol J. 1951. The distribution and excretion of uranium in mice, rats and dogs. In: Tannenbaum A, ed. Toxicology of uranium compounds. New York, NY: McGraw-Hill, 128-181.

*Thind KS. 1987. A comparison of ICRP Publication 30 lung model-based predictions with measured bioassay data for airborne natural uranium dioxide exposure. Health Phys 53:59-66.

*Thompson DL. 1976. Uranium in dental porcelain. Report. NTIS PB- 259624.

*Thun MJ, Baker DB, Smith AB, et al. 1981. Health hazard evaluation report HETA-81-055-954, Cotter Corp, Canon City, CO. NTIS PB83-127407.

*Thun MJ, Baker DB, Steenland K, et al. 1985. Renal toxicity in uranium mill workers. Scand J Work Environ Health 11(2):83-90.

*Ticknor KV. 1994. Uranium sorption on geological materials. Radiochimica Acta 64:229-236.

*Tobias CA. 1985. Failla Memorial Lecture. The future of heavy-ion science in biology and medicine. Radiat Res 103(1):1-33.

*Toole J, McKay K, Baxter M. 1991. Determination of uranium in marine sediment pore waters by isotope dilution inductively coupled plasma mass spectrometry. Analytica Chimica Acta 245:83-88.

*Tracy BL, Meyerhof DP. 1987. Uranium concentrations in air near a Canadian uranium refinery. Atmos Env 21:165-172.

*Tracy BL, Quinn JM, Lahey J, et al. 1992. Absorption and retention of uranim from drinking water by rats and rabbits. Health Phys 62(1):65-73.

*Twiss P, Watling RJ, Delev D. 1994. Determination of thorium and uranium in faecal material from occupationally-exposed workers using ICP-MS. Atomic Spectroscopy 15(1):36-39.

*Ubios AM, Braun EM, Cabrini RL. 1994. Lethality due to uranium poisoning is prevented by ethane-1-hydroxy-1,1-biphosphonate (EHBP). Health Phys 66(5):540-4.

*Ubios AM, Guglielmotti MB, Steimetz T, et al. 1991. Uranium inhibits bone formation in physiologic Alveolar bone modeling and remodeling. Environment Research 54:17-23.

*UCC. 1980. Union Carbide Corporation. United States Department of Energy, Paducah Gaseous Diffusion Plant. Environmental monitoring report.

*Ueda K, Koshino Y, Yamamoto Y. 1985. Preconcentration of uranium in seawater with hetercyclic azo dyes suported on silica gel. Analytical Letters 18:2345-2359.

*Uesugi K, Nagahiro T. 1983. A highly sensitive spectrophotometric determination of uranium with chromal blue G in the presence of cetytrimethylammonium chloride. Analytica Chimica Acta 148: 315-320.

*UNSCEAR. 1977. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. United Nations Document E.77.IX.1, New York, NY.

*UNSCEAR. 1982. United Nations Scientific Committee on the Effects of Atomic Radiation. Ionizing radiation: Sources and biological effects. United Nations Document E.82.IX.8, New York, NY.

*UNSCEAR. 1986. United Nations Scientific Committee on the Effects of Atomic Radiation. Genetic and somatic effects of ionizing radiation. New York: United Nations.

*UNSCEAR. 1988. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources, effects and risks of ionizing radiation. Report to the General Assembly, with annexes. New York, NY: United Nations Publications.

*Upton AC. 1993. Ionizing radiation. In: Rom WN, ed. Environmental and occupational medicine, 1071-1083.

*Uranium Institute. 1996. The nuclear fuel cycle. http://www.uilondon.org/nfc.htm

*USDOC. 1984. U.S. General imports and imports for consumption. Schedule A, commodity by country. Washington, DC: Bureau of Census, U.S. Department of Commerce, 2-61 to 2-62.

*USDOC. 1988. U.S. General imports and imports for consumption. Schedule A, commodity by country. Washington, DC: Bureau of Census, U.S. Department of Commerce, 2-70 to 2-71; 2-149.

*USDOC 1995. National Trade Data Bank. U.S. Department of Commerce, Bureau of the Census.

*USDOC. 1997. U.S. Merchandise import and export trade. Retrieved from National Trade Data Bank. United States Department of Commerce, Bureau of Census.

*USDOC. 1999. National Trade Data Bank. U.S. Department of Commerce, Bureau of the Census.

*USNRC. 1969. United States Nuclear Regulatory Commission.   Interpretations. Code of Federal Regulations. 10 CFR 8.

8. REFERENCES

*USNRC. 1981. United States Nuclear Regulatory Commission. Uranium fuel cycle environmental data. Federal Register 46:15154-15175.

*USNRC. 1986. United States Nuclear Regulatory Comission. Assessment of the public health impact from the accidental release of UP6 at the Sequoyah Fuels Corporation Facility at Gore, Oklahoma. Vol. 1. U.S. Report NUREG-1189. Washington DC. Doc No. 40-8027.

*USNRC. 1988. United States Nuclear Regulatory Commission. Maximum permissible concentrations for uranium and thorium. Code of Federal Regulations. 10 CFR 20.

*USNRC. 1992. United States Nuclear Regulatory Commission. Nuclear Regulatory Commission Information Digest, 1992 Edition. NUREG-1350-V4. Washington, DC.

*USNRC. 1993a. United States Nuclear Regulatory Commission. Federal Register. 58 FR 14178 (proposed).

*USNRC. 1993b. United States Nuclear Regulatory Commission. Federal Register. 58 FR 18049 (proposed).

*USNRC. 1993c. United States Nuclear Regulatory Commission. Federal Register. 58 FR 19784 (proposed).

*USNRC. 1993d. United States Nuclear Regulatory Commission. Federal Register. 58 FR 26257 (proposed).

*USNRC. 1993e. United States Nuclear Regulatory Commission. Federal Register. 58 FR 33570 (proposed).

*USNRC. 1993f. United States Nuclear Regulatory Commission. Annual limits on intake (ALIs) and derived air concentrations (DACs) of radionuclides for occupational exposure; effluent concentrations; concentrations for release to sewerage. Code of Federal Regulations. 10 CFR 20, Appendix B.

*USNRC. 1994a. United States Nuclear Regulatory Commission. Federal Register. 58 FR 43200 (proposed).

*USNRC. 1994b. United States Nuclear Regulatory Commission. Federal Register. 58 FR 30724 (proposed).

*USNRC. 1995a. United States Nuclear Regulatory Commission. Occupational dose limits. Code of Federal Regulations. 10 CFR 20, Subpart C.

*USNRC. 1995b. United States Nuclear Regulatory Commission. Requirements for transfer of low-level radioactive waste intended for disposal at licensed land disposal facilities and manifests. Code of Federal Regulations. 10 CFR 20, Appendix G.

*USNRC. 1997a. United States Nuclear Regulatory Commission. Standards for protection against radiation, general provisions, definitions. Code of Federal Regulations. 10 CFR 20.1003.

*USNRC. 1997b. United States Nuclear Regulatory Commission. Dose limits for individual members of the public. Code of Federal Regulations. 10 CFR 20.1301.

8. REFERENCES

*USNRC. 1997c. United States Nuclear Regulatory Commission. Radiological criteria for license termination. Code of Federal Regulations. 10 CFR 20, Subpart E.

*USNRC. 1999. United States Nuclear Regulatory Commission. Standards for protection against radiation, general provisions, scope. Code of Federal Regulations. 10 CFR 20.1002.

*USTUR. 1996. United States transuranium and uranium registries, Annual report October 1, 1995 - September 30, 1996. Washington State University, Richland, Washington.

*USTUR. 1999. U.S. transuranium and uranium registry. USTUR database. http://www.tricity.wsu.edu/~ustur/database.html.

*Van den Berg CMG, Nimmo M. 1987. Direct determination of uranium in water by cathodic stripping voltammetry. Anal Chem 59:924-928.

*Van Netten C, Morley DR. 1983. Uptake of uranium molybdenum copper and selenium by the radish from uranium rich soils. Arch Env Health 38:172-175.

*Vandergrift GF, Bowers DL, Gerding TJ, et al. 1984. Interaction of groundwater and basalt fissure surfaces and its effect on the migration of actinides. Washington DC: American Chemical Society.

*Velten RJ, Jacobs BJ. 1984. Determination of uranium in drinking water by laser induced fluorometry. EPA Method 908.2. Cincinnati, OH: Environmental Monitoring and Support Laboratory, Physical and Chemical Methods Branch, U.S. Environmental Protection Agency.

*Veselsky JC, Kwiecinska B, Wehrstein E, et al. 1988. Determination of uranium in minerals by laser fluorimetry. Analyst 113:451-455.

*Veska E, Eaton RS. 1991. Abandoned Rayrock uranium mill tailings in the Northwest Territories: environmental conditions and radiological impact. Health Phys 60(3):399-409.

*Vich Z, Kriklava J. 1970. Erythrocytes of uranium miners: The red blood picture. Br J Ind Med 27:83-85.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. European Journal of Biochemistry 238:476-483.

*Voegtlin C, Hodge HC, eds. 1949. Pharmacology and toxicology of uranium compounds. Vols 1 and 2. New York, NY: McGraw-Hill.

*Voegtlin C, Hodge HC, eds. 1953. Pharmacology and toxicology of uranium compounds. Vols 3 and 4. New York, NY: McGraw-Hill.

*Waite DT, Joshi SR, Sommerstad H. 1988. The effect of uranium mine tailings on radionuclide concentrations in Langley Bay, Saskatchewan Canada. Arch Env Contam Tox 17:373-380.

*Walinder G. 1989. Metabolism and sites of effects of uranium after incorporation along different routes in mice, rabbits and piglets. Radiation Protection Dosimetry 26(1/4):89-95.

8. REFERENCES

*Wang J, Wang J, Lu J, et al. 1994. Adsorptive stripping voltammetry of trace uranium critical comparison of various chelating agents. Analytica Chimica Acta 292:91-97.

*Wasserman J. 1986. Immunoligical indicators. In: Biological indicators for radiation dose assessment. Munchen: MMV Medizin Verlag, 85-105.

*Waxweiler RJ, Archer VE, Roscoe RJ, et al. 1983. Mortality patterns among a retrospective cohort of uranium mill workers. Presented at Epidemiology Applied to Health Physics: Proceedings of the Health Physics Society, 428-435.

*Waxweiler RJ, Roscoe RJ, Archer VE, et al. 1981a. Mortality follow-up through 1977 of the white underground uranium miners cohort examined by the United States Public Health Service.

*Waxweiler RJ, Roscoe RJ, Archer VE, et al. 1981b. In: Wiese WH, ed. Birth effects in the Four Corners area. Transcript of Meeting Held February 27, 1981. Department Family, Community, and Energency Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico.

*Weast R, ed. 1985. CRC handbook of chemistry and physics. 66th ed. Boca Raton, FL: CRC Press, B-146; B-440 to B-441.

*Wedeen RP. 1992. Renal diseases of occupational origin. Occupational Medicine 7(3):449

*Weigel F. 1983. Uranium and uranium compounds. In: Grayson M, ed. Kirk- Othmer encyclopedia of chemical technology, Vol. 23, 3rd ed. New York, NY: John Wiley & Sons, 502-547.

*Weissman SH, Carpenter RL, Newton GJ. 1983. Respirable aerosols from fluidized bed coal combustion: 3. Elemental composition of fly ash. Env Sci Tech 17:65-71.

*Welford GA, Baird R. 1967. Uranium levels in human diet and biological materials. Health Phys 13:1321-1324.

*Wersin P, Hochella MF, Persson P, et al. 1994. Interaction between aqueous uranium (VI) and sulfide minerals: Spectroscopic evidence for sorption and reduction. Geochimica et Cosmochimica Acta 58(13):2829-2843.

*Wessman RA. 1984. An overview of the radiochemical analysis of uranium. In: Biokinetics and analysis of uranium in man. Proceedings of a colloquium, Richland, WA, Aug 8-9, 1984. Prepared by the Hanford Environmental Health Foundation for the Department of Energy, J-1 to J-57.

*West CM, Scott LM. 1969. Uranium cases showing long chest burden retention an updating. Health Phys 17:781-791.

*West CM, Scott LM, Schultz NB. 1979. 16 years of uranium personnel monitoring experience--in retrospect. Health Phys 36:665-669.

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J. of Pediatrics 32a:10-18.

*Whittemore AS, McMillan A. 1983. Lung cancer mortality among USA uranium miners: A reappraisal. J Natl Cancer Inst 71:489-500.

*WHO. 1984. World Health Organization. Guidelines for Drinking Water Quality, Vol. 1
Recommendations.

*Wick RR, Chmelevsky D, Gossner W. 1986. 224 Ra risk to bone and haematopoietic tissue in ankylosing
spondylitis patients. In: Gossner W, Gerber GB, et al., eds. The radiobiology of radium and thorotrast.
Munich, West Germany: Urban and Schwarzenberg, 38-44.

*Widdowson EM, Dickerson JWT. 1964. Chapter 17: Chemical composition of the body. In: C.L. Comar
and Felix Bronner, eds. Mineral metabolism: An advanced treatise, Volume II - the elements part A. New
York, NY: Academic Press.

*Wiegand J, Yamamoto G, Gaston W. 1987. Elevated levels of radioactivity in water wells in Los Angeles
and Orange Counties, CA, USA. In: Graves B, ed. Radon in ground water, radon, radium and other
radioactivity in ground water: Hydrogeologic impact and application to indoor airborne contamination: Proc
National Water Well Association conference, Somerset, NJ, April 7-9, 1987. Chelsea, MI: Lewis
Publishers, Inc., 71-73.

*Wiese WH, Skipper BJ. 1986. Survey of reproductive outcomes in uranium and potash mine workers:
Results of first analysis. Ann Am Conf Gov Ind Hyg 14:187-192.

*Williams JK, Berven BA. 1986. Results of radiological measurements taken in the Niagara Falls, NY
area. Report: ISS ORNL/TM-10076. DE87002963.

*Woodard HQ. 1980. Radiation carcinogenesis in man: A critical review. Environmental measurments
laboratory report EML-380. U.S. Department of Energy, New York.

*Woodis TC Jr., Trimm JR, Holmes JH, et al. 1980. Determination of uranium in phosphate rock and
wet-process phosphoric acid by argon-plasma emission spectrometry. J Assoc Off Anal Chem 63:208-210.

*Woods DA. 1986. Final product dust activity median aerodynamic diameters in the product packing areas
of two Australian uranium mills. Health Phys 51:352-356.

*Wrenn ME, Durbin PW, Howard B. 1985. Metabolism of ingested uranium and radium. Health Phys
48:601-633.

*Wrenn ME, Durbin PW, Willis DL, et al. 1987. The potential toxicity of uranium in water. Am Water
Works Assoc J 79:177-184.

*Wrenn ME, Liese G, Torrey J, et al. 1986. The elimination rate of uranium from the kidney of the dog.
In: Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program.

*Wrenn ME, Lipsztein J, Bertelli L. 1988a. Pharmacokinetic models relevant to toxicity and metabolic for
uranium in humans and animals. DOE Report. DOE/NV/10574-2.

*Wrenn ME, Singh NP, Ruth H, et al. 1988b. Gastrointestinal absorption of soluble uranium from
drinking water. Govt Rep Announce Ind, Issue 17.

*Wrenn ME, Singh NP, Ruth H et al. 1989. Gastrointestinal absorption of soluble uranium from drinking
water by man. Radiat Prot Dosim 26:119-122.

8. REFERENCES

*Wrenn ME, Singh NP, Saccomanno G. 1983. Uranium and thorium isotopes and their state of equilibria in lungs from uranium miners. Health Phys 44(Suppl 1):385-389.

*Yamamoto T, Masuda K, Nukada K. 1971. Studies on environmental contamination by uranium. 6. Uranium in total diet and human urine from nonoccupationally exposed persons in Okayama Prefecture (1969-1971). J Radiation Res 13(1):5.

*Yamamoto T, Masuda K, Onishi N. 1968. Studies on environmental contamination by uranium. J Environ Surv of Uranium in Kamiscaibara Village, Okayama Prefecture. J Rad Res 9:92-99.

*Yang IC, Edwards KW. 1984. Releases of radium and uranium into Ralston Creek and Reservoir Colorado USA from uranium mining. In: Barney GS, Navratil JD, Schulz W, eds. 185th meeting: American Chemical Society Symposium Series 246. Geochemical behavior of disposed radioactive waste, Seattle WA, March 20-25, 1983. Washington, DC: American Chemical Society, 271-286.

*Yu RC, Sherwood RJ. 1996. The relationships between urinary elimination, airborne concentration, and radioactive hand contamination for workers exposed to uranium. AIHA 57(7):615-20.

*Yuile CL. 1973. Animal experiments. In: Hodge HC, Stannard JN, Hursh JB, eds. Handbook of experimental pharmacology, Vol. 36. Berlin: Springer- Verlag, 165-196.

*Zalups RK. 1991. An evaluation of Tiron (Sodium 4,5-dihydroxybenzene-1,3-disulfonate) as a rescue agent for the nephropathy induced by uranyl fluoride (UO2F2) in rats. Research Communications in Chemical Pathology and Pharmacology. 72(1):125-128.

*Zamora ML, Tracy BL, Zielinski JM, et al. 1998. Chronic ingestion of uranium in drinking water: A study of kidney bioeffects in humans. Toxicol Sci 43:68-77.

*Zhao S, Zhao F-Y. 1990. Nephrotoxic limit and annual limit of intake for natural U. Health Phys Society 619-623.

*Ziegler EE, Edwards BB, Jensen RL et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

*Zielinski RA, McKown DM. 1984. Determination of uranium concentration in water by liquid anion-exchange–delayed-neutron analysis. J Radioanal Nucl Chem 84:207-212.

9. GLOSSARY

Absorbed Dose, Chemical—The amount of a substance that is either absorbed into the body or placed in contact with the skin. For oral or inhalation routes, this is normally the product of the intake quantity and the uptake fraction divided by the body weight and, if appropriate, the time, expressed as mg/kg for a single intake or mg/kg/day for multiple intakes. For dermal exposure, this is the amount of material applied to the skin, and is normally divided by the body mass and expressed as mg/kg.

Absorbed Dose, Radiation—The mean energy imparted to the irradiated medium, per unit mass, by ionizing radiation. Units: rad (rad), gray (Gy).

Absorbed Fraction—A term used in internal dosimetry. It is that fraction of the photon energy (emitted within a specified volume of material) which is absorbed by the volume. The absorbed fraction depends on the source distribution, the photon energy, and the size, shape and composition of the volume.

Absorption—The process by which a chemical penetrates the exchange boundaries of an organism after contact, or the process by which radiation imparts some or all of its energy to any material through which it passes.

Absorption Coefficient—Fractional absorption of the energy of an unscattered beam of x- or gamma-radiation per unit thickness (linear absorption coefficient), per unit mass (mass absorption coefficient), or per atom (atomic absorption coefficient) of absorber, due to transfer of energy to the absorber. The total absorption coefficient is the sum of individual energy absorption processes (see Compton Effect, Photoelectric Effect, and Pair Production).

Absorption Coefficient, Linear—A factor expressing the fraction of a beam of x- or gamma radiation absorbed in a unit thickness of material. In the expression $I=I_o e^{-\mu x}$, I_o is the initial intensity, I the intensity of the beam after passage through a thickness of the material x, and μ is the linear absorption coefficient.

Absorption Coefficient, Mass—The linear absorption coefficient per cm divided by the density of the absorber in grams per cubic centimeter. It is frequently expressed as μ/ρ, where μ is the linear absorption coefficient and ρ the absorber density.

Absorption Ratio, Differential—Ratio of concentration of a nuclide in a given organ or tissue to the concentration that would be obtained if the same administered quantity of this nuclide were uniformly distributed throughout the body.

Activation—The process of making a material radioactive by bombardment with neutrons or protons.

Activity—The number of radioactive nuclear transformations occurring in a material per unit time (see Curie, Becquerel). The term for activity per unit mass is specific activity.

Activity Median Aerodynamic Diameter (AMAD)—The diameter of a unit-density sphere with the same terminal settling velocity in air as that of the aerosol particle whose activity is the median for the entire size distribution of the aerosol.

Acute Exposure, Chemical—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Acute Exposure, Radiation—The absorption of a relatively large amount of radiation (or intake of a radioactive material) over a short period of time.

Acute Radiation Syndrome—The symptoms which taken together characterize a person suffering from the effects of intense radiation. The effects occur within hours or days.

Ad libitum—Available in excess and freely accessible.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit surface area or per unit weight of organic carbon of a specific particle size in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)—The amount of a chemical adsorbed by a 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.

Alpha Particle—A positively charged particle ejected spontaneously from the nuclei of some radioactive elements. It is identical to a helium nucleus, i.e., 2 neutrons and two protons, with a mass number of 4 and an electrostatic charge of +2.

Alpha Track—The track of ionized atoms (pattern of ionization) left in a medium by an alpha particle that has traveled through the medium.

Annihilation (Positron-Electron)—An interaction between a positive and a negative electron in which they both disappear; their rest mass, being converted into electromagnetic radiation (called annihilation radiation) with two 0.51 MeV gamma photons emitted at an angle of 180E to each other.

Atom—The smallest particle of an element that cannot be divided or broken up by chemical means. It consists of a central core called the *nucleus*, which contains *protons* and *neutrons* and an outer shell of *electrons*.

Atomic Mass (u)—The mass of a neutral atom of a nuclide, usually expressed in terms of "atomic mass units." The "atomic mass unit" is one-twelfth the mass of one neutral atom of carbon-12; equivalent to 1.6604×10^{-24} g.

Atomic Number—The number of protons in the nucleus of an atom. The "effective atomic number" is calculated from the composition and atomic numbers of a compound or mixture. An element of this atomic number would interact with photons in the same way as the compound or mixture. (Symbol: Z).

Atomic Mass Number—See Mass Number.

Atomic Weight—The weighted mean of the masses of the neutral isotopes of an element expressed in atomic mass units.

Attenuation—A process by which a beam from a source of radiation is reduced in intensity by absorption and scattering when passing through some material.

Attenuation Coefficient—The fractional reduction in the intensity of a beam of radiation as it passes through an absorbing medium. It may be expressed as reduction per unit distance, per unit mass thickness, or per atom, and is called the linear, mass, or atomic attenuation coefficient, respectively.

Auger Effect—The emission of an electron from the extranuclear portion of an excited atom when the atom undergoes a transition to a less excited state.

Background Radiation—The amount of radiation to which a member of the general population is exposed from natural sources, such as terrestrial radiation from naturally occurring radionuclides in the soil, cosmic radiation originating from outer space, and naturally occurring radionuclides deposited in the human body.

Becquerel (Bq)—International System of Units unit of activity and equals that quantity of radioactive material in which one transformation (disintegration) occurs per second (see Units).

Beta Particle—An electron that is emitted from the nucleus of an atom during one type of radioactive transformation. A beta particle has a mass and charge equal in magnitude to that of the electron. The charge may be either +1 or -1. Beta particles with +1 charges are called positrons (symbolized β^+), and beta particles with -1 charges are called negatrons (symbolized β^-).

Biological Half-time—The time required for a biological system, such as that of a human, to eliminate by natural process half of the amount of a substance (such as a chemical substance, either stable or radioactive) that has entered it.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biologic Effectiveness of Radiation—See Relative Biological Effectiveness.

Body Burden, Chemical—The total amount of a chemical found in an animal or human body.

Body Burden, Radioactivity—The amount of radioactive material found in an animal or human body.

Bone Seeker—Any compound or ion which migrates in the body and preferentially deposits into bone.

Branching—The occurrence of two or more modes by which a radionuclide can undergo radioactive decay. For example, ^{214}Bi can undergo alpha or beta minus decay, ^{64}Cu can undergo beta minus, beta plus, or electron capture decay. An individual atom of a nuclide exhibiting branching disintegrates by one mode only. The fraction disintegrating by a particular mode is the "branching fraction" for that mode. The "branching ratio" is the ratio of two specified branching fractions (also called multiple disintegration).

Bremsstrahlung—X rays that are produced when a charged particle accelerates (speeds up, slows down, or changes direction) in the strong field of a nucleus.

Buildup Factor—The ratio of the radiation intensity, including both primary and scattered radiation, to the intensity of the primary (unscattered) radiation.

Cancer Effect Level (CEL)—The lowest dose of chemical or radiation in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Capture, Electron—A mode of radioactive decay involving the capture of an orbital electron by its nucleus. Capture from a particular electron shell, e.g., K or L shells, is designated as "K-electron capture" or "L-electron capture."

Capture, K-Electron—Electron capture from the K shell by the nucleus of the atom. Also loosely used to designate any orbital electron capture process.

Carcinogen—A chemical or radiation that is capable of inducing cancer.

Carcinoma—Malignant neoplasm composed of epithelial cells, regardless of their derivation.

Cataract—A clouding of the crystalline lens of the eye which obstructs the passage of light.

Ceiling Value—A concentration of a substance that should not be exceeded, even temporarily.

Charged Particle—A nuclear particle, atom, or molecule carrying a positive or negative charge.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Collective dose—The sum of the individual doses received in a given period of time by a specified population from exposure to a specified source of radiation. Collective dose is expressed in units such as man-rem and person-sievert.

Compton Effect—An attenuation process observed for x- or gamma radiation in which an incident photon interacts with an orbital electron of an atom to produce a recoil electron and a scattered photon whose energy is less than the incident photon.

Containment—The confinement of a chemical or radioactive substance in such a way that it is prevented from being dispersed from its container or into the environment, or is released only at a specified rate.

Contamination—Deposition of a stable or radioactive substance in any place where it is not desired.

Cosmic Rays—High-energy particulate and electromagnetic radiations which originate outside the earth's atmosphere.

Count (Radiation Measurements)—The external indication of a radiation-measuring device designed to enumerate ionizing events. It refers to a single detected event. The term "count rate" refers to the total number registered in a given period of time. The term is sometimes erroneously used to designate a disintegration, ionizing event, or voltage pulse.

Counter, Geiger-Mueller (GM counter)—Highly sensitive, gas-filled radiation-measuring device to detect (count) individual photons or particulate radiation.

Counter, Scintillation—The combination of phosphor, photomultiplier tube, and associated circuits for counting light emissions produced in the phosphors by ionizing radiation. Scintillation counters generally are more sensitive than GM counters for gamma radiation.

Curie (Ci)—A unit of radioactivity. One curie equals that quantity of radioactive material in which there are 3.7×10^{10} nuclear transformations per second. The activity of 1 gram of radium is approximately 1 Ci.

> **Attocurie (aCi)**—One-thousanth of a femtocurie (3.7×10^{-8} disintegrations per second).
>
> **Femtocurie (fCi)**—One-billionth of a microcurie (3.7×10^{-5} disintegrations per second).
>
> **Megacurie (MCi)**—One million curies (3.7×10^{16} disintegrations per sec).
>
> **Microcurie (μCi)**—One-millionth of a curie (3.7×10^{4} disintegrations per sec).
>
> **Millicurie (mCi)**—One-thousandth of a curie (3.7×10^{7} disintegrations per sec).
>
> **Nanocurie (nCi)**—One-billionth of a curie (3.7×10^{1} disintegrations per sec).
>
> **Picocurie (pCi)**—One-millionth of a microcurie (3.7×10^{-2} disintegrations per second.

Daughter Products—See Progeny and Decay Product

Decay, Radioactive—Transformation of the nucleus of an unstable nuclide by spontaneous emission of charged particles and/or photons (see Disintegration).

Decay Chain or Decay Series—A sequence of radioactive decays (transformations) beginning with one nucleus. The initial nucleus, the parent, decays into a daughter or progeny nucleus that differs from the first by whatever particles were emitted during the decay. If further decays take place, the subsequent nuclei are also usually called daughters or progeny. Sometimes, to distinguish the sequence, the daughter of the first daughter is called the granddaughter, etc.

Decay Constant (λ)—The fraction of the number of atoms of a radioactive nuclide which decay in unit time (see Disintegration Constant).

Decay Product, Daughter Product, Progeny—A new nuclide formed as a result of radioactive decay. A nuclide resulting from the radioactive transformation of a radionuclide, formed either directly or as the result of successive transformations in a radioactive series. A decay product (daughter product or progeny) may be either radioactive or stable.

Delta Ray—Electron removed from an atom during the process of ionization (also called secondary electron). Delta rays cause a track of ionizations along their path.

Depleted uranium (DU)—Uranium having a percentage of ^{235}U smaller than the 0.7% found in natural uranium. It is obtained as a by-product from ^{235}U enrichment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical or radiation prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Disintegration Constant—Synonymous with decay constant. The fraction of the number of atoms of a radioactive material that decays per unit time (see Decay Constant.)

Disintegration, Nuclear—A spontaneous nuclear transformation (radioactivity) characterized by the emission of energy and/or mass from the nucleus. When large numbers of nuclei are involved, the process is characterized by a definite half-life (see Transformation, Nuclear).

Dose—A general term denoting the quantity of a substance, radiation, or energy absorbed. For special purposes it must be appropriately qualified. If unqualified, it refers to radiation absorbed dose.

    Absorbed Dose—The energy imparted to matter by ionizing radiation per unit mass of irradiated material at the place of interest. The unit of absorbed dose is the rad. One rad equals 100 ergs per gram. In SI units, the absorbed dose is the gray which is 1 J/kg (see Rad).

    Cumulative Dose (Radiation)—The total dose resulting from repeated or continuous exposures to radiation.

    Dose Assessment—An estimate of the radiation dose to an individual or a population group usually by means of predictive modeling techniques, sometimes supplemented by the results of measurement.

    Dose Equivalent (DE)—A quantity used in radiation safety practice to account for the relative biological effectiveness of the several types of radiation. It expresses all radiations on a common scale for calculating the effective absorbed dose. It is defined as the product of the absorbed dose in rad and certain modifying factors. (The unit of dose equivalent is the rem. In SI units, the dose equivalent is the sievert, which equals 100 rem.)

    Dose, Radiation—The amount of energy imparted to matter by ionizing radiation per unit mass of the matter, usually expressed as the unit rad, or in SI units, the gray. 100 rad' 1 gray (Gy) (see Absorbed Dose).

    Maximum Permissible Dose Equivalent (MPD)—The greatest dose equivalent that a person or specified part thereof shall be allowed to receive in a given period of time.

    Median Lethal Dose (MLD)—Dose of radiation required to kill, within a specified period (usually 30 days), 50% of the individuals in a large group of animals or organisms. Also called the LD_{50}, or $LD_{50/30}$ if for 30 days..

    Threshold Dose—The minimum absorbed dose that will produce a detectable degree of any given effect.

    Tissue Dose—Absorbed dose received by tissue in the region of interest, expressed in rad (see Dose, Gray, and Rad).

Dose, Fractionation—A method of administering therapeutic radiation in which relatively small doses are given daily or at longer intervals.

Dose, Protraction—A method of administering therapeutic radiation by delivering it continuously over a relatively long period at a low dose rate.

Dose Rate—Absorbed dose delivered per unit time.

Dosimetry—Quantification of radiation doses to cells, tissues, organs, individuals or populations resulting from specified exposures.

Early Effects (of radiation exposure)—Effects that appear within 60 days of an acute exposure.

Electron—A stable elementary particle having an electric charge equal to $\pm 1.60210 \times 10^{-19}$ C (Coulombs) and a rest mass equal to 9.1091×10^{-31} kg. A positron is a positively charged "electron" (see Positron).

Electron Volt—A unit of energy equivalent to the energy gained by an electron in passing through a potential difference of one volt. Larger multiple units of the electron volt are frequently used: keV for thousand or kilo electron volts; MeV for million or mega electron volts (eV). 1 eV=1.6×10^{-12} erg.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Energy—Capacity for doing work. "Potential energy" is the energy inherent in a mass because of its spatial relation to other masses. "Kinetic energy" is the energy possessed by a mass because of its motion (SI unit: joules):

> **Binding Energy (Electron)**—The amount of energy that must be expended to remove an electron from an atom.

> **Binding Energy (Nuclear)**—The energy represented by the difference in mass between the sum of the component parts and the actual mass of the nucleus. It represents the amount of energy that must be expended to break a nucleus into its component neutrons and protons.

> **Excitation Energy**—The energy required to change a system from its ground state to an excited state. Each different excited state has a different excitation energy.

> **Ionizing Energy**—The energy required to knock an electron out of an atom. The average energy lost by electrons or beta particles in producing an ion pair in air or in soft tissue is about 34 eV.

> **Radiant Energy**—The energy of electromagnetic radiation, such as radio waves, visible light, x and gamma rays.

Enriched Material—Material in which the relative amount of one or more isotopes of a constituent has been increased.

Enriched Uranium—Uranium in which the abundance of the ^{235}U isotope is increased above normal.

Enrichment, Isotopic—An isotopic separation process by which the relative abundances of the isotopes of a given element are altered, thus producing a form of the element that has been enriched in one or more isotopes and depleted in others. In uranium enrichment, the percentage of uranium-235 in natural uranium can be increased from 0.7% to >90% in a gaseous diffusion process based on the different thermal velocities of the constituents of natural uranium (^{234}U, ^{235}U, ^{238}U) in the molecular form UF_6.

EPA Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Equilibrium, Radioactive—In a radioactive series, the state which prevails when the ratios between the activities of two or more successive members of the series remains constant.

> **Secular Equilibrium**—If a parent element has a very much longer half-life than the daughters (so there is not appreciable change in its amount in the time interval required for later products to attain equilibrium) then, after equilibrium is reached, equal numbers of atoms of all members of the series disintegrate in unit time. This condition is never exactly attained, but is essentially established in such a case as ^{226}Ra and its transformation series to stable ^{206}Pb. The half-life of ^{226}Ra is about 1,600 years; of ^{222}Rn, approximately 3.82 days, and of each of the subsequent members, a few minutes. After about a month, essentially the equilibrium amount of radon is present; then (and for a long time) all members of the series disintegrate the same number of atoms per unit time. At this time, the activity of the daughter is equal to the activity of the parent.

> **Transient Equilibrium**—If the half-life of the parent is short enough so the quantity present decreases appreciably during the period under consideration, but is still longer than that of successive members of the series, a stage of equilibrium will be reached after which all members of the series decrease in activity exponentially with the period of the parent. At this time, the ratio of the parent activity to the daughter activity is constant.

Equilibrium, Electron—The condition in a radiation field where the energy of the electrons entering a volume equals the energy of the electrons leaving that volume.

Equilibrium Fraction (F)—In radon-radon daughter equilibrium, the parents and daughters have equal radioactivity, that is, as many decay into a specific nuclide as decay out. However, if fresh radon is continually entering a volume of air or if daughters are lost by processes other than radioactive decay, e.g., plate out or migration out of the volume, a disequilibrium develops. The equilibrium fraction is a measure of the degree of equilibrium/disequilibrium. The equilibrium fraction is used to estimate working levels based on measurement of radon only. For radon, 1 working-level concentration is defined at 100 pCi of radon in equilibrium with its 4 successive progeny in 1 liter of air. Thus, 100 pCi/L radon at 50% equilibrium is 0.5 WL.

Excitation—The addition of energy to a system, thereby transferring it from its ground state to an excited state. Excitation of a nucleus, an atom, or a molecule can result from absorption of photons or from inelastic collisions with other particles. The excited state of an atom is an unstable or metastable state and will return to ground state by radiation of the excess energy.

Exposure (Chemical)—Contact of an organism with a chemical or physical agent. Exposure is quantified as the amount of the agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut) and available for absorption.

Exposure (Radiation)—Being exposed to ionizing radiation or to a radioactive material. A measure of the ionization produced in air by x or gamma radiation; the sum of the electric charges on all ions of one sign produced in air when all electrons liberated by photons in a volume of air are completely stopped in air (dQ), divided by the mass of the air in the volume (dm). The unit of exposure in air is the roentgen, or coulomb per kilogram (SI units). One roentgen is equal to 2.58×10^{-4} coulomb per kilogram (C/kg).

Fission, Nuclear—A nuclear transformation characterized by the splitting of a nucleus into at least two other nuclei and several neutrons, and is accompanied by the release of a relatively large amount of energy.

Gamma Ray, Penetrating—Short wavelength electromagnetic radiation of nuclear origin.

Genetic Effect of Radiation—Inheritable change, chiefly mutations, produced by the absorption of ionizing radiation by germ cells. Genetic effects have not been observed in any human population exposed at any dose level.

Gray (Gy)—SI unit of absorbed dose, 1 J/kg. One gray equals 100 rad (see Units).

Half-life, Radioactive—Time required for a radioactive substance to lose 50% of its activity by decay. Each radio-nuclide has a unique physical half-life. Known also as physical half-time and symbolized as T_r or T_{rad}.

Half-life, Effective—See Half-Time, Effective.

Half-time, Biological—Time required for an organ, tissue, or the whole body to eliminate one-half of any absorbed substance by regular processes of elimination. This is the same for both stable and radioactive isotopes of a particular element, and is sometimes referred to as half-time, symbolized as t_{biol} or T_b.

Half-time, Effective—Time required for a radioactive element in an organ, tissue, or the whole body to be diminished 50% as a result of the combined action of radioactive decay and biological elimination, symbolized as T_e or T_{eff}.

$$Effective\ Half\text{-}time = \frac{Biological\ half\text{-}time\ x\ Radioactive\ half\text{-}life}{Biological\ half\text{-}time\ +\ Radioactive\ half\text{-}life}$$

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube. Literally, "in glass."

In Vivo—Occurring within the living organism. Literally, "in life."

Intensity—Amount of energy per unit time passing through a unit area perpendicular to the line of propagation at the point in question.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Internal Conversion—Process in which a gamma ray knocks an electron out of the same atom from which the gamma ray was emitted. The ratio of the number of internal conversion electrons to the number of gamma quanta emitted in the de-excitation of the nucleus is called the "conversion ratio."

Ion—Atomic particle, atom or chemical radical bearing a net electrical charge, either negative or positive.

Ion Pair—Two particles of opposite charge, usually referring to the electron and positive atomic or molecular residue resulting after the interaction of ionizing radiation with the orbital electrons of atoms.

Ionization—The process by which a neutral atom or molecule acquires a positive or negative charge.

> **Primary Ionization**—(1) In collision theory: the ionization produced by the primary particles as contrasted to the "total ionization" which includes the "secondary ionization" produced by delta rays. (2) In counter tubes: the total ionization produced by incident radiation without gas amplification.

> **Specific Ionization**—Number of ion pairs per unit length of path of ionizing radiation in a medium; e.g., per centimeter of air or per micrometer of tissue.

> **Total Ionization**—The total electric charge of one sign on the ions produced by radiation in the process of losing its kinetic energy. For a given gas, the total ionization is closely proportional to the initial ionization and is nearly independent of the nature of the ionizing radiation. It is frequently used as a measure of absorption of radiation energy.

Ionization Density—Number of ion pairs per unit volume.

Ionization Path (Track)—The trail of ion pairs produced by an ionizing particle in its passage through matter.

Ionizing Radiation—Any radiation capable of knocking electrons out of atoms and producing ions. Examples: alpha, beta, gamma and x rays, and neutrons.

Isobars—Nuclides having the same mass number but different atomic numbers.

Isomers—Nuclides having the same number of neutrons and protons but capable of existing, for a measurable time, in different quantum states with different energies and radioactive properties. Commonly the isomer of higher energy decays to one with lower energy by the process of isomeric transition.

Isotopes—Nuclides having the same number of protons in their nuclei, and hence the same atomic number, but differing in the number of neutrons, and therefore in the mass number. Identical chemical properties exist in isotopes of a particular element. The term should not be used as a synonym for nuclide because isotopes refer specifically to different nuclei of the same element.

> **Stable Isotope**—A nonradioactive isotope of an element.

Kerma (k)—A measure of the kinetic energy transferred from gamma rays or neutrons to a unit mass of absorbing medium in the initial collision between the radiation and the absorber atoms. The SI unit is J/kg. The special name of this unit is the rad (traditional system of units) or Gray (SI).

Joule—The S.I. unit for work and energy. It is equal to the work done by raising a mass of one newton through a distance of one meter (J = Nm), which corresponds to about 0.7 ft-pound.

Labeled Compound—A compound containing one or more radioactive atoms intentionally added to its structure. By observations of radioactivity or isotopic composition, this compound or its fragments may be followed through physical, chemical, or biological processes.

Late Effects (of radiation exposure)—Effects which appear 60 days or more following an acute exposure.

LD$_{50/30}$—The dose of a chemical or radiation expected to cause 50% mortality in those exposed within 30 days. For radiation, this is about 350 rad (3.5 gray) received by humans over a short period of time.

Lethal Concentration$_{(LO)}$ (LC$_{LO}$)—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC$_{50}$)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population within a specified time, usually 30 days.

Lethal Dose$_{(LO)}$ (LD$_{LO}$)—The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals within a specified time, usually 30 days.

Lethal Dose$_{(50)}$ (LD$_{50}$)—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT$_{50}$)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Linear Energy Transfer (LET)—A measure of the energy that a charged particle transfers to a material per unit path length.

> **Low-LET**—Energy transfer characteristic of light charged particles such as electrons produced by x and gamma rays where the distance between ionizing events is large on the scale of a cellular nucleus.

> **High-LET**—Energy transfer characteristic of heavy charged particles such as protons and alpha particles where the distance between ionizing events is small on the scale of a cellular nucleus.

> **Average LET**—The energy of a charged particle divided by the length of the path over which it deposits all its energy in a material.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lung Clearance Class (fast, F; medium, M; slow, S)—A classification scheme for inhaled material according to its rate of clearance from the pulmonary region of the lungs to the blood and the gastrointestinal tract.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Mass Numbers (A)—The number of nucleons (protons and neutrons) in the nucleus of an atom.

Minimal Risk Level—An estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen—A substance that causes changes (mutations) in the genetic material in a cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a substance.

Neutrino (ν)—A neutral particle of infinitesimally small rest mass emitted during beta plus or beta minus decay. This particle accounts for conservation of energy in beta plus and beta minus decays. It plays no role in damage from radiation.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a substance at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Nuclear reactor—A power plant that heats water by using nuclear reactions instead of burning coal, oil, or natural gas. All of these sources of energy simply heat water and use the steam which is produced to turn turbines that make electricity or propel a ship.

Nucleon—Common name for a constituent particle of the nucleus. Applied to a proton or neutron.

Nuclide—A species of atom characterized by the constitution of its nucleus. The nuclear constitution is specified by the number of protons (Z), number of neutrons (N), and energy content; or, alternatively, by the atomic number (Z), mass number A' (N+Z), and atomic mass. To be regarded as a distinct nuclide, the atom must be capable of existing for a measurable time. Thus, nuclear isomers are separate nuclides, whereas promptly decaying excited nuclear states and unstable intermediates in nuclear reactions are not so considered.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Pair Production—An absorption process for x- and gamma radiation in which the incident photon is absorbed in the vicinity of the nucleus of the absorbing atom, with subsequent production of an electron and positron pair (see annihilation). This reaction can only occur for incident photon energies exceeding 1.02 MeV.

Parent—A radionuclide which, upon disintegration, yields a new nuclide, either directly or as a later member of a radioactive series.

Permissible Exposure Limit (PEL)—A maximum allowable atmospheric level of a substance in workplace air averaged over an 8-hour shift.

Photon—A quantum of electromagnetic energy (E) whose value is the product of its frequency (ν) in hertz and Planck's constant (h). The equation is: $E = h\nu$.

Photoelectric Effect—An attenuation process observed for x and gamma radiation in which an incident photon interacts with a tightly bound inner orbital electron of an atom delivering all of its energy to knock the electron out of the atom. The incident photon disappears in the process.

Positron—A positively charged electron.

Potential, Ionization—The energy expressed as electron volts (eV) necessary to separate one electron from an atom, resulting in the formation of an ion pair.

Power, Stopping—A measure of the ability of a material to absorb energy from an ionizing particle passing through it; the greater the stopping power, the greater the energy absorbing ability (see Linear Energy Transfer).

Progeny—The decay product or products resulting after a radioactive decay or a series of radioactive decays. The progeny can also be radioactive, and the chain continues until a stable nuclide is formed.

Proton—Elementary nuclear particle with a positive electric charge equal numerically to the charge of the electron and a rest mass of 1.007 mass units.

Quality—A term describing the distribution of the energy deposited by a particle along its track; radiations that produce different densities of ionization per unit intensity are said to have different "qualities."

Quality Factor (Q)—The linear-energy-transfer-dependent factor by which absorbed doses are multiplied to obtain (for radiation protection purposes) a quantity that expresses - on a common scale for all ionizing radiation - the approximate biological effectiveness of the absorbed dose.

Rad—The unit of absorbed dose equal to 100 ergs per gram, or 0.01 joule per kilogram (0.01 Gy) in any medium (see Absorbed Dose).

Radiation—The emission and propagation of energy through space or through a material medium in the form of waves (e.g., the emission and propagation of electromagnetic waves, or of sound and elastic waves). The term radiation or radiant energy, when unqualified, usually refers to electromagnetic radiation. Such radiation commonly is classified according to frequency, as microwaves, infrared, visible (light), ultraviolet, and x and gamma rays (see Photon.) and, by extension, corpuscular emission, such as alpha and beta radiation, neutrons, or rays of mixed or unknown type, as cosmic radiation.

Radiation, Annihilation—Photons produced when an electron and a positron unite and cease to exist. The annihilation of a positron-electron pair results in the production of two photons, each of 0.51 MeV energy.

Radiation, Background—See Background Radiation.

Radiation, Characteristic (Discrete)—Radiation originating from an excited atom after removal of an electron from an atom. The wavelength of the emitted radiation is specific, depending only on the element and particular energy levels involved.

Radiation, External—Radiation from a source outside the body.

Radiation, Internal—Radiation from a source within the body (as a result of deposition of radionuclides in body tissues).

Radiation, Ionizing—Any electromagnetic or particulate radiation capable of producing ions, directly or indirectly, in its passage through matter (see Radiation).

Radiation, Monoenergetic—Radiation of a given type in which all particles or photons originate with and have the same energy.

Radiation, Scattered—Radiation which during its passage through a substance, has been deviated in direction. It may also have been modified by a decrease in energy.

Radiation, Secondary—A particle or ray that is produced when the primary radiation interacts with a material, and which has sufficient energy to produce its own ionization, such as bremsstrahlung or electrons knocked from atomic orbitals with enough energy to then produce ionization (see Delta Rays).

Radioactive Material—Material containing radioactive atoms.

Radioactivity—Spontaneous nuclear transformations that result in the formation of new elements. These transformations are accomplished by emission of alpha or beta particles from the nucleus or by the capture of an orbital electron. Each of these reactions may or may not be accompanied by a gamma photon.

Radioactivity, Artificial—Man-made radioactivity produced by particle bombardment or nuclear fission, as opposed to naturally occurring radioactivity.

Radioactivity, Induced—Radioactivity produced in a substance after bombardment with neutrons or other particles. The resulting activity is "natural radioactivity" if formed by nuclear reactions occurring in nature and "artificial radioactivity" if the reactions are caused by man.

Radioactivity, Natural—The property of radioactivity exhibited by more than 50 naturally occurring radionuclides.

Radioisotope—An unstable or radioactive isotope of an element that decays or disintegrates spontaneously, emitting radiation. Approximately 5,000 natural and artificial radioisotopes have been identified.

Radionuclide—Any radioactive isotope of any element.

Radiosensitivity—Relative susceptibility of cells, tissues, organs, organisms, or any living substance to the injurious action of radiation. Radiosensitivity and its antonym, radioresistance, are currently used in a comparative sense, rather than in an absolute one.

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 NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to non-threshold effects such as cancer.

Relative Biological Effectiveness (RBE)—The RBE is a factor used to compare the biological effectiveness of absorbed radiation doses (i.e., rad) due to different types of ionizing radiation. More specifically, it is the experimentally determined ratio of an absorbed dose of a radiation in question to the absorbed dose of a reference radiation (typically ^{60}Co gamma rays or 200 keV x rays) required to produce an identical biological effect in a particular experimental organism or tissue (see Quality Factor).

Rem—A unit of dose equivalent that is used in the regulatory, administrative, and engineering design aspects of radiation safety practice. The dose equivalent in rem is numerically equal to the absorbed dose in rad multiplied by the quality factor (1 rem is equal to 0.01 sievert).

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Roentgen (R)—A unit of exposure (in air) to ionizing radiation. It is the amount of x or gamma rays required to produce ions carrying 1 electrostatic unit of electrical charge in 1 cubic centimeter of dry air under standard conditions. Named after William Roentgen, a German scientist who discovered x rays in 1895.

Self-Absorption—Absorption of radiation (emitted by radioactive atoms) by the material in which the atoms are located; in particular, the absorption of radiation within a sample being assayed.

Short-Term Exposure Limit (STEL)—The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

SI Units—The International System of Units as defined by the General Conference of Weights and Measures in 1960. These units are generally based on the meter/kilogram/second units, with special quantities for radiation including the becquerel, gray, and sievert.

Sickness, Acute Radiation (Syndrome)—The complex symptoms and signs characterizing the condition resulting from excessive exposure of the whole body (or large part) to ionizing radiation. The earliest of

these symptoms are nausea, fatigue, vomiting, and diarrhea, and may be followed by loss of hair (epilation), hemorrhage, inflammation of the mouth and throat, and general loss of energy. In severe cases, where the radiation dose is relatively high (over several hundred rad or several gray), death may occur within two to four weeks. Those who survive six weeks after exposure of a single high dose of radiation may generally be expected to recover.

Sievert (Sv)—The SI unit of any of the quantities expressed as dose equivalent. The dose equivalent in sieverts is equal to the absorbed dose, in gray, multiplied by the quality factor (1 sievert equals 100 rem).

Specific-activity—Radioactivity per unit mass of material containing a radionuclide, expressed, for example, as Ci/gram or Bq/gram.

Specific Energy—The actual energy per unit mass deposited per unit volume in a small target, such as the cell or cell nucleus, as the result of one or more energy-depositing events. This is a stochastic quantity as opposed to the average value over a large number of instance (i.e., the absorbed dose).

Standard Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Stopping Power—The average rate of energy loss of a charged particle per unit thickness of a material or per unit mass of material traversed.

Surface-seeking Radionuclide—A bone-seeking internal emitter that is deposited and remains on the bone surface for a long period of time, although it may eventually diffuse into the bone mineral. This contrasts with a volume seeker, which deposits more uniformly throughout the bone volume.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Target Theory (Hit Theory)—A theory explaining some biological effects of radiation on the basis that ionization, occurring in a discrete volume (the target) within the cell, directly causes a lesion which subsequently results in a physiological response to the damage at that location. One, two, or more "hits" (ionizing events within the target) may be necessary to elicit the response.

Teratogen—A chemical that causes birth defects.

Threshold Limit Value (TLV)—The maximum concentration of a substance to which most workers can be exposed without adverse effect. TLV is a term used exclusively by the ACGIH. Other terms used to express the same concept are the MAC (Maximum Allowable Concentration) and PEL (Permissible Exposure Limits).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

**Toxicosis **—A diseased condition resulting from poisoning.

Transformation, Nuclear—The process by which a nuclide is transformed into a different nuclide by absorbing or emitting particulate or electromagnetic radiation.

Transition, Isomeric—The process by which a nuclide decays to an isomeric nuclide (i.e., one of the same mass number and atomic number) of lower quantum energy. Isomeric transitions (often abbreviated I.T.) proceed by gamma ray and/or internal conversion electron emission.

Tritium—The hydrogen isotope with one proton and two neutrons in the nucleus (Symbol: ^{3}H). It is radioactive and has a physical half-life of 12.3 years.

Unattached Fraction—That fraction of the radon daughters, usually ^{218}Po and ^{214}Po, which has not yet attached to a dust particle or to water vapor. As a free atom, it has a high probability of being exhaled and not retained within the lung. It is the attached fraction which is primarily retained.

Uncertainty Factor (UF)—A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

Units, Radiological—

Units	Equivalents
Becquerel* (Bq)	1 disintegration per second = 2.7×10^{-11} Ci
Curie (Ci)	3.7×10^{10} disintegrations per second = 3.7×10^{10} Bq
Gray* (Gy)	1 J/kg = 100 rad
Rad (rad)	100 erg/g = 0.01 Gy
Rem (rem)	0.01 sievert
Sievert* (Sv)	100 rem

*International Units, designated (SI)

Working Level (WL)—Any combination of short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^5 MeV of potential alpha energy.

Working Level Month (WLM)—A unit of exposure to radon daughters corresponding to the product of the radon daughter concentration in Working Level (WL) and the exposure time in nominal months (1 nominal month = 170 hours). Inhalation of air with a concentration of 1 WL of radon daughters for 170 working hours results in an exposure of 1 WLM.

X rays—Penetrating electromagnetic radiations whose wave lengths are very much shorter than those of visible light. They are usually produced by bombarding a metallic target with fast electrons in a high vacuum. X rays (called characteristic x rays) are also produced when an orbital electron falls from a high energy level to a low energy level.

Zero-Threshold Linear Hypothesis—The assumption that a dose-response curve derived from data in the high dose and high dose-rate ranges may be extrapolated through the low dose and low dose range to zero, implying that, theoretically, any amount of radiation will cause some damage.

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect-level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral, inhalation, and external routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive end point considered to be a 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.

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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.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Uranium (Soluble Forms)
CAS number: Multiple
Date: July 2001
Profile status: Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 72
Species: Dog

MRL: 4×10^{-4} [ ] mg/kg/day [ ] ppm [x] mg/m^3

Reference: Rothstein A 1949a. Uranyl Fluoride. In: Voegtlin C, Hodge HC, eds. Pharmacology and toxicology of uranium compounds. National Nuclear Energy Series: Manhattan Project Technical Section, Division VI, Vol 1. New York, NY: McGraw-Hill. pp 548-560.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details):

Dogs (2–6 per group; sex and strain not specified) were exposed to 0.19, 2.8, or 12.2 mg/m^3 of uranyl fluoride dust (0.15, 2.2, or 9.2 mg U/m^3) for 6 hours/day, 6 days/week for 5 weeks. (Doses were analytically determined, not estimated.) Dogs were bodily exposed to the dust. The activity median aerodynamic diameter (AMAD) for the particles is assumed to be 1.5–2.1 µm; average 1.8 µm (see Pozzani 1949). Clinical signs of toxicity, mortality, body weight changes, hematology, blood and urine chemistries were monitored. At the termination of the study, the animals were sacrificed and selected organs were histopathologically examined and uranium levels determined.

Effects noted in study and corresponding doses: Severe toxicity was observed at the highest concentration (9.2 mg U/m^3) leading to death. The 2 animals in this group showed signs of anorexia, rhinitis, and polydipsia. Later, these animals vomited blood, had severe weight loss and muscle weakness, and exhibited lassitude prior to death. Histopathological examination of the kidney revealed "severe" tubular lesions. Dogs exposed to 0.15 or 2.2 mg U/m^3 (6 per group) had no clinical signs of toxicity or significant weight changes. Clinical chemistry results included increased blood nonprotein nitrogen (NPN) with the maximum value over 200 mg/L in the 2 dogs exposed to 9.2 mg U/m^3. At 0.15 mg U/m^3, blood NPN and urinary amino acid nitrogen were normal in 3 dogs, while 1 of the 3 had increased urinary protein (not all tests were run on all dogs). Histopathological examination of the kidneys revealed "moderate" damage at 2.2 mg U/m^3 and "slight" changes in 50% of the dogs at 0.15 mg U/m^3.

Dose endpoint used for MRL derivation:

[ ] NOAEL [x] LOAEL

0.15 mg/m^3; minimal microscopic lesions in the renal tubules in half the dogs examined. Proteinuria observed at 2.2 mg/m^3, severe renal damage at 9.2 mg/m^3.

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Uncertainty factors used in MRL derivation:

[ ] 1 [x] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [x] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
See calculations.

Was a conversion used from intermittent to continuous exposure?
Yes. See calculations.

Other additional studies or pertinent information that lend support to this MRL:
The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has stated that
limits for natural (and depleted) uranium in drinking water (the most important source of human exposure)
should be based on the chemical toxicity rather than on a hypothetical radiological toxicity in skeletal
tissues, which has not been observed in either man or animals (Wrenn et al. 1985).

Uranium is a nephrotoxin, exerting its toxic effect by chemical action mostly in the proximal tubule in
humans and animals.

Numerous intermediate-duration uranium exposure studies in animals show that the most sensitive effect is
renal toxicity (Dygert 1949a, 1949b, 1949c; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein
1949a, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). Dogs and rabbits appear to be the most sensitive
species while rats are less sensitive. Susceptibility also depends on the chemical form of the uranium, the
more water-soluble compounds being more toxic than the insoluble compounds. Nephrotoxic effects found
in these animals range from minimal tubular lesions without functional effects to proteinuria, acute tubular
necrosis, and renal failure.

Calculations

Since inhalation MRL's are derived for continuous exposure, the animal LOAEL derived from an
intermittent exposure must be adjusted to continuous exposure:

For an exposure of 6 hours a day, 6 days a week,

(0.15 mg/m^3) * (6/24) * (6/7) = 0.032 mg/m^3 adjusted to continuous exposure.

APPENDIX A

The adjusted animal NOAEL$_{(ADJ)}$ must be converted to Human Equivalent Concentration (LOAEL$_{HEC}$) before applying uncertainty factors (UFs) adjustments (EPA 1994) for the derivation of the inhalation MRL:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \ x \ RDDR$$

where:

NOAEL$_{[ADJ]}$ = duration adjusted laboratory animal NOAEL (in mg/m^3).
NOAEL$_{[HEC]}$ = human equivalent concentration of adjusted laboratory animal dose (in mg/m^3).
RDDR   = Regional Deposited Dose Ratio

Since RDDR values are unavailable for dogs (EPA 1994), ATSDR used a default uncertainty factor of 3 for extrapolating from animals to humans as it incorporates the differences in physiology between dogs and humans. A default factor of 3 was used rather than the standard factor of 10 because of similarities in renal physiology between the two species, i.e., both acidify the urine by active transport of bicarbonate. Additional uncertainty factors of 3 for use of a minimal LOAEL and 10 for human intraspecies variability are used to calculate the intermediate-duration intermediate MRL.

$$Intermediate \ Inhalation \ MRL = \frac{NOAEL_{(HEC)}}{\underset{j}{} \ UF \ Adjustments}$$

Therefore,

$$Intermediate \ Inhalation \ MRL = \frac{0.032 \ mg/m^3}{90} = 4 \ x \ 10^{-4} \ mg/m^3.$$

Agency Contact (Chemical Manager): Sam Keith.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Uranium (Insoluble Forms)
CAS number: Multiple
Date: July 2001
Profile status: Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 73
Species: Dog

MRL: 8×10^{-3} [ ] mg/kg/day [ ] ppm [x] mg/m^3

Reference: Rothstein A. 1949b. Uranium Dioxide. In: Voegtlin C, Hodge HC, eds. Pharmacology and toxicology of uranium compounds. National Nuclear Energy Series: Manhattan Project Technical Section, Division VI, Vol 1. New York, NY: McGraw-Hill. pp 614-621.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details):

Dogs (N=6–19; unspecified sex and strain) were exposed to uranium dioxide dust at concentrations of 1.1 mg U/m^3, 8.2 mg U/m^3, or 9.2 mg U/m^3 for 5 weeks, 6 days/weeks, 6 hours a day. (Doses were analytically determined, not estimated.) Studies conducted at 8.2 mg U/m^3 were conducted in head exposure units. Studies conducted at the other concentrations were performed in full exposure units. The activity median aerodynamic diameter (AMAD) for the particles is assumed to be 1.5–2.1 µm; average 1.8 µm (see Pozzani 1949). Mortality, body weight changes, standard hematology (except in the 8.2 mg U/m^3 group), blood and urine chemistries, pathology, and uranium distribution in tissues were measured.

Effects noted in study and corresponding doses: No dogs died from exposure to uranium dioxide dust. Additionally, no significant weight changes, or biochemical changes in blood or urine were seen at any concentration. No hematological changes were attributable to uranium dioxide dust. Histopathological changes in the kidney were not observed in any group except for "very slight" renal tubular degeneration in 2 of 6 dogs at 8.2 mg U/m^3.

Dose endpoint used for MRL derivation:

[x] NOAEL [] LOAEL

1.1 mg/m^3; (LOAEL for minimal microscopic lesions in the renal tubules observed at 8.2 mg/m^3 in 2 of 6 dogs examined).

APPENDIX A

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [x] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
See calculations.

Was a conversion used from intermittent to continuous exposure?
Yes. See calculations.

Other additional studies or pertinent information that lend support to this MRL:
The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has stated that
limits for natural (and depleted) uranium in drinking water (the most important source of human exposure)
should be based on the chemical toxicity rather than on a hypothetical radiological toxicity in skeletal
tissues, which has not been observed in either man or animals (Wrenn et al. 1985).

Uranium is a nephrotoxin, exerting its toxic effect by chemical action mostly in the proximal tubule in
humans and animals.

Numerous intermediate-duration uranium exposure studies in animals show that the most sensitive effect is
renal toxicity (Dygert 1949a, 1949b, 1949c; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein
1949a, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). Dogs and rabbits appear to be the most sensitive
species while rats are less sensitive. Susceptibility also depends on the chemical form of the uranium, the
more water-soluble compounds being more toxic than the insoluble compounds. Nephrotoxic effects found
in these animals range from minimal tubular lesions without functional effects to proteinuria, acute tubular
necrosis, and renal failure.

Calculations

Since inhalation MRL's are derived for continuous exposure, the animal NOAEL derived from an
intermittent exposure must be adjusted to continuous exposure:

For an exposure of 6 hours a day, 6 days a week,

$(1.1 \text{ mg/m}^3) * (6/24) * (6/7) = 0.2357 \text{ mg/m}^3$ adjusted to continuous exposure.

APPENDIX A

The adjusted animal NOAEL$_{(ADJ)}$ must be converted to Human Equivalent Concentration (LOAEL$_{HEC}$) before applying uncertainty factors (UFs) adjustments (EPA 1994) for the derivation of the inhalation MRL:

$$NOAEL_{[HEC]} \; ' \; NOAEL_{[ADJ]} \; x \; RDDR$$

where:

NOAEL$_{[ADJ]}$ = duration adjusted laboratory animal NOAEL (in mg/m^3).
NOAEL$_{[HEC]}$ = human equivalent concentration of adjusted laboratory animal dose (in mg/m^3).
RDDR = Regional Deposited Dose Ratio

Since RDDR values are unavailable for dogs (EPA 1994), ATSDR used a default uncertainty factor of 3 for extrapolating from animals to humans as it incorporates the differences in physiology between dogs and humans. A default factor of 3 was used rather than the standard factor of 10 because of similarities in renal physiology between the two species, i.e., both acidify the urine by active transport of bicarbonate. An additional uncertainty factor of 10 for human intraspecies variability is used to calculate the intermediate-duration inhalation MRL:

$$Intermediate \; Inhalation \; MRL \; ' \; \frac{NOAEL_{(HEC)}}{j \quad UF \; Adjustments}$$

Therefore,

$$Intermediate \; Inhalation \; MRL \; ' \; \frac{0.2357 \; mg/m^3}{30} \; ' \; 8 \; x \; 10^{\&3} \; mg/m^3.$$

Agency Contact (Chemical Manager): Sam Keith.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Uranium (Soluble forms)
CAS number: Multiple
Date: July 2001
Profile status: Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ]Intermediate [x] Chronic
Key to figure: 112
Species: Dog

MRL: 3×10^{-4} [ ] mg/kg/day [ ] ppm [x] mg/m^3

Reference: Stokinger et al. 1953. Uranium Tetrachloride: Toxicity following inhalation for 1 and 2 years. In: Voegtlin C, Hodge HC, eds. Pharmacology and toxicology of uranium compounds. National Nuclear Energy Series: Manhattan Project Technical Section, Division VI, Vol 1. New York, NY: McGraw-Hill. pp 1522-1553.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details):

Dogs of both sexes (11-12 M, 9-10 F) were exposed to uranium tetrachloride in inhalation chambers for 6 hours a day, M-F and 3 hours on Saturday (5.5 days a week) for 1 year at concentrations of 0, 0.05, and 0.20 mg U/m^3. (Doses were analytically determined, not estimated.) The activity median aerodynamic diameter (AMAD) of the aerosols was 1–2 μm. The animals were monitored for body weight alterations, clinical signs of toxicity, and biochemical alterations in the blood and urine. At the termination of the study, the animals were sacrificed and selected organs were histopathologically examined.

Effects noted in study and corresponding doses: All dogs survived the 1-year exposure period. No significant changes were observed in blood non-protein nitrogen, hematology, histopathology of liver, body weight, or urinary proteins. "Very slight" renal damage as reported in animals exposed to 0.20 mg U/m^3. Histological and biochemical examinations revealed a NOAEL level of 0.05 mg U/m^3 and minimal microscopic lesions in the renal tubules in the 0.20 mg U/m^3 dose level dogs. No significant weight loss was observed in the dogs.

Dose endpoint used for MRL derivation:

[x] NOAEL [] LOAEL

0.05 mg/m^3; (minimal microscopic lesions in the renal tubules in dogs of both sexes at a LOAEL of 0.20 mg U/m^3).

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [x] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

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Modification factors used in MRL derivation:

[ ] 1 [ ] 3 [ ]10

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
See calculations.

Was a conversion used from intermittent to continuous exposure?
Yes. See calculations.

Other additional studies or pertinent information that lend support to this MRL:
The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) stated that limits
for natural (and depleted) uranium in drinking water (the most important source of human exposure) should
be based on the chemical toxicity rather than on a hypothetical radiological toxicity in skeletal tissues,
which has not been observed in either man or animals (Wrenn et al. 1985).

Uranium has been identified as a weak metal nephrotoxin, exerting its toxic effect by chemical action
mostly in the proximal tubule in humans and animals. A study on the kidney functions of uranium mill
workers chronically exposed to insoluble uranium (uranium oxide) showed renal tubular dysfunction (as
manifested by mild proteinuria, aminoaciduria, and a dose-related clearance of β-2-microglobulin) relative
to that of creatinine and the length of time that the uranium workers had spent in the yellowcake (uranium
oxides) drying and packaging area. Serum β-2-microglobulin was also elevated in the serum of 22 of the
23 workers tested (Saccomanno et al. 1982; Thun 1985). However, a histopathological autopsy study of
individuals, who had been occupationally exposed uranium workers and then spent many years in
retirement, found that the damage potentially caused by internalized uranium during their years of
occupational exposure had been repaired and was not detectable at death (Russell et al. 1996)

In animal studies, chronic-duration studies with rat and dogs given inhalation uranium (uranium
tetrachloride, uranium tetrafluoride, uranyl nitrate hexahydrate, uranium dioxide) doses as low as
0.05 mg U/m^3 and as high as 10 mg U/m^3, administered for 1–5 years suffered nephrotoxicity. Nephrotoxic
effects found in these animals ranged from proteinuria and increased bromosulfalein retention (for low
doses) (Stokinger et al. 1953) to acute tubular necrosis (for high doses) (Leach et al. 1970). No treatment-
related renal effects were seen when Rhesus monkeys and dogs were exposed to uranium dioxide by
inhalation at doses as high as 5.1 mg U/m^3 for 1–5 years (Leach et al. 1973). Guinea pigs, mice, rat, cats,
rabbits, and dogs (Dygert 1949a, 1949b, 1949c; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein
1949a, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953), or guinea pigs, rabbits, and rats (Leach et al.
1984; Morrow et al. 1982; Roberts 1949; Stokinger et al. 1953) exposed to these uranium compounds in
intermediate- or acute-duration exposure and rats and dogs in chronic-duration studies (Leach et al. 1970;
Stokinger et al. 1953) suffered similar kidney damage.

Calculations

Since inhalation MRL's are derived for continuous exposure, the animal NOAEL derived from an
intermittent exposure must be adjusted to continuous exposure:

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$$NOAEL_{ADJ} \; ' \; 0.05 \; \textit{mg uranium/m}^3 \; x \; (\frac{6}{24}) \; \textit{hours} \; x \; (\frac{5.5}{7}) \; \textit{days} \; ' \; 0.01 \; \textit{mg uranium/m}^3.$$

The adjusted animal NOAEL$_{(ADJ)}$ must be converted to Human Equivalent Concentration (LOAEL$_{HEC}$) before applying uncertainty factors (UFs) adjustments (EPA 1994) for the derivation of the inhalation MRL:

$$NOAEL_{[HEC]} \; ' \; NOAEL_{[ADJ]} \; x \; RDDR$$

where:

NOAEL$_{[ADJ]}$ = duration adjusted laboratory animal NOAEL (in mg/m^3).
NOAEL$_{[HEC]}$ = human equivalent concentration of adjusted laboratory animal dose (in mg/m^3).
RDDR = Regional Deposited Dose Ratio

Since RDDR values are unavailable for dogs (EPA 1994), ATSDR used a default uncertainty factor of 3 for extrapolating from animals to humans as it incorporates the differences in physiology between dogs and humans. A default factor of 3 was used rather than the standard factor of 10 because of similarities in renal physiology between the two species, i.e., both acidify the urine by active transport of bicarbonate. An additional uncertainty factor of 10 for human intraspecies variability is used to calculate the chronic inhalation MRL:

$$\textit{Chronic Inhalation MRL} \; ' \; \frac{NOAEL_{(HEC)}}{\underset{j}{\text{UF Adjustments}}}$$

Therefore,

$$\textit{Chronic Inhalation MRL} \; ' \; \frac{0.01 \; \textit{mg/m}^3}{30} \; ' \; 3 \; x \; 10^{\&4} \; \textit{mg/m}^3.$$

Agency Contact (Chemical Manager): Sam Keith.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Uranium
CAS number: Multiple
Date: July 2001
Profile status: Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 57
Species: Rabbit

MRL: 2×10^{-3} [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Gilman AP, Villeneuve DC, Secours VE, et al. 1998b. Uranyl nitrate - 91-day toxicity studies in the New Zealand white rabbit Toxicol Sci. 41(1):129-137, Jan 1998.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details):

Groups of New Zealand rabbits (10/sex/dose, males 3,200 g, females 3,100 g) were exposed to uranium as uranyl nitrate in drinking water. The males were exposed to 0.96, 4.8, 24, 120, or 600 mg/L for 91 days, while females were exposed only to 4.8, 24 or 600 mg/L. A control group of 10 animals for each sex received tap water without uranyl nitrate (<0.001 mg U/L). All animals were fed chow containing <0.5 µg U/g. Clinical signs were monitored daily, fluid intake and feed consumption were measured 4 times during the experiment and body weights were measured weekly. After 30, 60, and 91 days of exposure, urine was collected from 4 male rabbits in each dosing group and analyzed for uranium, glucose, creatinine, urea nitrogen, total protein, albumin, lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (gamma-GT), leucine aminopeptidase (LAP), and N-acetyl-β-D-glucosaminidase (NAG). After 30 and 90 days, urine was collected from all 10 female rabbits in the 600 mg/L group and analyzed for glucose, creatinine, urea nitrogen, total protein, albumin, and NAG. Dye clearance tests were performed 1 week prior to termination using standard bromsulfophthalein (BSP) and phenolsulfonphthalein (PSP) test procedures for liver and kidney function, respectively.   Four males from each dosing group (3 from group 3) were administered both dyes intravenously and clearance measured; six females from each exposure group were administered the PSP test only. After 91 days, animals were sacrificed and hematological parameters and serum chemistry were analyzed. Organ weights were measured on brain, heart, liver, spleen, and kidney in all groups and the incidence of 12 types of tubular/ interstitial kidney lesions in both females and males were examined. Uranium residues were measured in samples of kidney and femur from 5–6 males in each dosing group and in all female rabbits.

Effects noted in study and corresponding doses: Time-weighted average doses (as mg U/kg/day) calculated by the authors from fluid intake data were: males: 0.05, 0.20, 0.88, 4.82, and 28.70 mg U/kg/day; females: 0.49, 1.32, and 43.02 mg U/kg/day. Four males showed evidence of Pasteurella multocida infection and were excluded from the study. Two other males in the highest dose groups died prematurely, one from apparent mucoid enteritis and one from apparent acute renal failure. Two others were removed after developing hairball obstructions of the GI tract. No evidence of Pasturella infection was observed in the females. No significant differences in weight gain, food consumption or water intake were noted, except that females drank 65% more water than males. These observed hematological and biochemical parameters

did not appear to be dose-dependent. Dose-dependent differences consisted of histopathological changes limited primarily to kidney and were more pronounced in males. In males, a significantly increased incidence of anisokaryosis and nuclear vesiculation was observed in all treated groups, which essentially peaked in the 0.05 and 0.20 mg U/kg/day groups in a threshold-like manner. Nuclear pyknosis, tubular dilation, and atrophy were observed in all treated groups. Hyperchromicity was observed in all treated groups except at 0.05 mg U/kg/day, protein casts in all but the 0.88 mg U/kg/day group, and collagen sclerosis was observed at 0.20, 0.88 and 28.70 mg U/kg/day. Reticulin sclerosis was observed at 0.88, 4.82, and 28.70 mg U/kg/day.

In summary, the following effects were noted in males but not in a dose related manner: (1) renal cytoplasmic vacuolation, anisokaryosis, nuclear vesiculation, nuclear pyknosis, tubular dilatation, tubular atrophy, and reticulin sclerosis were observed at 0.05 mg U/kg/day and above (all dose levels); (2) nuclear hyperchromicity was observed at 0.20 mg U/kg/day and above; and (3) apical displacement of nuclei, protein casts, and collagen sclerosis were observed at low and high doses, but not at some intermediate doses.

The following effects were noted in females but not in a dose related manner: (1) renal cytoplasmic vacuolation, anisokaryosis, nuclear vesiculation, tubular dilation, tubular atrophy, and pigmentation were observed at 0.49 mg U/kg/day and above (all dose levels); (2) nuclear hyperchromicity and collagen sclerosis were observed only at 43.02 mg U/kg/day (highest dose); (3) cytoplasmic inclusions were not observed in any group; and (4) protein casts decreased with dose. The females drank 65% more water than the males, yet appeared to be less affected by the exposure regimen, although they also developed significant tubular nuclear changes in their lowest exposure group. In male rabbits, no urinary parameters were affected after 30 days of treatment. Among males, a significant increase in urinary NAG was observed at 60 days in the 0.88 mg U/kg/day group only, along with a significantly higher total protein in the 28.70 mg U/kg/day group. No parameters were affected at 90 days. No urinary parameters were affected in females. No effect was observed in the BSP dye clearance test (liver function) in male rabbits, however, there was a significant linear relationship between exposure level and the rate of PSP excretion. No effect was observed in females.

Dose endpoint used for MRL derivation: 0.05 mg U/kg/day, renal toxicity. This is considered a minimal LOAEL.

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [x] 3 [ ] 10 (for use of a minimal LOAEL)
[x] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

Modification factors used in MRL derivation:

[ ] 1 [ ] 3 [ ]10

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain:
No, doses were calculated by the authors on the basis of measured water intake..

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Not applicable.

Was a conversion used from intermittent to continuous exposure?
Not applicable.

Other additional studies or pertinent information that lend support to this MRL:
In other intermediate-duration oral exposures with uranium, dogs exhibited similar to more severe effects at
doses of soluble uranium compounds at least one order of magnitude greater and at doses of less soluble
compounds several orders of magnitude greater: (1) moderate degeneration of the tubular epithelium of the
kidney after a 30-day administration of 15.4 mg U/kg/day as uranyl fluoride or 37.5 mg U/kg/day as sodium
diuranate; (2) minimal microscopic lesions in tubular epithelium of the kidney after a 30-day administration
of 15.4 mg U/kg/day as uranium tetroxide; (3) minimal microscopic lesions in tubular epithelium of the
kidney after a 30-day administration of 15.4 mg U/kg/day as uranium dioxide; (4) severe degeneration
changes in tubular epithelium of the kidney after a 30-day administration of 83 mg U/kg/day as uranium
trioxide; (5) proteinuria, glucosuria, and minimal microscopic lesions in tubular epithelium of the kidney
after a 30-day administration of 5,653 mg U/kg/day as triuranium octaoxide; (6) severe necrotic
degeneration in tubular epithelium of the kidney after a 30-day administration of 237 mg U/kg/day as
uranyl nitrate hexahydrate; necrosis of the tubular epithelium of the kidney after administration of
313 mg U/kg/day as uranium tetrachloride for 30 days; and (7) increases in blood urea nitrogen, proteinuria,
glucosuria, and minimal microscopic lesions in tubular epithelium of the kidney after oral administration
with 3,790 mg U/kg/day as uranium tetrafluoride for 30 days (Maynard and Hodge 1949).

In intermediate-duration oral exposures with uranium, rats showed minimal microscopic lesions in tubular
epithelium of the kidney after a 30-day administration of 138 mg U/kg/day as uranium tetroxide,
27 mg U/kg/day as uranyl fluoride, 7,859 mg U/kg/day as uranyl acetate dihydrate, 16.6 mg U/kg/day as
uranyl nitrate hexahydrate or as uranium tetrachloride; and increases in blood urea nitrogen, proteinuria,
glucosuria, and minimal microscopic lesions in tubular epithelium of the kidney after oral administration
with 38 mg U/kg/day as ammonium diuranate for 30 days (Maynard and Hodge 1949). Similarly, in a
study in which rats were administered 1.5 mg U/kg/day as uranyl nitrate hexahydrate for 15–27 days,
desquamation of the tubular epithelium and glomerular degeneration in the kidney of the rats were reported
(Goel et al. 1980). Mice also had nodular development on kidney surfaces after administration of single
oral doses of 452 U/kg/day as uranyl fluoride for 48 weeks (Tannenbaum and Silverstone 1951). In rabbits,
oral administration of uranyl nitrate hexahydrate at a dose of 2.8 mg U/kg/day for 30 days resulted in slight
to moderate renal tubular degeneration (Maynard and Hodge 1949).

The MRL level for intermediate-duration oral exposure is also protective for chronic-duration oral
exposure. This is because the renal effects of uranium exposure are more dependent on the dose than on the
duration of the exposure. Data from a large number of animal studies indicate that renal damage caused by
threshold and sublethal doses was overcome and obscured by regeneration of the tubular epithelium,
especially in the corticomedullary region, despite continuing exposure (Bentley et al. 1985; Dygert 1949a,
1949b, 1949c; Leach et al. 1984; Maynard and Hodge 1949; Maynard et al. 1953; Pozzani 1949; Roberts
1949; Rothermel 1949; Rothstein 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). This was also
observed among long-term occupational workers whose tissues were histologically evaluated at autopsy
(Russell et al. 1996). Such repair, once completed, is histologically indistinguishable from undamaged
kidney tissue.

APPENDIX A

Calculations

The minimal LOAEL of 0.05 mg/kg/day is divided by a total uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability) to calculate the intermediate oral MRL. No adjustment was made for interspecies variation because the rabbit is the most sensitive mammalian species to uranium toxicity and is likely to be more sensitive than humans.

$$Intermediate\ Oral\ MRL = \frac{LOAEL}{\sum (UF\ Adjustments)\ x \sum (Modification\ Factor\ Adjustment}$$

Therefore,

$$Intermediate\ Oral\ MRL = \frac{0.05\ mg\ /\ kg\ /\ day}{30} = 2x10^{-3}\ mg\ /\ kg\ /\ day$$

Agency Contact (Chemical Manager): Sam Keith.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were 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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) 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, minimal risk levels (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 No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND
See LSE Table 2-1

(1) <u>Route of Exposure</u> 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. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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(2)   <u>Exposure Period</u> 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)   <u>Health Effect</u> 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)   <u>Key to Figure</u> 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 2 "18r" data points in Figure 2-1).

(5)   <u>Species</u> The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "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)   <u>Exposure Frequency/Duration</u> The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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)   <u>System</u> 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, 1 systemic effect (respiratory) was investigated.

(8)   <u>NOAEL</u> A No-Observed-Adverse-Effect Level (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 0.0006 ppm (see footnote "c").

(9)   <u>LOAEL</u> A Lowest-Observed-Adverse-Effect Level (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 endpoint 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) <u>Reference</u> The complete reference citation is given in chapter 8 of the profile.

(11) <u>CEL</u> A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) <u>Footnotes</u> Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0006 ppm.

LEGEND

See Figure 2-1

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) <u>Exposure Period</u> The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) <u>Health Effect</u> These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) <u>Levels of Exposure</u> 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) <u>NOAEL</u> In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. 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 0.0006 ppm (see footnote "c" in the LSE table).

(17) <u>CEL</u> Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) <u>Estimated Upper-Bound Human Cancer Risk Levels</u> 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) <u>Key to LSE Figure</u> The Key explains the abbreviations and symbols used in the figure.

SAMPLE

| 1 | 6 |

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (mg/m³)	LOAEL (effect)		Reference
					Less serious (mg/m³)	Serious (mg/m³)	
		5	6	7	8	9			10

| 2 | 6 | INTERMEDIATE EXPOSURE

| 3 | 6 | Systemic | 9 | 9 | 9 | 9 | 9 | | 9 |

| 4 | 6 | 18 | Rat | 13 wk 5d/wk 6hr/d | Resp | 3[b] | 10 (hyperplasia) | | Nitschke et al. 1981 |

- -

CHRONIC EXPOSURE

| | | | | | | 11 | |

Cancer						9	
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

| 12 | 6 | [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10⁻³ 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).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**
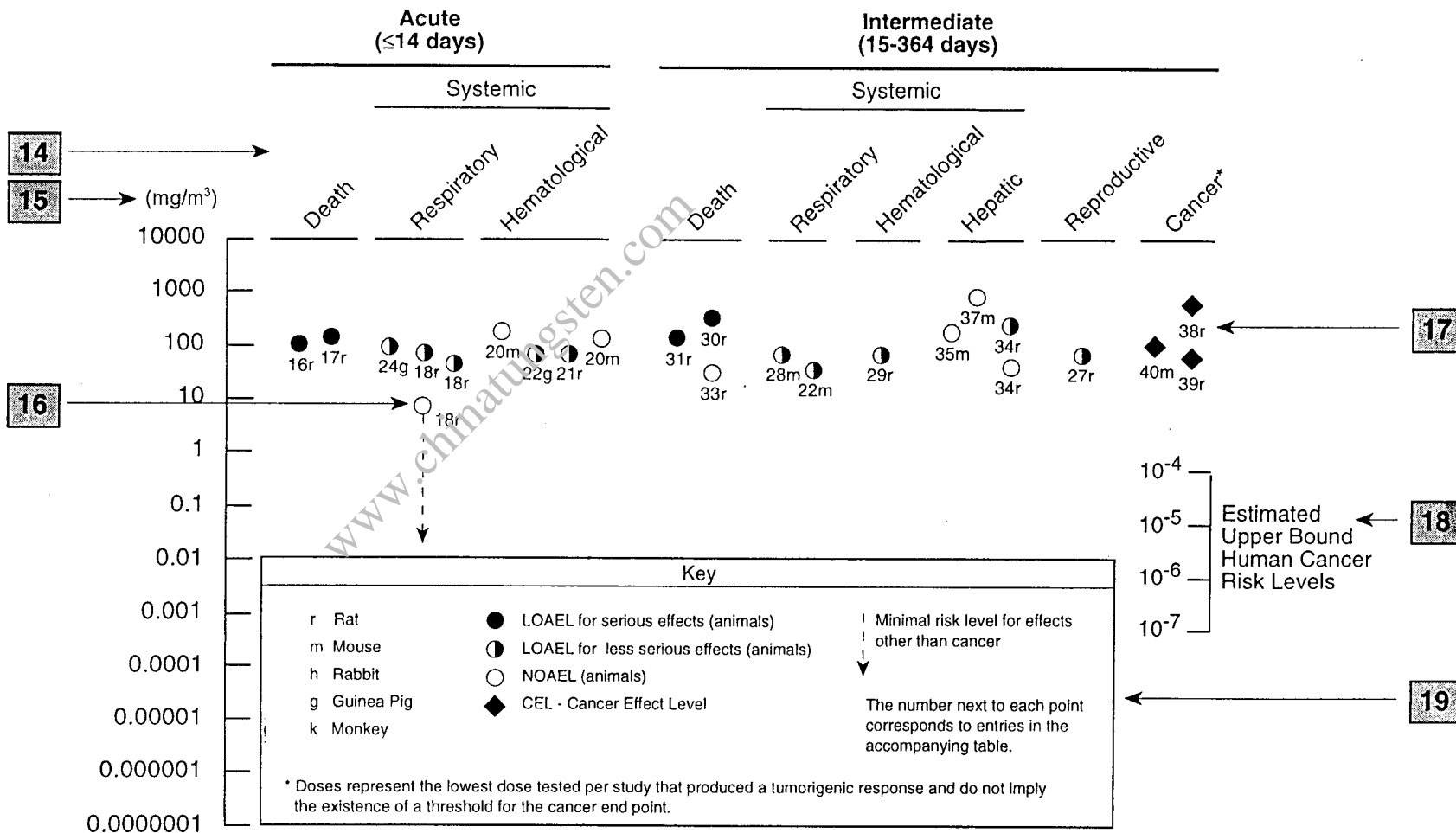
Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section 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 section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, 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 section. If data are located in the scientific literature, a table of genotoxicity information is included.

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 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (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. They 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 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

APPENDIX B

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs). To derive an MRL, ATSDR generally selects the most sensitive endpoint 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 endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest 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 LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AMAD	activity median aerodynamic diameter
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
Bq	Becquerel
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Celsius
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
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
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

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DOT/UN/	Department of Transportation/United Nations/
NA/IMCO	North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit or equilibrium factor
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
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
Gy	Gray
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LET	linear energy transfer
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level

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LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
Mg	megagram
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
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
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
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; also Nuclear Regulatory Commission
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

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OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
QF	Quality Factor
R	Roentgen
RAD	Radiation Absorbed Dose
REL	recommended exposure level/limit
rem	a unit of ionizing radiation, normalized to human tissue response
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard 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 Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act

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TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
USNRC	Nuclear Regulatory Commission
UF	uncertainty factor
VOC	Volatile Organic Compound
WHO	World Health Organization
wk	week
WL	Working Level
WLM	Working Level Month
yr	year
$>$	greater than
$\geq$	greater than or equal to
$=$	equal to
$<$	less than
$\leq$	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

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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 charac-terized 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 transformation 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

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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 oa 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] Air	Path length[b] Solid	Comments
Alpha (α)	4.00 amu	+2	4–10 MeV	5–10 cm	25–80 μm	Identical to ionized He nucleus
Negatron (β⁻)	5.48×10^{-4} amu; 0.51 MeV	–1	0–4 Mev	0–10 m	0–1 cm	Identical to electron
Positron (β⁺)	5.48×10^{-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 (p) (e.m. photon)	–	0	10 keV–3 MeV	b	b	Photon from nuclear transformation

[a] The rest mass (in amu) has an energy equivalent in MeV that is obtained using the equation E=mc², 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 fined as the activity per unit mass or per unit volume. This activity is usually expressed in curies per gram and may be calculated by

curies/gram   = $1.3 \times 10^8 / (T_{rad})$ (atomic weight)   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:

$$T_{eff} = (T_{biol} \text{ x } T_{rad}) / (T_{biol} + T_{rad}).$$

Table D-2 presents representative effective half-lives of particular interest.

Table D-2. Half-Lives of Some Radionuclides in Adult Body Organs

Radionuclide	Critical organ	Half-life[a]		
		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 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 (&) is a high-velocity electron ejected from a disintegrating nucleus. The particle may be either a negatively charged electron, termed a negatron (&-) or a positively charged electron, termed a positron (&+). Although the precise definition of "beta emission" refers to both &- and &+, common usage of the term generally applies only to the negative particle, as distinguished from the positron emission, which refers to the &+ particle.

D.2.4.2.1 Beta Negative Emission.   Beta particle (&-) emission is another process by which a radionuclide, with a neutron excess achieves stability. Beta particle emission decreases the number of neutrons by one and increases the number of protons by one, while the atomic mass number remains unchanged.[4] 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.

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[4]Neutrinos also accompany negative beta particles and positron emissions.

D.2.4.2.2 Positron Emission.   In cases in which there are too many protons in the nucleus, positron emission may occur. In this case a proton may be thought of as being converted into a neutron, and a positron (&+) is emitted.[4] This increases the number of neutrons by one, decreases the number of protons by one, and again leaves the atomic mass number unchanged. The gamma radiation resulting from the annihilation (see glossary) of the positron makes all positron emitting isotopes more of an external radiation hazard than pure & emitters of equal energy.

D.2.4.2.3 Gamma Emission.   Radioactive decay by alpha, beta, or positron emission, or electron capture often leaves some of the energy resulting from these changes in the nucleus. As a result, the nucleus is raised to an excited level. None of these excited nuclei can remain in this high-energy state. Nuclei release this energy returning to ground state or to the lowest possible stable energy level. The 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 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.4.2 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 and Dose Equivalent Rate.

Dose equivalent or rem 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 ICRU has defined 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 x Q. The dose equivalent concept is applicable only to doses that are not great enough to produce biomedical effects.

The quality 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 for various radiation types are provided in Table D-3. The dose equivalent rate is the time rate of change of the dose equivalent to organs and tissues and is expressed as rem/unit time or sievert/unit time.

Table D-3. Quality Factors (Q) and Absorbed Dose Equivalencies

Type of radiation	Quality factor (Q)	Absorbed dose equal to a unit dose equivalent*
X, gamma, or beta radiation	1	1
Alpha particles, multiple-charged particles, fission fragments and heavy particles of unknown charge	20	0.05
Neutrons of unknown energy	10	0.1
High-energy protons	10	0.1

* Absorbed dose in rad equal to 1 rem or the absorbed dose in gray equal to 1 sievert.

Source: USNRC. 1999. Standards for the protection against radiation, table 1004(b).1. 10 CFR 20.1004. U.S. Nuclear Regulatory Commission, Washington, D.C.

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 used in calculations of dose equivalents 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 and Effective Dose Equivalent Rate.

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) has derived a concept of effective dose equivalent. The effective dose equivalent, H_E, is

H_E = (the sum of) $W_t H_t$

where H_t is the dose equivalent in the tissue, W_t is the weighting factor, 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). 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. Weighting Factors for Calculating Effective Dose
Equivalent for Selected Tissues**

Tissue	Weighting factor		
	ICRP60	NCRP115/ ICRP60	NRC
Bladder	0.040	0.05	–
Bone marrow	0.143	0.12	0.12
Bone surface	0.009	0.01	0.03
Breast	0.050	0.05	0.15
Colon	0.141	0.12	–
Liver	0.022	0.05	–
Lung	0.111	0.12	0.12
Esophagus	0.034	0.05	–
Ovary	0.020	0.05	–
Skin	0.006	0.01	–
Stomach	0.139	0.12	–
Thyroid	0.021	0.05	0.03
Gonads	0.183	0.20	0.25
subtotal	0.969	1	0.70
Remainder	0.031	0.05	0.30

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.
NRC = Nuclear Regulatory Commission, Title 10, Code of Federal Regulations, Part 20

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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 (Š)	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 (rem)	10^{-2} Jkg^{-1}	sievert (Sv)	Jkg^{-1}
Dose equivalent rate ( )	rem per second (rem s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	sievert per second (Sv s^{-1})	Jkg^{-1} s^{-1}
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

REFERENCES FOR APPENDIX D

ATSDR. 1990a. Toxicological profile for thorium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

ATSDR. 1990b. Toxicological profile for radium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

ATSDR. 1990c. Toxicological profile for radon. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

ATSDR. 1999. Toxicological profile for uranium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA.

BEIR III. 1980. The effects on populations of exposure to low levels of ionizing radiation. Committee on the Biological Effects of Ionizing Radiations, National Research Council. Washington, DC: National Academy Press.

BEIR IV. 1988. Health risks of radon and other internally deposited alpha emitters. Committee on the Biological Effects of Ionizing Radiations, National Research Council. Washington, DC: National Academy Press.

BEIR V. 1988. Health effects of exposure to low levels of ionizing radiation. Committee on the Biological Effects of Ionizing Radiations, National Research Council. Washington, DC: National Academy Press.

Brodsky A. 1996. Review of radiation risks and uranium toxicity with application to decisions associated with decommissioning clean-up criteria. Hebron,Connecticut: RSA Publications.

Cember H. 1996. Introduction to health physics. New York., NY: McGraw Hill.

Early P, Razzak M, Sodee D. 1979. Nuclear medicine technology. 2nd ed. St. Louis: C.V. Mosby Company.

Eichholz G. 1982. Environmental aspects of nuclear power. Ann Arbor, MI: Ann Arbor Science.

Hendee W. 1973. Radioactive isotopes in biological research. New York, NY: John Wiley and Sons.

Hobbs C, McClellan R. 1986. Radiation and radioactive materials. In: Doull J, et al., eds. Casarett and Doull's Toxicology. 3rd ed. New York, NY: Macmillan Publishing Co., Inc., 497-530.

ICRP. 1977. International Commission on Radiological Protection. Recommendations of the International Commission on Radiological Protection. ICRP Publication 26. Vol 1. No. 3. Oxford: Pergamon Press.

ICRP. 1979. International Commission on Radiological Protection. Limits for intakes of radionuclides by workers. ICRP Publication 20. Vol. 3. No. 1-4. Oxford: Pergamon Press.

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ICRP. 1979. Limits for Intakes of Radionuclides by Workers. Publication 30. International Commission on Radiological Protection. Pergamon Press.

ICRP. 1984. International Commission on Radiological Protection. A compilation of the major concepts and quantities in use by ICRP. ICRP Publication 42. Oxford: Pergamon Press.

ICRP. 1990. International Commission on Radiological Protection 1990 Recommendations of the ICRP

ICRU. 1980. International Commission on Radiation Units and Measurements. ICRU Report No. 33. Washington, DC.

James A. 1987. A reconsideration of cells at risk and other key factors in radon daughter dosimetry. In: Hopke P, ed. Radon and its decay products: Occurrence, properties and health effects. ACS Symposium Series 331. Washington, DC: American Chemical Society, 400-418.

James A, Roy M. 1987. Dosimetric lung models. In: Gerber G, et al., ed. Age-related factors in radionuclide metabolism and dosimetry. Boston: Martinus Nijhoff Publishers, 95-108.

Kondo S. 1993. Health effects of low-level radiation. Kinki University Press, Osaka, Japan (available from Medical Physics Publishing, Madison, Wisconsin).

Kato H, Schull W. 1982. Studies of the mortality of A-bomb survivors. Report 7 Part 8, Cancer mortality among atomic bomb survivors, 1950-78. Radiat Res 90;395-432.

Mettler F, Moseley R. 1985. Medical effects of ionizing radiation. New York: Grune and Stratton.

NCRP. 1971. Basic radiation protection criteria. National Council on Radiation Protection and Measurements. Report No. 39. Washington, DC.

NCRP. 1985. A handbook of radioactivity measurements procedures. 2nd ed. National Council on Radiation Protection and Measurements. Report No. 58. Bethesda, MD:

NCRP. 1993. Risk estimates for radiation protection. National Council on Radiation Protection and Measurements. Report 115. Bethesda, Maryland

Otake M, Schull W. 1984. Mental retardation in children exposed in utero to the atomic bombs: A reassessment. Technical Report RERF TR 1-83, Radiation Effects Research Foundation, Japan.

Rubin P, Casarett G. 1968. Clinical radiation pathology. Philadelphia: W.B. Sanders Company, 33.

UNSCEAR. 1977. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. New York: United Nations.

UNSCEAR. 1982. United Nations Scientific Committee on the Effects of Atomic Radiation. Ionizing radiation: Sources and biological effects. New York: United Nations.

UNSCEAR. 1986. United Nations Scientific Committee on the Effects of Atomic Radiation. Genetic and somatic effects of ionizing radiation. New York: United Nations.

UNSCEAR. 1988. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources, effects and risks of ionization radiation. New York: United Nations.