TOXICOLOGICAL PROFILE FOR COBALT

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

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INFORMATION
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UPDATE STATEMENT

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

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

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

FOREWORD

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

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

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

Each profile includes the following:

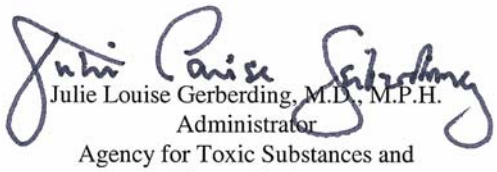
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

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

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

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

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



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Background Information

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

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

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

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

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

Other Sections of Interest:

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

ATSDR Information Center

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

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

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

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

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

Other Agencies and Organizations

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

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

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

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

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Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact:

AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

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

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

PEER REVIEW

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

1. Dr. Herman Cember, C.H.P., Ph.D., PE., Adjunct Professor, School of Health Sciences, Purdue University, Lafayette, Indiana;

2. Dr. James Hansen, Ph.D., Environmental Contaminant Specialist, U.S. Fish and Wildlife Service, Spokane, WA;

3. Dr. Dominique Lison, M.D., Ph.D., Vice-Chairman of the Doctoral School in Genetics and Immunology, Catholic University of Louvain, Brussels, Belgium, and

4. Dr. Nancy Pedigo, Ph.D., Research Assistant Professor, Department of Pharmacology, University of Kentucky Medical Center, Lexington, KY.

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

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

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

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about cobalt 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. Stable cobalt has been found in at least 426 of the 1,636 current or former NPL sites. Radioactive cobalt, as ^{60}Co, has been found in at least 13 of the 1,636 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 cobalt 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 exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact. External exposure to radiation may occur from natural or man-made sources. Naturally occurring sources of radiation are cosmic radiation from space or radioactive materials in soil or building materials. Man-made sources of radioactive materials are found in consumer products, industrial equipment, atom bomb fallout, and to a smaller extent from hospital waste and nuclear reactors.

If you are exposed to cobalt, 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 COBALT?

Cobalt is a naturally-occurring element that has properties similar to those of iron and nickel. It has an atomic number of 27. There is only one stable isotope of cobalt, which has an atomic mass number of 59. (An element may have several different forms, called isotopes, with different weights depending on the number of neutrons that it contains. The isotopes of an element, therefore, have different atomic mass numbers [number of protons and neutrons], although the atomic number [number of protons] remains the same.) However, there are many unstable or radioactive isotopes, two of which are commercially important, cobalt-60 and cobalt-57, also written as Co-60 or ^{60}Co and Co-57 or ^{57}Co, and read as cobalt sixty and cobalt fifty-seven. All isotopes of cobalt behave the same chemically and will therefore have the same chemical behavior in the environment and the same chemical effects on your body. However, isotopes have different mass numbers and the radioactive isotopes have different radioactive properties, such as their half-life and the nature of the radiation they give off. The half-life of a cobalt isotope is the time that it takes for half of that isotope to give off its radiation and change into a different isotope. After one half-life, one-half of the radioactivity is gone. After a second half-life, one-fourth of the original radioactivity is left, and so on. Radioactive isotopes are constantly changing into different isotopes by giving off radiation, a process referred to as radioactive decay. The new isotope may be a different element or the same element with a different mass.

Small amounts of cobalt are naturally found in most rocks, soil, water, plants, and animals, typically in small amounts. Cobalt is also found in meteorites. Elemental cobalt is a hard, silvery grey metal. However, cobalt is usually found in the environment combined with other elements such as oxygen, sulfur, and arsenic. Small amounts of these chemical compounds can be found in rocks, soil, plants, and animals. Cobalt is even found in water in dissolved or ionic form, typically in small amounts. (Ions are atoms, collections of atoms, or molecules containing a positive or negative electric charge.) A biochemically important cobalt compound is vitamin B_{12} or cyanocobalamin. Vitamin B_{12} is essential for good health in animals and humans. Cobalt is not currently mined in the United States, but has been mined in the past. Therefore, we

obtain cobalt and its other chemical forms from imported materials and by recycling scrap metal that contains cobalt.

Cobalt metal is usually mixed with other metals to form alloys, which are harder or more resistant to wear and corrosion. These alloys are used in a number of military and industrial applications such as aircraft engines, magnets, and grinding and cutting tools. They are also used in artificial hip and knee joints. Cobalt compounds are used as colorants in glass, ceramics, and paints, as catalysts, and as paint driers. Cobalt colorants have a characteristic blue color; however, not all cobalt compounds are blue. Cobalt compounds are also used as trace element additives in agriculture and medicine.

Cobalt can also exist in radioactive forms. A radioactive isotope of an element constantly gives off radiation, which can change it into an isotope of a different element or a different isotope of the same element. This newly formed nuclide may be stable or radioactive. This process is called radioactive decay. ^{60}Co is the most important radioisotope of cobalt. It is produced by bombarding natural cobalt, ^{59}Co, with neutrons in a nuclear reactor. ^{60}Co decays by giving off a beta ray (or electron), and is changed into a stable nuclide of nickel (atomic number 28). The half-life of ^{60}Co is 5.27 years. The decay is accompanied by the emission of high energy radiation called gamma rays. ^{60}Co is used as a source of gamma rays for sterilizing medical equipment and consumer products, radiation therapy for treating cancer patients, and for manufacturing plastics. ^{60}Co has also been used for food irradiation; depending on the radiation dose, this process may be used to sterilize food, destroy pathogens, extend the shelf-life of food, disinfest fruits and grain, delay ripening, and retard sprouting (e.g., potatoes and onions). ^{57}Co is used in medical and scientific research and has a half-life of 272 days. ^{57}Co undergoes a decay process called electron capture to form a stable isotope of iron (^{57}Fe). Another important cobalt isotope, ^{58}Co, is produced when nickel is exposed to a source of neutrons. Since nickel is used in nuclear reactors, ^{58}Co may be unintentionally produced and appear as a contaminant in cooling water released by nuclear reactors. ^{58}Co also decays by electron capture, forming another stable isotope of iron (^{58}Fe). ^{60}Co may be similarly produced from cobalt alloys in nuclear reactors and

released as a contaminant in cooling water. ^{58}Co has a half-life of 71 days and gives off beta and gamma radiation in the decay process.

Quantities of radioactive cobalt are normally measured in units of radioactivity (curies or becquerels) rather than in units of mass (grams). The becquerel (Bq) is a new international unit, and the curie (Ci) is the traditional unit; both are currently used. A becquerel is the amount of radioactive material in which 1 atom transforms every second, and a curie is the amount of radioactive material in which 37 billion atoms transform every second. For an overview of basic radiation physics, chemistry, and biology see Appendix D of this profile. For more information on radiation, see the *ATSDR Toxicological Profile for Ionizing Radiation*.

To learn more about the properties and uses of cobalt, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO COBALT WHEN IT ENTERS THE ENVIRONMENT?

Cobalt may enter the environment from both natural sources and human activities. Cobalt occurs naturally in soil, rock, air, water, plants, and animals. It may enter air and water, and settle on land from windblown dust, seawater spray, volcanic eruptions, and forest fires and may additionally get into surface water from runoff and leaching when rainwater washes through soil and rock containing cobalt. Soils near ore deposits, phosphate rocks, or ore smelting facilities, and soils contaminated by airport traffic, highway traffic, or other industrial pollution may contain high concentrations of cobalt. Small amounts of cobalt may be released into the atmosphere from coal-fired power plants and incinerators, vehicular exhaust, industrial activities relating to the mining and processing of cobalt-containing ores, and the production and use of cobalt alloys and chemicals. ^{58}Co and ^{60}Co may be released to the environment as a result of nuclear accidents (i.e, Chernobyl), radioactive waste dumping in the sea or from radioactive waste landfills, and nuclear power plant operations.

Cobalt cannot be destroyed in the environment. It can only change its form or become attached or separated from particles. Cobalt released from power plants and other combustion processes

is usually attached to very small particles. Cobalt contained in windborne soil is generally found in larger particles than those released from power plants. These large particles settle to the ground or are washed out of the air by rain. Cobalt that is attached to very small particles may stay in the air for many days. Cobalt released into water may stick to particles in the water column or to the sediment at the bottom of the body of water into which it was released, or remain in the water column in ionic form. The specific fate of cobalt will depend on many factors such as the chemistry of the water and sediment at a site as well as the cobalt concentration and water flow. Cobalt deposited on soil is often strongly attached to soil particles and therefore would not travel very far into the ground. However, the form of the cobalt and the nature of the soil at a particular site will affect how far cobalt will penetrate into the soil. Both in soil and sediment, the amount of cobalt that is mobile will increase under more acidic conditions. Ultimately, most cobalt ends up in the soil or sediment.

Plants can accumulate very small amounts of cobalt from the soil, especially in the parts of the plant that you eat most often, such as the fruit, grain, and seeds. While animals that eat these plants will accumulate cobalt, cobalt is not known to biomagnify (produce increasingly higher concentrations) up the food chain. Therefore, vegetables, fruits, fish, and meat that you consume will generally not contain high amounts of cobalt. Cobalt is an essential element, required for good health in animals and humans, and therefore, it is important that foodstuffs contain adequate quantities of cobalt.

^{60}Co and ^{58}Co are moderately short-lived, manufactured radioactive isotopes that are produced in nuclear reactors. Although these isotopes are not produced by nuclear fission, small amounts of these radioisotopes are also produced by the neutron interaction with the structural materials found in the reactor of nuclear plants, and are produced during the routine operation of nuclear plants. Small amounts may be released to the environment as contaminants in cooling water or in radioactive waste. Since these isotopes are not fission products, they are not produced in nuclear weapons testing and are not associated with nuclear fallout. In the environment, radioactive isotopes of cobalt will behave chemically like stable cobalt. However, ^{60}Co and ^{58}Co

will also undergo radioactive decay according to their respective half-lives, 5.27 years and 71 days.

For more information about what happens to cobalt in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO COBALT?

Cobalt is widely dispersed in the environment in low concentrations. You may be exposed to small amounts of cobalt by breathing air, drinking water, and eating food containing it. Children may also be exposed to cobalt by eating dirt. You may also be exposed by skin contact with soil, water, cobalt alloys, or other substances that contain cobalt. Analytical methods used by scientists to determine the levels of cobalt in the environment generally do not determine the specific chemical form of cobalt present. Therefore, we do not always know the chemical form of cobalt to which a person may be exposed. Similarly, we do not know what forms of cobalt are present at hazardous waste sites. Some forms of cobalt may be insoluble or so tightly attached to particles or embedded in minerals that they are not taken up by plants and animals. Other forms of cobalt that are weakly attached to particles may be taken up by plants and animals.

The concentration of cobalt in soil varies widely, generally ranging from about 1 to 40 ppm (1 ppm=1 part of cobalt in a million parts of soil by weight), with an average level of 7 ppm. Soils containing less than about 3 ppm of cobalt are considered cobalt-deficient because plants growing in them do not have sufficient cobalt to meet the dietary requirements of cattle and sheep. Such cobalt-deficient soils are found in some areas in the southeast and northeast parts of the United States. On the other hand, soils near cobalt-containing mineral deposits, mining and smelting facilities, or industries manufacturing or using cobalt alloys or chemicals may contain much higher levels of cobalt.

Usually, the air contains very small amounts of cobalt, less than 2 nanograms (1 nanogram=one-billionth part of a gram) per cubic meter (ng/m^3). The amount of cobalt that you breathe in a day

is much less than what you consume in food and water. You may breathe in higher levels of cobalt in dust in areas near cobalt-related industries or near certain hazardous waste sites.

The concentration of cobalt in surface and groundwater in the United States is generally low—between 1 and 10 parts of cobalt in 1 billion parts of water (ppb) in populated areas; concentration may be hundreds or thousands times higher in areas that are rich in cobalt-containing minerals or in areas near mining or smelting operations. In most drinking water, cobalt levels are less than 1–2 ppb.

For most people, food is the largest source of cobalt intake. The average person consumes about 11 micrograms of cobalt a day in their diet. Included in this food is vitamin B_{12}, which is found in meat and diary products. The recommended daily intake of vitamin B_{12} is 6 micrograms (1 microgram=one-millionth part of a gram).

You may also be exposed to higher levels of cobalt if you work in metal mining, smelting, and refining, in industries that make or use cutting or grinding tools, or in other industries that produce or use cobalt metal and cobalt compounds. If good industrial hygiene is practiced, such as the use of exhaust systems in the workplace, exposure can be reduced to safe levels. Industrial exposure results mainly from breathing cobalt-containing dust.

When we speak of exposure to ^{60}Co, we are interested in exposure to the radiation given off by this isotope, primarily the gamma rays. The general population is rarely exposed to this radiation unless a person is undergoing radiation therapy. However, workers at nuclear facilities, irradiation facilities, or nuclear waste storage sites may be exposed to ^{60}Co or ^{58}Co. Exposures to radiation at these facilities are regulated and carefully monitored and controlled.

You can find more information on how you may be exposed to cobalt in Chapter 6.

1.4 HOW CAN COBALT ENTER AND LEAVE MY BODY?

Cobalt can enter your body when you breathe in air containing cobalt dust, when you drink water that contains cobalt, when you eat food that contains cobalt, or when your skin touches materials that contain cobalt. If you breathe in air that contains cobalt dust, the amount of inhaled cobalt that stays in your lungs depends on the size of the dust particles. The amount that is then absorbed into your blood depends on how well the particles dissolve. If the particles dissolve easily, then it is easier for the cobalt to pass into your blood from the particles in your lungs. If the particles dissolve slowly, then they will remain in your lungs longer. Some of the particles will leave your lungs as they normally clean themselves out. Some of the particles will be swallowed into your stomach. The most likely way you will be exposed to excess cobalt is by eating contaminated food or drinking contaminated water. Levels of cobalt normally found in the environment, however, are not high enough to result in excess amounts of cobalt in food or water. The amount of cobalt that is absorbed into your body from food or water depends on many things including your state of health, the amount you eat or drink, and the number of days, weeks, or years you eat foods or drink fluids containing cobalt. If you do not have enough iron in your body, the body may absorb more cobalt from the foods you eat. Once cobalt enters your body, it is distributed into all tissues, but mainly into the liver, kidney, and bones. After cobalt is breathed in or eaten, some of it leaves the body quickly in the feces. The rest is absorbed into the blood and then into the tissues throughout the body. The absorbed cobalt leaves the body slowly, mainly in the urine. Studies have shown that cobalt does not readily enter the body through normal skin, but it can if the skin has been cut.

Further information on how cobalt can enter or leave your body can be found in Chapter 3.

1.5 HOW CAN COBALT 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 use many tests.

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

Cobalt has both beneficial and harmful effects on human health. Cobalt is beneficial for humans because it is part of vitamin B_{12}, which is essential to maintain human health. Cobalt (0.16–1.0 mg cobalt/kg of body weight) has also been used as a treatment for anemia (less than normal number of red blood cells), including in pregnant women, because it causes red blood cells to be produced. Cobalt also increases red blood cell production in healthy people, but only at very high exposure levels. Cobalt is also essential for the health of various animals, such as cattle and sheep. Exposure of humans and animals to levels of cobalt normally found in the environment is not harmful.

When too much cobalt is taken into your body, however, harmful health effects can occur. Workers who breathed air containing 0.038 mg cobalt/m^3 (about 100,000 times the concentration normally found in ambient air) for 6 hours had trouble breathing. Serious effects on the lungs, including asthma, pneumonia, and wheezing, have been found in people exposed to 0.005 mg cobalt/m^3 while working with hard metal, a cobalt-tungsten carbide alloy. People exposed to 0.007 mg cobalt/m^3 at work have also developed allergies to cobalt that resulted in asthma and skin rashes. The general public, however, is not likely to be exposed to the same type or amount of cobalt dust that caused these effects in workers.

In the 1960s, some breweries added cobalt salts to beer to stabilize the foam (resulting in exposures of 0.04–0.14 mg cobalt/kg). Some people who drank excessive amounts of beer (8–25 pints/day) experienced serious effects on the heart. In some cases, these effects resulted in

death. Nausea and vomiting were usually reported before the effects on the heart were noticed. Cobalt is no longer added to beer so you will not be exposed from this source. The effects on the heart, however, may have also been due to the fact that the beer-drinkers had protein-poor diets and may have already had heart damage from alcohol abuse. Effects on the heart were not seen, however, in people with anemia treated with up to 1 mg cobalt/kg, or in pregnant women with anemia treated with 0.6 mg cobalt/kg. Effects on the thyroid were found in people exposed to 0.5 mg cobalt/kg for a few weeks. Vision problems were found in one man following treatment with 1.3 mg cobalt/kg for 6 weeks, but this effect has not been seen in other human or animal studies.

Being exposed to radioactive cobalt may be very dangerous to your health. If you come near radioactive cobalt, cells in your body can become damaged from gamma rays that can penetrate your entire body, even if you do not touch the radioactive cobalt. Radiation from radioactive cobalt can also damage cells in your body if you eat, drink, breathe, or touch anything that contains radioactive cobalt. The amount of damage depends on the amount of radiation to which you are exposed, which is related to the amount of activity in the radioactive material and the length of time that you are exposed. Most of the information regarding health effects from exposure to radiation comes from exposures for only short time periods. The risk of damage from exposure to very low levels of radiation for long time periods is not known. If you are exposed to enough radiation, you might experience a reduction in white blood cell number, which could lower your resistance to infections. Your skin might blister or burn, and you may lose hair from the exposed areas. This happens to cancer patients treated with large amounts of radiation to kill cancer. Cells in your reproductive system could become damaged and cause temporary sterility. Exposure to lower levels of radiation might cause nausea, and higher levels can cause vomiting, diarrhea, bleeding, coma, and even death. Exposure to radiation can also cause changes in the genetic materials within cells and may result in the development of some types of cancer.

Studies in animals suggest that exposure to high amounts of nonradioactive cobalt during pregnancy might affect the health of the developing fetus. Birth defects, however, have not been

found in children born to mothers who were treated with cobalt for anemia during pregnancy. The doses of cobalt used in the animal studies were much higher than the amounts of cobalt to which humans would normally be exposed.

Nonradioactive cobalt has not been found to cause cancer in humans or in animals following exposure in the food or water. Cancer has been shown, however, in animals who breathed cobalt or when cobalt was placed directly into the muscle or under the skin. Based on the animal data, the International Agency for Research on Cancer (IARC) has determined that cobalt is possibly carcinogenic to humans.

Much of our knowledge of cobalt toxicity is based on animal studies. Cobalt is essential for the growth and development of certain animals, such as cows and sheep. Short-term exposure of rats to high levels of cobalt in the air results in death and lung damage. Longer-term exposure of rats, guinea pigs, hamsters, and pigs to lower levels of cobalt in the air results in lung damage and an increase in red blood cells. Short-term exposure of rats to high levels of cobalt in the food or drinking water results in effects on the blood, liver, kidneys, and heart. Longer-term exposure of rats, mice, and guinea pigs to lower levels of cobalt in the food or drinking water results in effects on the same tissues (heart, liver, kidneys, and blood) as well as the testes, and also causes effects on behavior. Sores were seen on the skin of guinea pigs following skin contact with cobalt for 18 days. Generally, cobalt compounds that dissolve easily in water are more harmful than those that are hard to dissolve in water.

Much of what we know about the effects of radioactive cobalt comes from studies in animals. The greatest danger of radiation seen in animals is the risk to the developing animal, with even moderate amounts of radiation causing changes in the fetus. High radiation doses in animals have also been shown to cause temporary or permanent sterility and changes in the lungs, which affected the animals' breathing. The blood of exposed animals has lower numbers of white blood cells, the cells that aid in resistance to infections, and red blood cells, which carry oxygen in the blood. Radioactive cobalt exposures in animals have also caused genetic damage to cells, cancer, and even death.

More information on how cobalt can affect your health can be found in Chapter 3.

1.6 HOW CAN COBALT AFFECT CHILDREN?

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

Children can be exposed to cobalt in the same ways as adults. In addition, cobalt may be transferred from the pregnant mother to the fetus or from the mother to the infant in the breast milk. Children may be affected by cobalt the same ways as adults. Studies in animals have suggested that children may absorb more cobalt from foods and liquids containing cobalt than adults. Babies exposed to radiation while in their mother's womb are believed to be much more sensitive to the effects of radiation than adults.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO COBALT

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

Since cobalt is naturally found in the environment, people cannot avoid being exposed to it. However, the relatively low concentrations present do not warrant any immediate steps to reduce exposure. If you are accidentally exposed to large amounts of cobalt, consult a physician immediately.

Children living near waste sites containing cobalt are likely to be exposed to higher environmental levels of cobalt through breathing, touching soil, and eating contaminated soil. Some children eat a lot of dirt. You should discourage your children from eating dirt. Make sure

they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or hand-to-mouth activity.

You are unlikely to be exposed to high levels of radioactive cobalt unless you are exposed as part of a radiotherapy treatment, there is an accident involving a cobalt sterilization or radiotherapy unit, or there is an accidental release from a nuclear power plant. In such cases, follow the advice of public health officials who will publish guidelines for reducing exposure to radioactive material when necessary. Workers who work near or with radioactive cobalt should follow the workplace safety guidelines of their institution carefully to reduce the risk of accidental irradiation.

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

We have reliable tests that can measure cobalt in the urine and the blood for periods up to a few days after exposure. The amount of cobalt in your blood or urine can be used to estimate how much cobalt you had taken into your body. The tests are not able to accurately predict potential health effects following exposure to cobalt.

It is difficult to determine whether a person has been exposed only to external radiation from radioactive cobalt unless the radiation dose was rather large. Health professionals examining people who have health problems similar to those resulting from radiation exposure would need to rely on additional information in order to establish if such people had been near a source of radioactivity. It is relatively easy to determine whether a person has been internally exposed to radioactive cobalt, as discussed in Chapter 7. More information on medical tests can be found in Chapters 3 and 7.

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

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

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

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

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

EPA requires that the federal government be notified if more than 1,000 pounds of cobalt (as the bromide, formate, and sulfamate compounds) are released into the environment in a 24-hour period. OSHA regulates levels of nonradioactive cobalt in workplace air. The limit for an 8-hour workday, 40-hour workweek is an average of 0.1 mg/m^3. The USNRC and the Department of Energy (DOE) regulate occupational exposures as well as exposures of the general public to radioactive cobalt.

1.10 WHERE CAN I GET MORE INFORMATION?

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

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

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

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

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

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

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO COBALT IN THE UNITED STATES

Cobalt is a naturally-occurring element that has properties similar to those of iron and nickel. The largest use of metallic cobalt is in superalloys that are used in gas turbine aircraft engines. Cobalt compounds are used as pigments in glass, ceramics, and paints; as catalysts in the petroleum industry; as paint driers; and as trace element additives in agriculture and medicine.

Cobalt may be released to the environment by human activities, as well by weathering of rocks and soil. The primary anthropogenic sources of cobalt in the environment are from the burning of fossil fuels, application of cobalt-containing sludge or phosphate fertilizers, mining and smelting of cobalt-containing ores, processing of cobalt-containing alloys, and industries that use or process cobalt compounds. Cobalt released to the atmosphere is deposited onto soil or water surfaces by wet and dry deposition. In soils, cobalt generally has low mobility and strong adsorption. However its mobility increases in moist, acidic soils. In water, cobalt largely partitions to sediment and to suspended solids in the water column; however, the amount that is adsorbed to suspended solids is highly variable.

Exposure of the general population to cobalt occurs through inhalation of ambient air and ingestion of food and drinking water. In general, intake from food sources is much greater than from drinking water and air. The cobalt intake in food has been estimated to be 5.0–40.0 µg/day. Occupational exposure to cobalt occurs for workers in the hard metal industry (tool production, grinding, etc.) and in industries such as coal mining, metal mining, smelting and refining, cobalt dye painters, and the cobalt chemical production industry. The concentrations of cobalt in the air of hard metal manufacturing, welding, and grinding factories may range from 1 to 300 µg/m^3, compared to normal atmospheric levels of 0.4–2.0 ng/m^3.

While there is only one stable isotope of cobalt, ^{59}Co, there are many radioactive isotopes of cobalt. Of these radioactive isotopes, two are commercially important, ^{60}Co and ^{57}Co. ^{60}Co is produced by irradiating ^{59}Co with thermal neutrons in a nuclear reactor, and is used as a source of gamma rays for sterilizing medical equipment or consumer products, food irradiation, radiation therapy for treating cancer

patients, and for manufacturing plastics. The general population is not significantly exposed to radioactive forms of cobalt. Cancer patients being treated with radiation therapy may be exposed to gamma rays from a ^{60}Co source; however, the effects of external exposure to gamma radiation is not unique to ^{60}Co, but is similar for all gamma-emitting radionuclides. Workers at nuclear facilities and nuclear waste storage sites may be exposed to potentially high levels of radioactive cobalt.

2.2 SUMMARY OF HEALTH EFFECTS

As a component of cyanocobalmin (vitamin B_{12}), cobalt is essential in the body; the Recommended Dietary Allowance of vitamin B_{12} is 2.4 µg/day, which contains 0.1 µg of cobalt. Cobalt has been identified in most tissues of the body, with the highest concentrations found in the liver.

Following inhalation exposure to cobalt-containing particles, the primary target of exposure is the respiratory tract. Occupational exposure of humans to cobalt metal or cobalt-containing hard metal have reported primarily respiratory effects, including decreased pulmonary function, asthma, interstitial lung disease, wheezing, and dyspnea; these effects were reported at occupational exposure levels ranging from 0.015–0.13 mg Co/m^3. Animal studies have further identified respiratory tract hyperplasia, pulmonary fibrosis, and emphysema as sensitive effects of inhaled cobalt on respiratory tissues. Many of the respiratory tract effects are believed to be the result of the generation of oxidants and free radicals by the cobalt ion. In particular, hard metal (a tungsten carbide/cobalt alloy) is a potent generator of free electrons, resulting in the generation of active oxygen species. However, some of the respiratory effects, such as cobalt-induced asthma, are likely the result of immunosensitization to cobalt.

Other sensitive targets of cobalt inhalation in humans include effects on the thyroid and allergic dermatitis, manifesting as eczema and erythema; it is believed that the allergic dermatitis is due, at least in part, to concurrent dermal exposure and the development of immunosensitization to cobalt.

Adequate chronic studies of the oral toxicity of cobalt or cobalt compounds in humans and animals are not presently available. The most sensitive endpoint following oral exposure to cobalt in humans appears to be an increase in erythrocyte numbers (polycythemia). This effect has been observed in both normal subjects and in patients who were anemic as a result of being anephric. However, treatment of pregnant women with cobalt did not prevent the reduction in hematocrit and hemoglobin levels often found during

pregnancy. Exposure of humans to beer containing cobalt as a foam stabilizer resulted in severe effects on the cardiovascular system, including cardiomyopathy and death, as well as gastrointestinal effects (nausea, vomiting) and hepatic necrosis. However, the subjects in these studies were alcoholics, and it is not known what effect excessive alcohol consumption may have played in the development of the observed effects.

Following dermal exposure, the most commonly observed effect is dermatitis, as demonstrated by a large number of human studies. Using patch tests and intradermal injections, it has been demonstrated that the dermatitis is probably caused by an allergic reaction to cobalt, with the cobalt ion functioning as a hapten.

Available studies of the carcinogenic effects of cobalt in occupationally-exposed humans have reported mixed results, with both positive and negative results. Lifetime inhalation of cobalt sulfate resulted in increased tumor incidences in both rats and mice; NTP reported that there was some evidence of carcinogenicity in male Fischer 344 (F344) strain rats, and clear evidence of carcinogenicity in female F344 strain rats and male and female B6C3F1 strain mice following inhalation exposure. Oral data on the carcinogenic effects of cobalt and cobalt compounds are not available. IRIS does not report a cancer classification for cobalt or cobalt compounds. IARC has classified cobalt and cobalt compounds as *possibly carcinogenic to humans (Group 2B)*.

A more detailed discussion of the health effects of cobalt and cobalt compounds is presented in Chapter 3. An enhanced discussion of sensitive end points of stable cobalt toxicity is presented below.

Respiratory Effects. The primary effects of cobalt on respiratory tissues are seen following inhalation exposure, and include diminished pulmonary function, increased frequency of cough, respiratory inflammation, and fibrosis; reported effect levels in occupationally-exposed humans have ranged from 0.015–0.13 mg Co/m^3. Animal studies have further identified respiratory tract hyperplasia, pulmonary fibrosis, and emphysema as sensitive effects of cobalt on respiratory tissues. A number of these effects are believed to be the result of the generation of oxidants and free radicals by the cobalt ion. *In vitro* exposure to soluble cobalt increases indices of oxidative stress, including diminished levels of reduced glutathione, increased levels of oxidized glutathione, activation of the hexose monophosphate shunt, and free-radical-induced DNA damage. Cobalt exposure also results in sensitization of the immune system, which may result in asthmatic attacks following inhalation of cobalt in sensitized individuals.

Hard metal is a metal alloy with a tungsten carbide and cobalt matrix. It is used to make cutting tools because of its hardness and resistance to high temperature. Exposure to hard metal has been shown in a number of studies to cause respiratory effects, including respiratory irritation, diminished pulmonary function, asthma, and fibrosis, at exposure levels lower than those that would produce similar effects following exposure to cobalt metal alone (0.007–0.14 mg Co/m^3). Studies suggest that cobalt and not tungsten carbide is the probable causative agent for the respiratory effects observed in hard metal workers (see Section 3.5). A mechanism by which hard metal may exert its effects has been proposed by a group of Belgian researchers. In this proposed mechanism, tungsten carbide, which is a very good conductor of electrons, facilitates the oxidation of cobalt metal to ionic cobalt (presumably Co^{2+}) by transferring electrons from the cobalt atom to molecular oxygen adjacent to the tungsten carbide molecule. The result is an increased solubility of cobalt, relative to cobalt metal alone, and the generation of active oxygen species. *In vitro* evidence for this mechanism includes the ability of hard metal particles, but neither cobalt nor tungsten carbide alone at the same concentrations, to generate oxidant species and cause lipid peroxidation. Hard metal particles have also been shown to increase the levels of inducible nitric oxide synthase (iNOS), a gene responsive to oxidant stress.

Hematological Effects. Exposure to cobalt and cobalt compounds has been demonstrated to increase levels of erythrocytes and hemoglobin in both humans and animals. Davis and Fields reported increased (~16–20%) erythrocyte levels in six of six healthy men exposed orally to cobalt chloride (~1 mg Co/kg-day); erythrocyte counts returned to normal 9–15 days after cessation of cobalt administration. Increased levels of erythrocytes were also found following oral treatment of anephric patients (with resulting anemia) with cobalt chloride. The increase in hemoglobin resulted in a decreased need for blood transfusions. Treatment of pregnant women for 90 days with cobalt chloride, however, did not prevent the reduction in hematocrit and hemoglobin levels often found during pregnancy.

Increased levels of hemoglobin were observed in rats and guinea pigs, but not in dogs, exposed to cobalt hydrocarbonyl by inhalation. Polycythemia was reported in rats, but not mice, exposed to airborne cobalt sulfate. Significantly increased erythrocyte (polycythemia), hematocrit, and hemoglobin levels were found in animals treated orally with cobalt as either a single dose or with longer-term exposure. Of particular note is an 8-week study in rats, which reported dose- and time-related increases in erythrocyte number following oral administration of cobalt chloride.

The mechanisms regarding cobalt-induced polycythemia are not well understood. Cobalt is thought to inhibit heme synthesis *in vivo* by acting upon at least two different sites in the biosynthetic pathway. This inhibitory activity might result in the formation of cobalt protoporphyrin rather than heme. Cobalt treatment also stimulates heme oxidation in many organs, due to the induction of heme oxygenase. Conversely, cobalt acts, through a mechanism believed to involve a heme-containing protein, to increase erythropoietin, which stimulates the production of red blood cells. The regulatory mechanisms behind this apparent dichotomy have not been fully elucidated.

Cardiac Effects. Cardiomyopathy has been reported in both humans and animals following exposure to cobalt. Occupational exposure of humans to cobalt-containing dust, either as cobalt metal or as hard metal, is believed to result in cardiomyopathy characterized by functional effects on the ventricles and enlargement of the heart, but the exposure levels associated with cardiac effects of inhaled cobalt in humans have not been determined. Rats exposed to 11.4 mg Co/m^3 for 13 weeks developed a mild cardiomyopathy; however, rats and mice exposed to 1.14 mg Co/m^3 for 2 years showed no signs of cardiomyopathy.

Beer-cobalt cardiomyopathy was observed in people who heavily consumed beer that contained cobalt sulfate as a foam stabilizer. The beer drinkers ingested an average of 0.04 mg Co/kg/day to 0.14 mg Co/kg/day for a period of years. The cardiomyopathy was characterized by sinus tachycardia, left ventricular failure, cardiogenic shock, diminished myocardial compliance, absence of a myocardial response to exercise or catecholamine, enlarged heart, pericardial effusion, and extensive intracellular changes (changes in the myofibers, mitochondria, glycogen, and lipids). The beer-cobalt cardiomyopathy appeared to be similar to alcoholic cardiomyopathy and beriberi, but the onset of beer-cobalt cardiomyopathy was very abrupt. It should be noted, however, that the cardiomyopathy may have also been due to the fact that the beer-drinkers had protein-poor diets and may have had prior cardiac damage from alcohol abuse. Studies in animals, and limited human data, have supported this possibility, as much greater oral exposure levels (on the order of 8-30 mg Co/kg-day) are necessary to induce cardiac effects.

The mechanism for cobalt-induced cardiomyopathy is not presently understood. Exposure to cobalt may result in accumulation in cardiac tissues, and is thought to stimulate carotid-body chemoreceptors, mimicking the action of hypoxia. Microscopic analysis of the hearts of those with beer-cobalt cardiomyopathy revealed fragmentation and degeneration of myofibers and aggregates of abnormal mitochondria. These mitochondrial changes are indicative of disturbances in energy production or

utilization may possibly be related to cobalt effects on lipoic acid. Cobalt irreversibly chelates lipoic acids under aerobic conditions. Lipoic acid is a required cofactor for oxidative decarboxylation of pyruvate to acetyl CoA and of α-ketoglutarate to succinate. In the myocardium of rats treated with cobalt, oxidation of pyruvate or fatty acids is impaired. However, the relative contribution of these mechanisms to the cardiac effects of cobalt has not been determined.

Dermal Effects. Dermatitis is a common result of dermal exposure to cobalt in humans. Using patch tests and intradermal injections, it has been demonstrated that the dermatitis is probably caused by an allergic reaction to cobalt. Exposure levels associated with the development of dermatitis have not been identified. It appears that cobalt metal may be a more potent allergen than some cobalt salts, as Nielsen et al. demonstrated that daily repeated exposure to aqueous cobalt salts did not result in hand eczema in patients known to have cobalt allergy. In animals, scabs and denuded areas were found after six doses of 51.75 mg Co/kg (5 days/week) as dicobalt octacarbonyl were applied to the shaved abdomens (uncovered area of approximately 50 cm^2) of guinea pigs. By the 11th dose, the lesions disappeared. No adverse effects were observed in vehicle controls (methyl ethyl ketone). It is not known whether or not a similar reaction would result from metallic or inorganic forms of cobalt.

Immunological Effects. Exposure of humans to cobalt by the inhalation and dermal routes has resulted in sensitization to cobalt. Exposure to inhaled cobalt chloride aerosols can precipitate an asthmatic attack in sensitized individuals, believed to be the result of an allergic reaction within the lungs. Similarly, the dermatitis seen in dermally-exposed subjects is likely the result of an allergic reaction, with cobalt functioning as a hapten. IgE and IgA antibodies specific to cobalt have been reported in humans. There is evidence that cobalt sensitivity in humans may also be regulated by T-lymphocytes; a human helper T-lymphocyte cell line specific for cobalt ($CoCl_2$) has been established. Cobalt may also interact directly with immunologic proteins, such as antibodies or Fc receptors, to result in immunosensitization. *In vitro*, cobalt(III) has been shown to reduce the proliferation of both B and T lymphocytes, as well as the release of the cytokines IL-2, IL-6, and IFN-Gamma. Interrelationships exist between nickel and cobalt sensitization, with cross-reactivity between the two having been reported in several studies.

Radioactive Cobalt. Exposure to radioisotopes of cobalt is also a human health concern. Energy released by radioactive isotopes can result in significant damage to living cells. Both ^{60}Co and ^{57}Co emit beta particles and gamma rays, which may ionize molecules within cells penetrated by these emissions and result in tissue damage and disruption of cellular function. The most important exposure route for

radioisotopes of cobalt is external exposure to the radiation released by the radioisotopes. It should be noted that there is nothing unique about the effects of external exposure to ^{60}Co and ^{57}Co when compared to other gamma- and beta-emitting radionuclides.

Generally, acute radiation doses below 15 rad (0.15 Gy) do not result in observable adverse health effects. At doses in the range of 15–50 rad (0.15–0.5 Gy), subclinical responses such as chromosomal breaks and transient changes in formed elements of the blood may be seen in sensitive individuals. Symptoms of acute radiation syndrome begin to be observed at radiation doses above 50 rad, characterized by transient hematopoietic manifestations, nausea and vomiting, and moderate leukopenia at doses near 100 rad (1 Gy), progressing through more serious hematopoietic symptoms, clinical signs, and gastrointestinal symptoms with increasing dose (100–800 rad or 1–8 Gy), and usually death in persons receiving total doses ≥1,000 rad (10 Gy). Other health effects from acute or continued high-level exposure to ionizing radiation may include reproductive, developmental, and latent cancer effects.

Signs and symptoms of acute toxicity from external and internal exposure to high levels of radiation from ^{60}Co and ^{57}Co are typical of those observed in cases of high exposure to ionizing radiation in general. Depending on the radiation dose, symptoms may include those typical of acute radiation syndrome (vomiting, nausea, and diarrhea), skin and ocular lesions, neurological signs, chromosomal abnormalities, compromised immune function, and death.

Acute or repeated exposure of humans or animals to ionizing radiation (from radioisotopes of cobalt or other radioactive elements) may result in reduced male fertility, abnormal neurological development following exposure during critical stages of fetal development, and genotoxic effects such as increased frequencies of chromosomal aberrations, sister-chromatid exchanges, and micronucleus formation.

Due to the ionizing properties of radionuclides such as ^{60}Co and ^{57}Co, increased cancer risk would be expected among exposed individuals. However, studies of increased cancer risk specifically associated with exposure of humans to radioactive cobalt isotopes were not located. Similarly, studies of the carcinogenic effects of radioactive cobalt isotopes in animals were not located.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

- An MRL of 0.0001 mg cobalt/m^3 has been derived for chronic-duration inhalation exposure (>365 days) to cobalt.

An MRL for inhalation exposure to cobalt was derived for chronic duration only. The chronic inhalation MRL of 0.0001 mg cobalt/m^3 was based on a no-observed-adverse-effect-level (NOAEL) of 0.0053 mg cobalt/m^3 and a LOAEL of 0.0151 mg cobalt/m^3 (both NOAEL and LOAEL values were adjusted for continuous exposure prior to MRL derivation) for decreases in forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory flow between 25 and 75% of the FVC (MMEF), and mean peak expiratory flow rate (PEF) in diamond polishers (Nemery et al. 1992); a further discussion of the results and limitations of this study is presented in Appendix A.

The National Toxicology Program (NTP) has conducted a chronic-duration carcinogenicity study in rats and mice. Exposure of rats and mice to aerosols of cobalt (as cobalt sulfate) at concentrations ranging from 0.11 to 1.14 mg cobalt/m^3 for 2 years resulted in a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice (NTP 1998). Squamous metaplasia of the larynx occurred in rats and mice at exposure concentrations of 0.11 mg cobalt/m^3, with severity of the lesion increasing with increased exposure concentration. Hyperplastic lesions of the nasal epithelium occurred in rats at concentrations of 0.11 mg cobalt/m^3, and in mice at concentrations of 0.38 mg cobalt/m^3. Both sexes of rats had greatly increased incidences (>90% incidence) of alveolar lesions at all exposure levels, including inflammatory changes, fibrosis, and metaplasia. Similar changes were seen in mice at all exposure levels, though the changes in mice were less severe. The study in diamond polishers, being a well-conducted study in humans, was selected as the critical study for the derivation of a MRL because it examined a human population and identified a NOAEL, neither of which occurred in the NTP study. The chronic inhalation MRL was derived by adjusting the NOAEL of 0.0053 mg Co/m^3 for intermittent exposure (adjusted to 0.0013 mg/m^3 to simulate continuous exposure), and applying an uncertainty factor of 10 (for human variability). It should be noted that this MRL may not be protective for individuals already sensitive to cobalt.

An acute inhalation MRL was not derived because the threshold was not defined for human effects and animal studies reported effects that were serious and occurred at levels above those reported in the few

human studies. An acute-duration study of hard metal exposure in humans (Kusaka et al. 1986b) was not utilized for MRL derivation because the toxicity of hard metal is not directly due to cobalt metal, but rather to an interaction between cobalt metal and tungsten carbide. An intermediate-duration MRL was not derived because available studies did not examine the dose-response relationship at low doses; the chronic inhalation MRL should be protective for intermediate exposures (see Appendix A).

Oral MRLs

- An MRL of 0.01 mg Co/kg-day has been derived for intermediate-duration oral exposure (<365 days) to cobalt.

An intermediate-duration MRL of 0.01 mg Co/kg/day was derived based on a LOAEL of 1 mg cobalt/kg-day for polycythemia as reported in a study by Davis and Fields (1958). The authors exposed six men to 120 or 150 mg/day of cobalt chloride (~1 mg Co/kg/day) for up to 22 days. Exposure to cobalt resulted in the development of polycythemia in all six patients, with increases in red blood cell numbers ranging from 0.5 to 1.19 million (~16–20% increase above pre-treatment levels). Polycythemic erythrocyte counts returned to normal 9–15 days after cessation of cobalt administration. An 8–week study in rats (Stanley et al. 1947) also reported increases in erythrocyte number, with a no-observed-effect-level (NOEL) of 0.6 mg/kg-day and a lowest-observed-effect-level (LOEL) of 1 mg/kg/day. The intermediate oral MRL was derived by dividing the LOAEL of 1 mg Co/kg-day by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Oral MRL values were not derived for acute or chronic exposure to cobalt. An acute MRL was not derived because the reported effects in animals were serious and occurred at levels above those reported in the few human oral studies. No chronic oral studies were available in animals; the chronic studies of beer-cobalt cardiomyopathy (Alexander 1969, 1972; Bonenfant et al. 1969; Morin et al. 1967, 1971; Sullivan et al. 1969) were not used because the effects were serious (death) and because the effects of concurrent alcoholism were not controlled for. Therefore, a chronic oral MRL was not derived for cobalt.

MRLs for External Exposure to Cobalt Isotopes

Two MRLs have been derived for ionizing radiation (Agency for Toxic Substances and Disease Registry 1999) and are applicable to external exposure to radioisotopes of cobalt:

- An MRL of 400 mrem (4.0 mSv) has been derived for acute-duration external exposure to ionizing radiation (14 days or less).

The acute MRL is based on results of a study by Schull et al. (1988) in which neurological effects of radiation, measured by intelligence test scores, were evaluated in children 10–11 years of age who had been exposed at critical stages of fetal development (gestation weeks 8–15) during the atomic bombing of Hiroshima and Nagasaki. When IQ scores were regressed on radiation dose estimates, IQ diminished linearly with increasing dose, resulting in an estimated decrease in IQ score of approximately 25 points per 100 rad (or 100 rem in dose equivalent) or 0.25 points/rem (25 points/Sv). To derive the MRL of 400 mrem (4.0 mSv), Agency for Toxic Substances and Disease Registry (1999) divided the dose associated with a predicted change of 0.25 IQ points/rem by an uncertainty factor of 3 (for human variability and/or the potential existence of sensitive populations). Agency for Toxic Substances and Disease Registry (1999) noted that a change in IQ points of 0.25 is less than the reported difference of 0.3 IQ points between separated and unseparated identical twins (Burt 1966).

The USNRC set a radiation exposure limit of 500 mrem (5 mSv) for pregnant working women over the full gestational period (USNRC 1991). For the critical gestational period of 8–15 weeks, Agency for Toxic Substances and Disease Registry believes that the acute MRL of 400 mrem (4 mSv) is consistent with the USNRC limit and could be applied to either acute (0–14-day) or intermediate (15–365-day) exposure periods.

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

The MRL is based on the BEIR V (1990) report that the average annual effective dose of ionizing radiation to the U.S. population is 360 mrem/year (3.6 mSv/year), a dose not expected to produce adverse noncancerous health effects. This dose is obtained mainly by naturally-occurring radiation from external sources, medical uses of radiation, and radiation from consumer products. An uncertainty factor of 3 (for human variability) was applied to the NOAEL of 360 mrem/year to derive the MRL of 100 mrem/year.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of cobalt. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. Section 3.2 contains a discussion of the chemical toxicity of stable cobalt; radiation toxicity associated with exposure to radioactive cobalt (primarily ^{60}Co) is discussed in Section 3.3. The chemical properties of stable and radioactive cobalt isotopes are identical and are described in Chapter 4.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

Section 3.2 discusses the chemical toxicity of stable cobalt. Radiation toxicity resulting from exposure to radioactive cobalt is discussed in Section 3.3.

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death,

or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

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

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

bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

Studies have shown that soluble cobalt compounds are generally more acutely toxic than insoluble cobalt compounds. When expressed in terms of the cobalt ion for the sake of comparison, however, the differences in lethality values from the available studies are within an order of magnitude and therefore do not warrant presentation in separate LSE tables and figures. Therefore, data regarding both soluble and insoluble cobalt compounds are presented in Tables 3-1, 3-2, and 3-3.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Conclusive evidence for human deaths related to inhalation exposure to cobalt has not been reported; however, results of several studies and case reports suggest a possible relationship between exposure and deaths from lung cancer and cardiomyopathy, respectively.

In general, available cohort studies in humans have not reported a significant increase in total mortality as a result of cobalt exposure. Several studies have noted increased mortality rates resulting from lung cancer following occupational exposure to cobalt, either as a mixture of cobalt compounds (Mur et al. 1987) or as hard metal, a metal alloy with a tungsten carbide and cobalt matrix (Lasfargues et al. 1994; Moulin et al. 1998). Fatal cases of hard metal disease (Figueroa et al. 1992; Ruokonen et al. 1996) and cardiomyopathy (Barborik and Dusek 1972) believed to have resulted from occupational cobalt exposure have also been reported. However, in the majority of these and other reported occupational studies, co-exposure to other substances was common, and was unable to be corrected for in the analysis.

Cobalt inhalation can be lethal in animals if exposure is sufficiently high or prolonged. The acute LC^{50} for a 30-minute inhalation exposure in rats was 165 mg cobalt/m^3 as cobalt hydrocarbonyl (Palmes et al. 1959). Exposure to 9 mg cobalt/m^3 as cobalt hydrocarbonyl for 6 hours/day, 5 days/week for

3 months resulted in 16 deaths out of 75 rats (Palmes et al. 1959). Death was reported in rats and mice exposed to 19 mg cobalt/m^3 (but not 1.9 mg cobalt/m^3) as cobalt sulfate over 16 days, but exposure to 11.4 mg cobalt/m^3 over 13 weeks was lethal only to mice and not to rats (Bucher et al. 1990; NTP 1991). Exposure to 1.14 mg cobalt/m^3 as cobalt sulfate for 104 weeks resulted in no increase in mortality in rats and mice of either sex (Bucher et al. 1999; NTP 1998). Lethal levels for each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No data were located regarding dermal effects in humans or animals after inhalation exposure to stable cobalt. Inhalation of stable cobalt by humans and/or animals resulted in respiratory, cardiovascular, hematological, hepatic, renal, endocrine, ocular, and body weight effects. For each effect, the highest NOAEL values and all reliable LOAEL values for each species and duration category are reported in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Hard metal is a metal alloy with a tungsten carbide and cobalt matrix. It is used to make cutting tools because of its hardness and resistance to high temperature. Studies (Davison et al. 1983; Harding 1950) suggest that cobalt (and not tungsten carbide) is the probable causative agent for the respiratory effects observed in hard metal workers (see Section 3.6).

The effects of chronic occupational exposure to cobalt and cobalt compounds on the respiratory system in humans are well-documented. These effects include respiratory irritation, diminished pulmonary function, wheezing, asthma, pneumonia, and fibrosis and occurred at exposure levels ranging from 0.007 to 0.893 mg cobalt/m^3 (exposure from 2 to 17 years) (Anttila et al. 1986; Davison et al. 1983; Demedts et al. 1984a, 1984b; Deng et al. 1991; Gennart and Lauwerys 1990; Gheysens et al. 1985; Hahtola et al. 2000; Hartung et al. 1982; Kusaka et al. 1986a, 1986b, 1996a, 1996b; Nemery et al. 1992; Raffn et al. 1988; Rastogi et al. 1991; Ruokonen et al. 1996; Shirakawa et al. 1988, 1989; Sprince et al. 1988; Sundaram et al. 2001; Swennen et al. 1993; Tabatowski et al. 1988; Van Cutsem et al. 1987; Zanelli et al. 1994). These effects have been observed in workers employed in cobalt refineries, as well as hard metal workers, diamond polishers, and ceramic dish painters (painting with cobalt blue dye).

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
	ACUTE EXPOSURE								
	Systemic								
1	Human	6 hr	Resp		0.038	(bronchial irritation, reduced FVC)			Kusaka et al. 1986b Hard Metal
2	Rat SD-Jcl	5 hr	Resp	2.72					Kyono et al. 1992 Metal
3	Rat SD-Jcl	4 d	Resp		2.12 M	(Slight damage to respiratory tissues, assessed by electron microscopy)			Kyono et al. 1992 Metal
4	Rat	30 min	Resp	7	26	(edema)	83	(severe edema)	Palmes et al. 1959 Hydrocarbonyl
	INTERMEDIATE EXPOSURE								
	Death								
5	Rat	16 d 5 d/wk 6 hr/d		1.9			19	(2/5 males died)	NTP 1991 Sulfate

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
6	Mouse	13 wk 5 d/wk 6 hr/d		3.8			11.4	(2 males died)	NTP 1991 Sulfate
	Systemic								
7	Rat	13 wk 5 d/wk 6 hr/d	Resp		0.11	(laryngial squamous metaplasia and polyps)	0.38	(chronic inflammation of larynx)	NTP 1991 Sulfate
			Cardio		11.4	(increase in severity of cardiomyopathy)			
			Hemato		1.14[b] M	(polycythemia)			
			Renal	11.4					
			Bd Wt		11.4	(15% lower body weight in males)			
8	Rat	3 mo 5 d/wk 7 h/d	Resp		9	(lung inflamm)			Palmes et al. 1959 Hydrocarbonyl
			Hemato		9[b]	(10% increase in hemoglobin)			
			Bd Wt	9					

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
9	Mouse	16d 5 d/wk 6 hr/d	Resp	0.2	1.9	(respiratory tract inflammation)	19	(necrosis)	NTP 1991 Sulfate
			Cardio	76					
			Gastro	76					
			Musc/skel	76					
			Hepatic				19	(necrosis)	
			Renal	76					
			Dermal	76					

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
10	Mouse	13 wk 5 d/wk 6 hr/d	Resp		0.11	(larynx metaplasia)	3.8 M	(acute inflam of nose)	NTP 1991 Sulfate
							1.14 F[c]	(acute inflam of nose)	
			Gastro	11.4					
			Hemato	11.4					
			Musc/skel	11.4					
			Hepatic	11.4					
			Renal	11.4					
			Dermal	11.4					
			Bd Wt		11.4	(13-20% decrease in body weight)			
11	Gn Pig (Hartley)	66 d	Resp				2.4 F	(Increased lung weight, increased retention of lavage fluid)	Camner et al. 1993 Chloride

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
12	Gn Pig	3 mo 5 d/wk 7 h/d	Hemato		9[b] (5% increase in hemoglobin)		Palmes et al. 1959 Hydrocarbonyl
13	Dog	3 mo 3d/wk 7h/d	Hemato	9			Palmes et al. 1959 Hydrocarbonyl
			Bd Wt		9 (wt loss)		
14	Rabbit	4 mo 5 d/wk 6 h/d	Resp		0.4 (moderate lung inflammation)	2 (severe lung inflammation)	Johansson et al. 1987
15	Rabbit	4 mo	Resp	0.5 M			Johansson et al. 1991 Chloride
16	Rabbit	4 mo	Resp		0.6 M (Histologic alterations in pulmonary tissue; altered BAL parameters)		Johansson et al. 1992 Chloride

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
17	Pig	3 mo 5d/wk 6hr/d	Resp		0.1 (decr compliance)		Kerfoot 1975 Metal
			Cardio		0.1 (EKG changes)		
			Hepatic	1			
			Renal	1			
			Bd Wt		0.1 (decr wt gain)		
	Immuno/ Lymphoret						
18	Rat	16 d 5 d/wk 6 hr/d			19 (necrosis of thymus)		NTP 1991 Sulfate
19	Mouse	13 wk 5 d/wk 6 hr/d			11.4 (lymph node hyperplasia)		NTP 1991 Sulfate
	Neurological						
20	Rat	16 d 5 d/wk 6 hr/d			19 (congestion of vessels in brain)		NTP 1991 Sulfate
21	Mouse	16 d 5 d/wk 6 hr/d			19 (congestion of vessels in brain)		NTP 1991 Sulfate

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
	Reproductive						
22	Rat	16 d 5 d/wk 6 hr/d				19 M (testes atrophy)	NTP 1991 Sulfate
23	Mouse	13 wk 5 d/wk 6 hr/d			1.14 M (decreased sperm motility)	11.4 (testes atrophy- increased length estrous cycle)	NTP 1991 Sulfate
	CHRONIC EXPOSURE						
	Systemic						
24	Human	occup (occup)	Resp	0.0175			Deng et al. 1991 Metal
25	Human	occup (occup)	Resp		0.1355 (Decreased FEV1 and FVC ~10%; increased cough, sputum, dyspnea)		Gennart and Lauwerys 1990 Hard-Metal
26	Human	occup (occup)	Resp	0.0053[d]	0.0151 (Decreased FEV1, FVC increased cough and upper airway irritation)		Nemery et al. 1992 Metal
27	Human	occup (occup)	Endocr		0.05 F (Decreased thyroid volume; increases in T4 and FT4I levels)		Prescott et al. 1992 Zinc-Silicate Dye

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
28	Human	occup	Resp				0.007	(asthma)	Shirakawa et al. 1988 Hard Metal
29	Human	occup	Resp				0.051	(interst lung dis)	Sprince et al. 1988 Hard Metal
30	Human	8 yr (occup)	Resp		0.125	(Dyspnoea and wheezing)			Swennen et al. 1993 Metal
			Hemato		0.125	(Decreased red cell counts ~5%; decreased total hemoglobin ~4%)			
			Endocr		0.125	(Slight (~7%) decrease in T3 levels)			
			Dermal		0.125	(Eczema and erythema)			
31	Rat (Fischer- 344)	104 wk	Resp				0.11	(Hyper- and metaplasia of respiratory tract tissues; pulmonary fibrosis)	NTP 1998 Sulfate
32	Mouse (B6C3F1)	104 wk	Resp		0.11	(Laryngial metaplasia)			NTP 1998 Sulfate

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
33	Hamster	life 5d/wk 7h/d	Resp			7.9 (emphysema)	Wehner et al. 1977 Oxide
			Bd Wt	7.9			
	Immuno/ Lymphoret						
34	Human	occup			0.007 (sensitization)		Shirakawa et al. 1986a Hard Metal
35	Human	8 yr (occup)			0.125 (Increased white cell count by 19%)		Swennen et al. 1993 Metal
	Cancer						
36	Rat (Fischer- 344)	104 wk				1.14 M (alveoloar/bronchiolar neoplasms)	NTP 1998 Sulfate
						1.14 F (pheochromocytoma)	
						0.38 F (alveoloar/bronchiolar neoplasms)	

Table 3-1 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL			Reference Chemical Form
					Less Serious (mg/m³)		Serious (mg/m³)	
37	Mouse (B6C3F1)	104 wk					1.14 M (Combined alveolar/bronchiolar adenoma/carcinoma)	NTP 1998 Sulfate
							0.38 F (Combined alveolar/bronchiolar adenoma/carcinoma)	

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

[b] An increase in hemoglobin or red blood cells (polycythemia) is not necessarily considered an adverse effect.

[c] Differences in levels of health effects and cancer effect between males and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

[d] Used to derive a chronic inhalation Minimal Risk level (MRL) of 0.0001 mg Co/m3., dose adjusted for intermittent exposure, and divided by an uncertainty factor of 10 (for human variability).

Bd = body weight; Cardio = cardiovascular, d = day(s); Derm = dermal; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; (occup) = occupational; Resp = respiratory; wk = week(s); yr = year(s).

Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation

Acute (≤14 days)

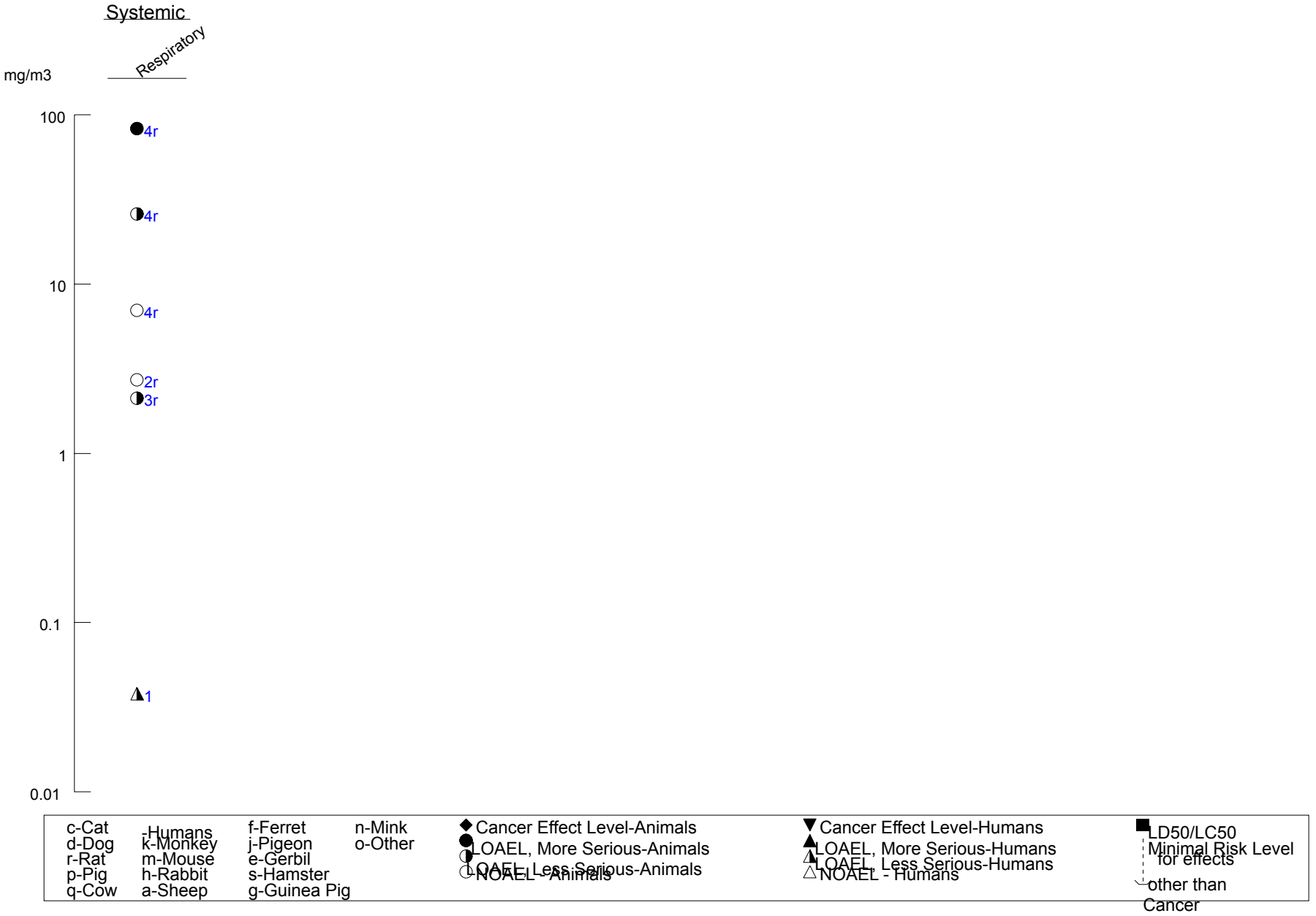


Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (*Continued*)

Intermediate (15-364 days)

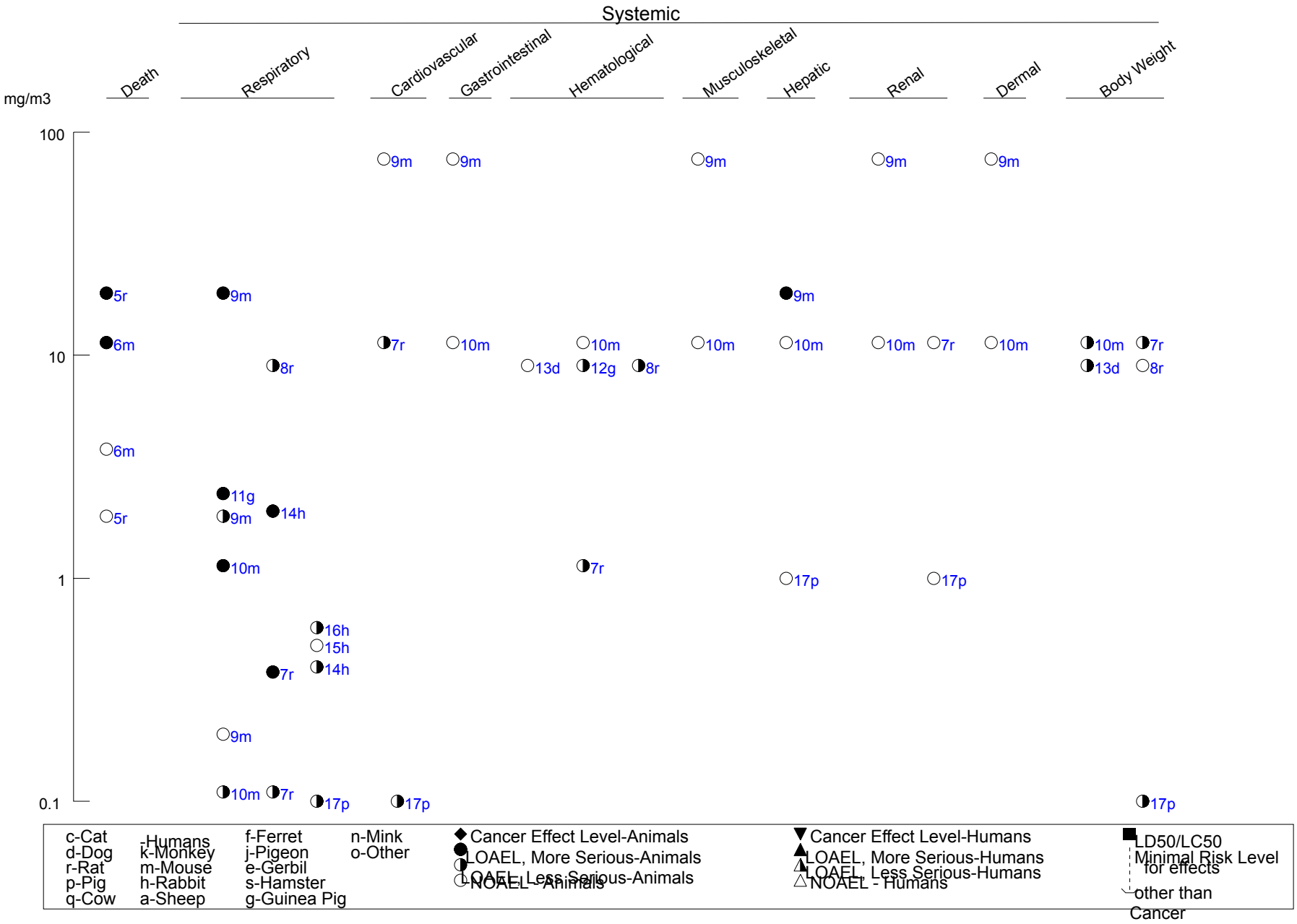


Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (*Continued*)

Intermediate (15-364 days)

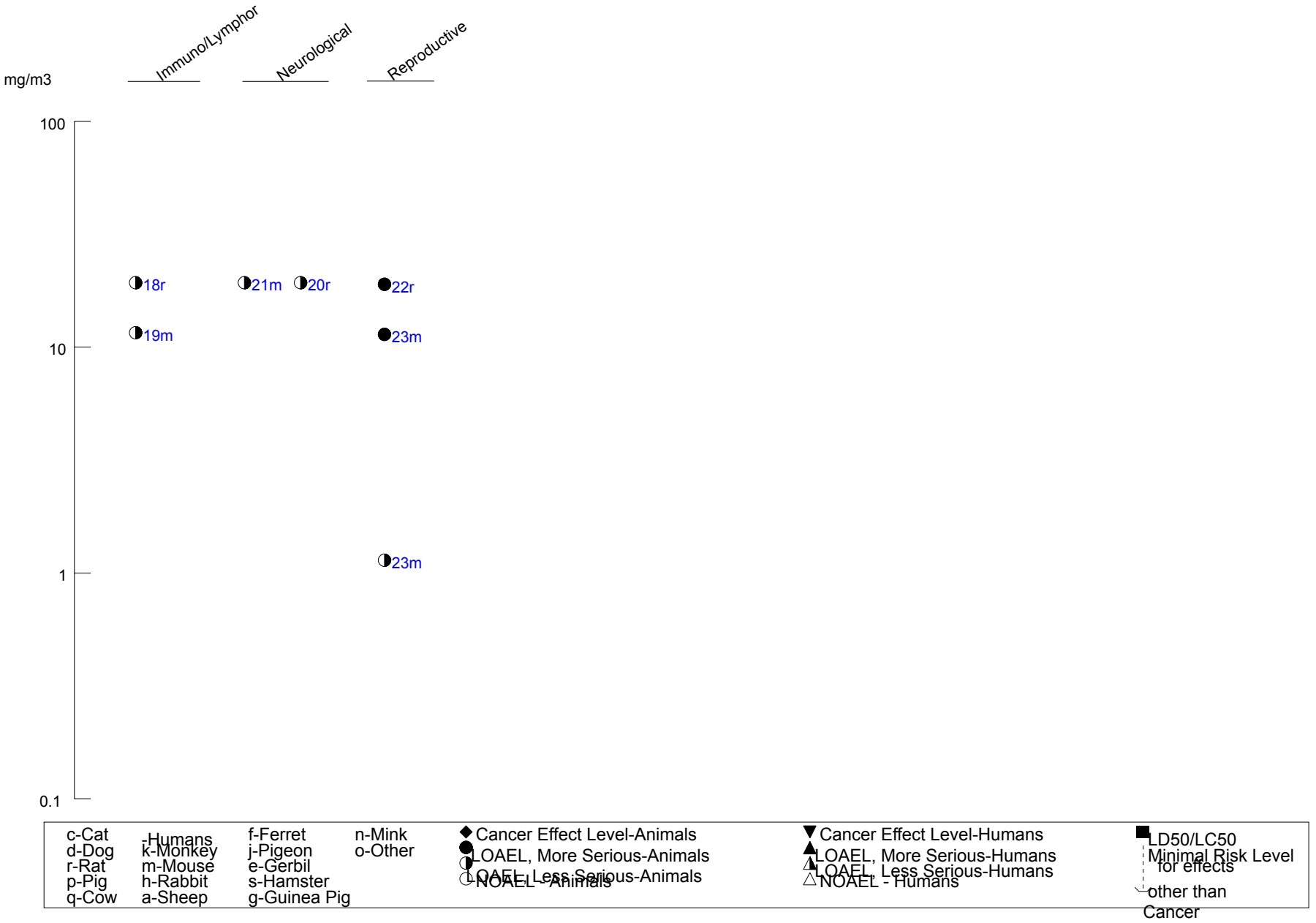
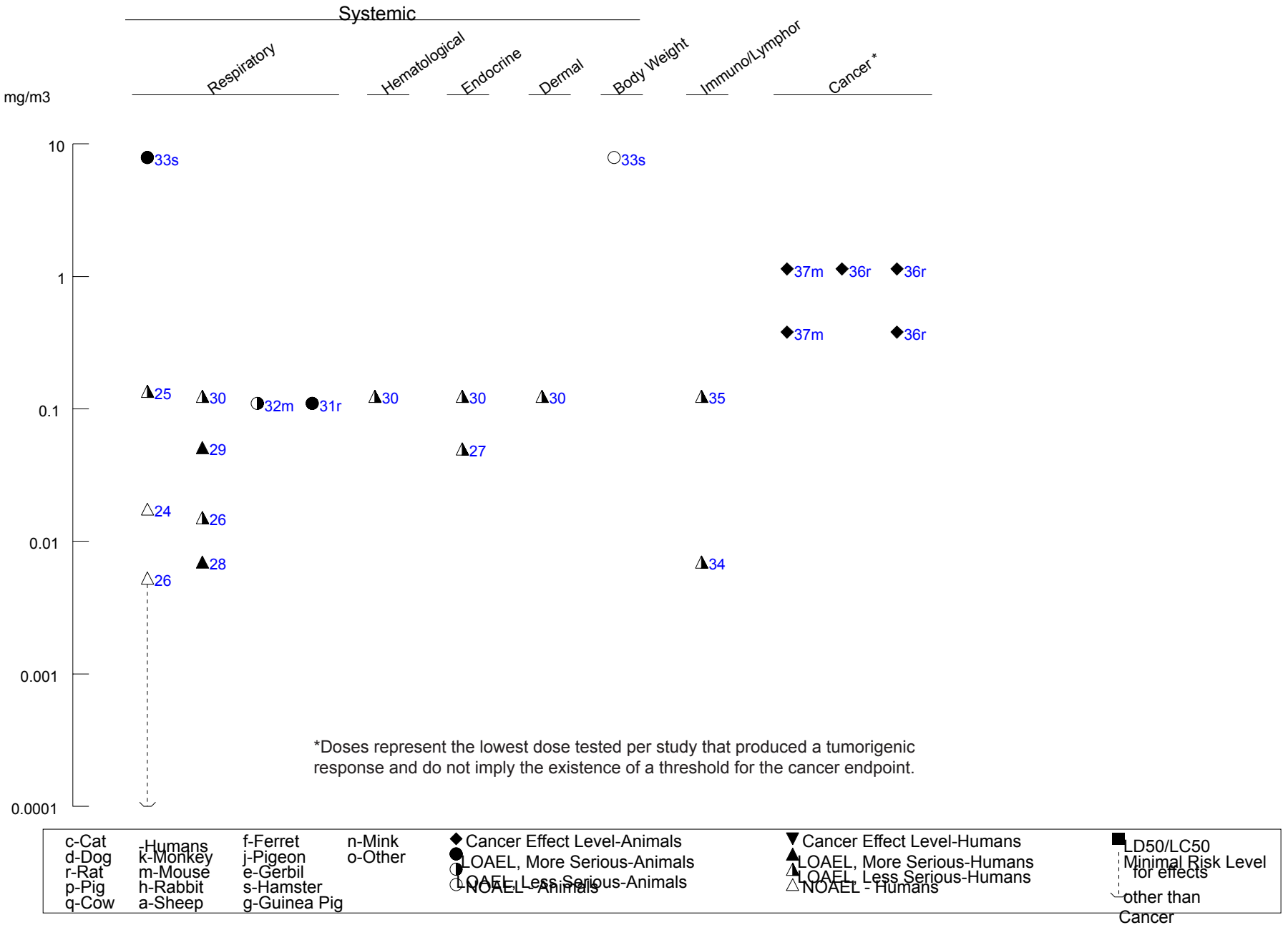


Figure 3-1. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Inhalation (*Continued*)

Chronic (≥365 days)



Kusaka et al. (1986b) described an acute exposure of 15 healthy young men to atmospheres of hard metal dust containing 0.038 mg cobalt/m^3 for 6 hours. Forced vital capacity (FVC) was reduced, but no dose-response relation could be discerned. By contrast, 42 workers occupationally exposed to hard metal showed no decrease in ventilatory function at 0.085 mg cobalt/m^3, but significant changes in FEV_1 (forced expiratory volume in 1 second) at 0.126 mg cobalt/m^3 (Kusaka et al. 1986b). Several other studies of hard metal workers have shown respiratory effects, including decreased ventilatory function, wheezing, asthma, and fibrosis (Kusaka et al. 1996a, 1996b; Ruokonen et al. 1996; Zanelli et al. 1994), but have had less complete reports of exposure.

Swennen et al. (1993) performed a cross-sectional study on 82 workers in a cobalt refinery. Workers were examined for cobalt in blood and urine, a number of erythropoietic variables, thyroid metabolism, pulmonary function, skin lesions, and several serum enzymes. The concentrations of cobalt in blood and in urine after the shift were significantly correlated with those in air. Workers exposed to airborne cobalt metal, salts, or oxides (mean concentration 0.125 mg/m^3, range 0.001–7.7 mg/m^3) showed an increased ($p<0.05$) prevalence of dyspnea and wheezing and had significantly more skin lesions (eczema, erythema) than control workers. A dose-effect relation was found between the reduction of the FEV_1 and the intensity of the current exposure to cobalt, as assessed by measurement of cobalt in blood, air, or urine.

Gennart and Lauwerys (1990) examined the ventilatory functions of 48 diamond polishing workers, relative to 23 control workers. Exposure occurred mainly in one of two rooms, with mean airborne concentrations of 0.0152 and 0.1355 mg cobalt/m^3; control subjects worked in other areas of the facilities, where no exposure to cobalt occurred. Significant decreases in ventilatory function were found in the exposed workers relative to the control workers. Duration of exposure played a significant factor, with no significant differences in workers who had been exposed for ≤5 years; reported decreases in ventilatory function were noted in workers exposed for > 5 years. Inhalation exposure to cobalt salts (exposure levels not reported) among glass bangle workers resulted in decreases in decreased ventilatory function, generally restrictive in nature, relative to controls (Rastogi et al. 1991).

Nemery et al. (1992) conducted a cross-sectional study of cobalt exposure and respiratory effects in diamond polishers. Exposure occurred mainly from the generation of airborne cobalt resulting from the use of cobalt-containing polishing discs. The study groups were composed of 194 polishers working in 10 different workshops, and were divided into control, low-, and high-exposure groups. The low-exposure group (n=102) was exposed to an average of 0.0053 mg cobalt/m^3, based on personal sampling

measurements, while the exposure level for the high dose group (n=92) was 0.0151 mg cobalt/m^3; there was considerable overlap in the total range of concentrations for the low- and high-exposure groups. Workers in the high-exposure group were more likely than those in the other groups to complain about respiratory symptoms; the prevalence of eye, nose, and throat irritation and cough, as well as the fraction of these symptoms related to work, were significantly increased in the high-exposure group. Workers in the high-exposure group also had significantly reduced lung function compared to controls and low-exposure group workers, as assessed by FVC, FEV_1, MMEF (forced expiratory flow between 25 and 75% of the FVC) and mean PEF (peak expiratory flow rate). Results in the low-exposure group did not differ from controls. Based on the NOAEL of 0.0053 mg cobalt/m^3 for decreased ventilatory function in exposed workers, a chronic inhalation MRL of 1x10-4 mg cobalt/m^3 was calculated as described in footnote (d) in Table 3-1. It should be noted that this MRL value may not be protective for some hypersensitive individuals.

As with exposures in humans, exposures of animals to cobalt-containing aerosols have resulted in pronounced respiratory effects. Animals exposed to aerosols of cobalt oxides and cobalt sulfate developed respiratory effects that varied in severity with exposure level and duration. A single 30-minute exposure of rats to relatively high levels (26–236 mg cobalt/m^3 as cobalt hydrocarbonyl) resulted in congestion, edema, and hemorrhage of the lung (Palmes et al. 1959). Prolonged exposure (3–4 months) of rats and rabbits to mixed cobalt oxides (0.4–9 mg cobalt/m^3) resulted in lesions in the alveolar region of the respiratory tract characterized histologically by nodular accumulation of Type II epithelial cells, accumulations of enlarged highly vacuolated macrophages, interstitial inflammation, and fibrosis (Johansson et al. 1984, 1987, 1991, 1992; Kyono et al. 1992; Palmes et al. 1959). In at least one instance, the lesions appeared to regress when exposure was terminated (Palmes et al. 1959). Guinea pigs sensitized to cobalt by repeated dermal application and then exposed to 2.4 mg cobalt/m^3 as cobalt chloride showed pulmonary inflammatory changes (altered BAL fluid recovery, increased neutrophils and eosinophils in the recovered BAL fluid) that were different than those in exposed animals not sensitized to cobalt (Camner et al. 1993). Decreased lung compliance was found in pigs exposed to 0.1 mg cobalt/m^3 as cobalt dust for 3 months (Kerfoot 1975). Lifetime exposure of hamsters to 7.9 mg cobalt/m^3 as cobalt oxide resulted in emphysema (Wehner et al. 1977).

Necrosis and inflammation of the respiratory tract epithelium (nasal turbinates, larynx, trachea, bronchioles) were reported in rats exposed to 19 mg cobalt/m^3 and mice exposed to 1.9 mg cobalt/m^3 or greater as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991). Exposure of rats and mice to

cobalt as cobalt sulfate for 13 weeks resulted in adverse effects on all parts of the respiratory tract, with the larynx being the most sensitive part (Bucher et al. 1990; NTP 1991). At concentrations of ≥0.11 mg cobalt/m^3, rats and mice developed squamous metaplasia of the larynx. Histiocytic infiltrates in the lung were also reported at similar levels in both the rats and mice. In rats, chronic inflammation of the larynx was found at ≥0.38 mg cobalt/m^3, and more severe effects on the nose, larynx, and lung were reported at higher exposures. In mice, acute inflammation of the nose was found at ≥1.14 mg cobalt/m^3, and more severe effects on the nose, larynx, and lung were reported at higher exposures. Exposure of rats and mice to aerosols of cobalt (as cobalt sulfate) at concentrations from 0.11 to 1.14 mg cobalt/m^3 for 2 years resulted in a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice (Bucher et al. 1999; NTP 1998). Squamous metaplasia of the larynx occurred in rats and mice at exposure concentrations of ≥0.11 mg cobalt/m^3, with severity of the lesion increasing with increased cobalt concentration. Hyperplastic lesions of the nasal epithelium occurred in rats at concentrations of ≥0.11 mg cobalt/m^3, and in mice at concentrations of ≥0.38 mg cobalt/m^3. Both sexes of rats had greatly increased incidences (>90% incidence) of alveolar lesions at all exposure levels, including inflammatory changes, fibrosis, and metaplasia. Similar changes were seen in mice at all exposure levels, though the changes in mice were less severe.

Cardiovascular Effects. Occupational exposure of humans to cobalt-containing dust, either as cobalt metal or as hard metal, has been shown to result in cardiomyopathy, characterized by functional effects on the ventricles (Horowitz et al. 1988) and/or enlargement of the heart (Barborik and Dusek 1972; Jarvis et al. 1992), but the exposure levels associated with cardiac effects of inhaled cobalt in humans have not been determined. Jarvis et al. (1992) reported on two patients (exposure histories not specified) who had been admitted to the emergency room for cardiac failures; these failures were believed to be associated with cobalt exposure. Barborik and Dusek (1972) reported a case of a 41-year-old man who was admitted to the hospital with cardiac failure following occupational exposure to cobalt; cobalt concentrations in heart, liver, lung, spleen, and kidney were elevated over two control patients. Horowitz et al. (1988) reported that in a cohort of 30 hard metal workers (exposure histories not specified), significant decreases in exercise right ventricular ejection fraction (EF) were seen in workers with abnormal chest x-rays relative to those with normal chest x-rays. It is possible that these effects were secondary to the respiratory effects of inhaled cobalt. It was concluded that cobalt is a weak cardiomyopathic agent following occupational exposure (Horowitz et al. 1988). Cardiomyopathy is a characteristic toxic effect of cobalt following oral exposure in both humans and animals (Section 3.2.2.2).

In rats, exposure to 11.4 mg cobalt/m^3 as cobalt sulfate over 13 weeks resulted in a marginal increase in the severity of cardiomyopathy as compared to controls (minimal-mild in treated animals versus minimal in controls; 3/10 animals affected in either group) (Bucher et al. 1990; NTP 1991). Cardiomyopathy was not observed in mice exposed to ≤76 mg cobalt/m^3 as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991), nor in mice or rats exposed to up to 1.14 mg cobalt/m^3 for 2 years (Bucher et al. 1999; NTP 1998). Electrocardiogram abnormalities that may reflect ventricular impairment have been observed in miniature swine (n=5) exposed to 0.1 mg cobalt dust/m^3 for 6 hours/day, 5 days/week for 3 months (Kerfoot 1975).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to stable cobalt.

No histological lesions were reported in the esophagus, stomach, duodenum, ileum, jejunum, cecum, colon, or rectum of rats or mice of either sex exposed to 76 mg cobalt/m^3 or less as cobalt sulfate for 16 days, up to 11.4 mg cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998).

Hematological Effects. Swennen et al. (1993) reported slightly, but statistically significantly, decreased levels of red cells and total hemoglobin (~4–5% decreases) in a group of 82 workers occupationally exposed to a mean concentration of 0.125 mg cobalt/m^3 as cobalt metal dust. No other studies were located regarding hematological effects in humans after inhalation exposure to cobalt.

Increased levels of hemoglobin and increased numbers of basophils and monocytes have been observed in rats and guinea pigs, but not in dogs, exposed to 9 mg cobalt/m^3 as cobalt hydrocarbonyl for 3 months (Palmes et al. 1959). Polycythemia was reported in rats, but not mice, exposed to 1.14 mg cobalt/m^3 as cobalt sulfate for 13 weeks (Bucher et al. 1990; NTP 1991).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to cobalt.

No histological lesions were reported in the sternebrae (segments of the sternum), including the bone marrow, of rats or mice exposed to ≤76 mg cobalt/m^3 as cobalt sulfate for 16 days, up to 11.4 mg

cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998) (see the above section on respiratory effects for detailed descriptions of exposure conditions).

Hepatic Effects. Congestion of the liver was observed upon autopsy of a metal worker (exposure history not reported) who had been occupationally exposed to an unknown level of cobalt for 4 years (Barborik and Dusek 1972). The cause of death was determined to be cardiomyopathy.

Necrosis and congestion of the liver were observed in both rats and mice that died following exposure to 19 mg cobalt/m^3 as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991). No histological effects on the liver were found in pigs exposed to up to 1.0 mg cobalt/m^3 as cobalt metal dust for 3 months (Kerfoot 1975).

Renal Effects. Congestion of the kidneys was observed upon autopsy of a metal worker who had been occupationally exposed to an unknown level of cobalt for 4 years (Barborik and Dusek 1972). The cause of death was determined to be cardiomyopathy.

A significant increase in the relative weight of the kidneys was reported in male rats exposed to 0.11 mg cobalt/m^3 or greater as cobalt sulfate for 13 weeks (Bucher et al. 1990; NTP 1991). No effects were observed upon histological examination of the kidneys in rats or mice following exposure to ≤76 mg cobalt/m^3 as cobalt sulfate for 16 days, up to 11.4 mg cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998). No histological effects on the kidneys were found in pigs exposed to up to 1.0 mg cobalt/m^3 as cobalt metal for 3 months (Kerfoot 1975).

Dermal Effects. No studies were located regarding dermal effects in humans or animals after inhalation exposure to stable cobalt.

Endocrine Effects. A group of female workers occupationally exposed to a semisoluble cobalt glaze (cobalt-zinc silicate, estimated concentrations of 0.05 mg Co/m^3) showed significantly elevated levels of serum thyroxine (T4) and free thyroxine, but no change in T3 levels (Prescott et al. 1992). In contrast to this, Swennen et al. (1993) reported no significant change in serum T4 levels, but a significant reduction in serum T3 in workers occupationally exposed to cobalt oxides, cobalt salts, and cobalt metal.

Ocular Effects. Congestion of the conjunctiva was observed in a metal worker after occupational exposure to an unknown level of cobalt for 4 years (Barborik and Dusek 1972); however, due to the nature of the exposure, this effect may also have been the result of direct dermal or ocular contact. Upon autopsy, the cause of death was determined to be cardiomyopathy.

No histological lesions were reported in the eyes or on the skin of rats or mice exposed to ≤76 mg cobalt/m^3 as cobalt sulfate for 16 days, up to 11.4 mg cobalt/m^3 for 13 weeks, or up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1990, 1999; NTP 1991, 1998).

Body Weight Effects. Weight loss, measured individually from time of initial examination throughout followup, was observed in a group of five diamond polishers suffering from cobalt-induced interstitial lung disease (Demedts et al. 1984b), but the exposure level of cobalt was not reported.

Decreased body weight, relative to controls at study termination, was reported in both rats and mice exposed to 19 mg cobalt/m^3 as cobalt sulfate over 16 days or to 11.4 mg cobalt/m^3 for 13 weeks (Bucher et al. 1990; NTP 1991). A 13-week exposure to 11.4 mg cobalt /m^3 resulted in ruffled fur in male rats, with no clinical signs reported in female rats or either sex of mice (Bucher et al. 1990; NTP 1991). Chronic exposure of rats and mice to up to 1.14 mg cobalt/m^3 did not result in decreased body weight (Bucher et al. 1999; NTP 1998).

Weight loss was found in dogs, but not rats or guinea pigs, exposed for 3 months to cobalt at a level of 9 mg cobalt/m^3 as cobalt hydrocarbonyl (Palmes et al. 1959). Lifetime exposure of hamsters to a similar concentration (7.9 mg cobalt/m^3 as cobalt oxide) did not result in decreased body weight gain (Wehner et al. 1977).

3.2.1.3 Immunological and Lymphoreticular Effects

Cobalt is known to function as a hapten, resulting in the generation of antibodies against cobalt-protein complexes. Although the minimum exposure level associated with cobalt sensitization has not been determined, sensitization has been demonstrated in hard metal workers with work-related asthma who have experienced prolonged occupational exposure (>3 years) to levels ranging from 0.007 to 0.893 mg cobalt/m^3 (Shirakawa et al. 1988, 1989). The lower end of this range, 0.007 mg/m^3, is reported in

Table 3-1 and plotted in Figure 3-1 as a LOAEL. The sensitization phenomenon includes the production of IgE and IgA antibodies to cobalt (Bencko et al. 1983; Shirakawa et al. 1988, 1989). Exposure to inhaled cobalt chloride aerosols can precipitate an asthmatic attack in sensitized individuals (Shirakawa et al. 1989), believed to be the result of an allergic reaction within the lungs.

Necrosis of the thymus was reported in rats exposed to 19 mg cobalt/m^3 as cobalt sulfate over 16 days, and hyperplasia of the mediastinal lymph nodes was found in mice exposed to 11.4 mg cobalt/m^3 for 13 weeks (Bucher et al. 1990; NTP 1991). Tests of immunological function, however, were not performed on the rats or mice.

3.2.1.4 Neurological Effects

Occupational exposure to cobalt in humans has been reported to cause several effects on the nervous system, including memory loss (Wechsler Memory Scale-Revised), nerve deafness, and a decreased visual acuity (Jordan et al. 1990; Meecham and Humphrey 1991). It should be noted, though, that both of these studies had small numbers of subjects (n=38 for Jordan et al. 1990, n=1 for Meecham and Humphrey 1991), and exposure characterization was not reported.

Congestion in the vessels of the brain/meninges was reported in rats and mice exposed to 19 mg cobalt/m^3 or greater as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991).

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to cobalt.

In animals, long-term exposure to cobalt-containing aerosols has resulted in effects on reproductive end points. Testicular atrophy was reported in rats, but not in mice, exposed to 19 mg cobalt/m^3 as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991). Following exposure of mice to cobalt (as cobalt sulfate) for 13 weeks, a decrease in sperm motility was found at 1.14 mg cobalt/m^3, and testicular atrophy was found at 11.4 mg cobalt/m^3. A significant increase in the length of the estrous cycle was reported in female mice exposed to 11.4 mg cobalt/m^3 for 13 weeks (Bucher et al. 1990; NTP 1991). No effects on

the male or female reproductive systems were observed in rats similarly treated for 13 weeks (Bucher et al. 1990; NTP 1991), or in mice or rats exposed to up to 1.14 mg cobalt/m^3 for 104 weeks (Bucher et al. 1999; NTP 1998).

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to cobalt.

3.2.1.7 Cancer

Several studies have evaluated the effects of inhalation of cobalt-containing compounds on possible carcinogenicity in humans. The mortality of a cohort of 1,143 workers in a plant that refined and processed cobalt and sodium was analyzed (Mur et al. 1987); the French national population mortality data were used as a reference population. An increase in deaths due to lung cancer was found in workers exposed only to cobalt (standardized mortality ratio [SMR] of 4.66; four cases in the exposed group versus one case in the controls). In a study within the cohort that controlled for date of birth, age at death, and smoking habits, 44% (four workers) in the group exposed to cobalt and 17% (three workers) in the group not exposed to cobalt died of lung cancer. The authors, however, indicated that the difference was not statistically significant and that the workers were exposed to both arsenic and nickel as well as cobalt. The nonneoplastic lung diseases commonly found in cobalt-exposed workers (see Section 3.2.1.2) were not reported in this group. These lung diseases may have been present in these workers, but if they were not listed as the cause of death on the death certificate, they would not have been mentioned. Inhalation was probably a prominent route of exposure to cobalt; however, oral and dermal exposure probably occurred as well. No adjustments were made for smoking habits in the larger study, and the exposure levels of cobalt were not reported for either study. However, a followup study of this cohort (Moulin et al. 1993) did not report significant increases in mortality due to respiratory or circulatory diseases. Similarly, no increase in the SMR for lung cancer was noted in exposed workers, relative to controls. While an elevated SMR for lung cancer was seen in maintenance workers (SMR=1.80, 95% confidence interval [CI]=0.78–3.55), it was not statistically significant, since the 95% confidence interval included an SMR of 1.

Lasfargues et al. (1994) reported on the mortality of a cohort of 709 male workers in a French hard metal plant, using the national rates for French males for comparison. The overall mortality did not differ from expected, but there was a significant increase in mortality due to cancer of the trachea, bronchus, and lung (SMR=2.13, 95% CI=1.02–3.93). Smoking alone did not account for the lung cancer excesses, although the influence of smoking on the observed mortality could not be entirely ruled out.

A cohort of 5,777 males and 1,682 females who were exposed occupationally to cobalt (concentrations ranging from 1 to 515 μg/m^3, means of exposure levels ranging from 39.37 to 169.0 μg/m^3) and tungsten carbide (as hard metal dust) was examined by Moulin et al. (1998). A significantly increased mortality rate (SMR=1.30, 95% CI=1.00–1.66) was seen for lung cancer in exposed workers, when compared to the national average. Within this study group, 61 cases and 180 controls were selected for a case-control study of cancer risk. When exposures during the last 10 years were ignored, presumably because cancer is a late-developing disease, a significant increase in lung cancer mortality (OR=1.93, 95% CI=1.03–3.62) relative to controls was seen among workers simultaneously exposed to cobalt and tungsten carbide. Significant trends for increasing cancer risk with increasing cumulative exposure and exposure duration were noted. Adjustments for smoking and for coexposures to other carcinogens did not change the results, though occupational risk was greatest among smokers.

A later study by the same group (Moulin et al. 2000) examined the lung cancer mortality of 4,288 male and 609 female workers employed in the production of stainless and alloyed steel from 1968 to 1992. No significant changes in mortality rate from lung cancer were seen among exposed workers (SMR=1.19, 95% CI=0.88–1.55), and a concurrent case control study identified no correlation between lung cancer excess and for exposure to cobalt (OR=0.64, 95% CI=0.33–1.25).

Wild et al. (2000) reported on a cohort of 2,216 male hard metal workers who had been employed for at least 3 months; this cohort was the same as that in Moulin et al. (2000), with some modifications. The total mortality was not increased in workers, relative to local mortality rates. However, lung cancer mortality was significantly increased (SMR=1.70, 95% CI=1.24–2.26). The risks increased with increasing exposure scores, even after adjustment for smoking and coexposure to other known or suspected carcinogens.

Inhalation exposure to 7.9 mg cobalt/m^3 as cobalt oxide intermittently for a lifetime did not increase the incidence of malignant or benign tumors in hamsters (Wehner et al. 1977).

NTP (1998) exposed groups of rats and mice of both sexes to 0, 0.11, 0.38, or 1.14 mg cobalt/m^3 as cobalt sulfate for 2 years. Increased incidence of alveolar/bronchiolar neoplasms was noted following lifetime exposure of male rats to 1.14 mg cobalt/m^3 and in female rats exposed to 0.38 mg cobalt/m^3 (Bucher et al. 1999; NTP 1998). Statistical analysis revealed that tumors occurred with significantly positive trends in both sexes of rats. Similarly, mice of both sexes exposed to 1.14 mg cobalt/m^3 showed an increase in alveolar/bronchiolar neoplasms, again with lung tumors occurring with significantly positive trends.

3.2.2 Oral Exposure

3.2.2.1 Death

In several studies, lethal cardiomyopathy was reported in people who consumed large quantities of beer containing cobalt sulfate (Alexander 1969, 1972; Bonenfant et al. 1969; Morin et al. 1967, 1971; Sullivan et al. 1969). The deaths occurred during the early to mid 1960s, at which time, breweries in Canada, the United States, and Europe were adding cobalt to beer as a foam stabilizer (Alexander 1969, 1972; Bonenfant et al. 1969; Morin et al. 1967, 1971; Sullivan et al. 1969); this practice has been discontinued. Deaths occurred following ingestion of beer containing 0.04–0.14 mg cobalt/kg/day for a period of years (approximately 8–30 pints of beer each day). "Acute mortality" (death within several days of admission) accounted for 18% of the deaths (Alexander 1972). Approximately 43% of the patients admitted to the hospital with cardiomyopathy died within several years of the initial hospital visit. It should be noted, however, that the cardiomyopathy may have also been due to the fact that the beer-drinkers had protein-poor diets and may have had prior cardiac damage from alcohol abuse.

Treatment of both pregnant and nonpregnant anemic patients with doses of cobalt (0.6–1 mg/kg/day) that were much higher than the doses in the beer did not result in mortality (Davis and Fields 1958; Holly 1955). A 19-month-old male child who swallowed an unknown amount of a cobalt chloride solution died approximately 6.5 hours after ingestion, despite repeated induced vomiting, gastric lavage, and supportive therapy (Jacobziner and Raybin 1961).

Oral LD_{50} values for several cobalt compounds have been determined in Wistar rats (FDRL 1984a, 1984b, 1984c; Singh and Junnarkar 1991; Speijers et al. 1982). The LD_{50} values ranged from 42.4 mg cobalt/kg as cobalt chloride to 317 mg cobalt/kg as cobalt carbonate. An LD_{50} of 3,672 mg cobalt/kg was also found for tricobalt tetraoxide, a highly insoluble cobalt compound (FDRL 1984c). The exact cause of death in rats is unknown, but effects on the heart, liver, gastrointestinal tract, and kidneys have been observed. In Sprague-Dawley rats, death has been reported to occur at 161 mg cobalt/kg given by gavage as cobalt chloride (Domingo and Llobet 1984). In male Swiss mice, the LD_{50} values for cobalt chloride and cobalt sulfate have been reported to be 89.3 and 123 mg cobalt/kg, respectively (Singh and Junnarkar 1991).

Following 5 weeks of exposure to 20 mg cobalt/kg/day as cobalt sulfate by gavage, 20–25% of the guinea pigs died (Mohiuddin et al. 1970). The animals were given cobalt sulfate alone or in combination with ethanol (as part of a liquid diet) to compare the effects seen in animals to those seen in humans suffering from beer-cobalt cardiomyopathy. Although effects on the heart were found in the treated animals, alcohol did not appear to intensify the toxic effect.

The LD_{50} and all reliable LOAEL values for each species and duration category are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

Oral cobalt exposure in humans and/or animals resulted in respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, dermal, ocular, hypothermic, and body weight effects. For each effect, the highest NOAEL values and all reliable LOAEL values for each species and duration category are reported in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. In 50 patients with beer-cobalt cardiomyopathy, pulmonary rales and pulmonary edema were observed and were attributed to cobalt-induced cardiac failure (Morin et al. 1971). These patients had ingested, over a period of years, an average of 0.04 mg cobalt/kg/day in beer containing cobalt sulfate that was added to stabilize the foam. It should be noted that these patients consumed significant quantities of alcohol, and the effect that this may have had on the symptoms seen is not known.

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	1x (GW)				161.1 (LD50)	Domingo and Llobet 1984 Chloride
2	Rat (Wistar)	1x (GW)				42.4 (LD50)	Singh and Junnarkar 1991 Chloride
3	Rat (Wistar)	1x (GW)				194 (LD50)	Singh and Junnarkar 1991 Sulfate
4	Rat (Wistar)	1 x (GO)				91 (LD50)	Speijers et al. 1982 Fluoride
5	Rat (Wistar)	1 x (GO)				187 (LD50)	Speijers et al. 1982 Phosphate
6	Rat (Wistar)	1 x (GW)				109 (LD50)	Speijers et al. 1982 Bromide
7	Rat (Wistar)	1 x (GO)				159 (LD50)	Speijers et al. 1982 Oxide

Table 3-2 Levels of Significant Exposure to Cobalt - 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)		
8	Rat (Wistar)	1 x (GW)					168	(LD50)	Speijers et al. 1982 Acetate
9	Rat (Wistar)	1 x (GW)					190	(LD50)	Speijers et al. 1982 Chloride
10	Rat (Wistar)	1 x (GW)					140	(LD50)	Speijers et al. 1982 Bromide
11	Rat (Wistar)	1 x (GW)					161	(LD50)	Speijers et al. 1982 Sulfate
12	Mouse (Swiss-Webster)	1x (GW)					123	(LD50)	Singh and Junnarkar 1991 Sulfate
13	Mouse (Swiss-Webster)	1x (GW)					89.3	(LD50)	Singh and Junnarkar 1991 Chloride
	Systemic								
14	Human	2 wk (C)	Endocr		1	(decreased Iodine uptake in thyroid)			Roche and Layrisse 1958 Chloride

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
15	Rat	1x (GW)	Hemato		161.1[b]	(increased hematocrit 8%)			Domingo and Llobet 1984 Chloride
16	Rat	1 x (GW)	Other	110	209	(Clinical signs, including decreased activity, ataxia, diarrhea, salivation)			FDRL 1984a Sulfate
17	Rat (Sprague-Dawley)	1 x (GO)	Other		149	(Decreased activity, diarrhea)			FDRL 1984b Carbonate
18	Rat (Wistar)	1x (GW)	Renal		19.4	(Increased urinary output)			Singh and Junnarkar 1991 Sulfate
19	Rat (Wistar)	1 x (GO)	Cardio	109.6			176.6	(proliferative interstitial tissues, swollen muscle fibers, focal myocardial degeneration)	Speijers et al. 1982 Fluoride
			Hepatic	42.6			68.2	(hyperemia)	
			Renal		42.6	(swollen proximal tubules)	176.6	(degeneration of proximal tubules)	
			Other				109.6	(hypothermia)	

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
20	Rat (Wistar)	1 x (GO)	Cardio			794.5 (hemorrhage)	Speijers et al. 1982 Oxide
			Hepatic			157.3 (hyperemia)	
			Renal			157.3 (hyperemia)	
			Other			157.3 (hypothermia)	
21	Mouse (Swiss-Webster)	48 hr (W)	Hemato		76.4 M (Alteration in electrophoretic profile of serum proteins)		Bryan and Bright, 1973 Chloride
22	Mouse (Swiss-Webster)	3 mo (W)	Hemato	76.4 M			Bryan and Bright, 1973 Chloride
	Neurological						
23	Rat (Wistar)	1x (GW)			19.4 (Mild depression of spontaneous activity, muscle tone, and respiration)		Singh and Junnarkar 1991 Sulfate

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
24	Rat (Wistar)	1x (GW)			4.25	(Mild depression of spontaneous activity, muscle tone, and respiration)			Singh and Junnarkar 1991 Chloride
	Developmental								
25	Rat	Gd 6-15 (GW)		24.8					Paternian et al. 1988 Chloride
26	Mouse	Gd 8-12 (GW)		81.7					Seidenberg 1986 Chloride
	INTERMEDIATE EXPOSURE								
	Death								
27	Human	NR (W)					0.04	(death)	Morin et al. 1971 Sulfate
28	Gn Pig	5 wk (F)					20	(death)	Mohiuddin et al. 1970 Sulfate
	Systemic								
29	Human	NR (W)	Cardio				0.07	(beer-cobalt cardiomyopathy)	Alexander 1972 Sulfate

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
30	Human	1x/d 25 d (C)	Hemato		1[c] (polycythemia)		Davis and Fields 1958 Chloride
31	Human	12-32 wk (C)	Gastro		0.18 (nausea)		Duckham and Lee 1976b Chloride
			Hemato		0.18[b] (increased hemoglobin, 23-102% increase)		
32	Human	90 d (C)	Gastro		0.5 (gastric intolerance)		Holly 1955 Chloride
			Hemato	0.6			
			Hepatic	0.6			
33	Human	NR (W)	Resp		0.04 (edema)		Morin et al. 1971 Sulfate
			Cardio			0.04 (beer-cobalt cardiomyopathy)	
			Gastro		0.04 (vomiting, nausea)		
			Hepatic		0.04 (necrosis)		

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
34	Human	10-25 d 1x/d (C)	Other		0.54 (decreased Iodine uptake)		Paley et al. 1958
35	Human	12-32 wk 7d/wk (C)	Hemato		0.16[b] (increased hemoglobin)		Taylor et al. 1977 Chloride
36	Rat (Sprague-Dawley)	4 wk (F)	Bd Wt		3.79 M (45-65% reduction in body weight gain)		Chetty et al. 1979 Chloride
37	Rat	8 wk 1x/d (F)	Bd Wt		4.2 (33% decrease in body weight gain)		Clyne et al. 1988

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Rat	3 mo (W)	Resp		30.2 (increased lung weight 33%)		Domingo et al. 1984
			Cardio		30.2 (increased heart weight 9.4%)		
			Gastro	30.2			
			Hemato		30.2 (increased hematocrit 29%)c		
			Musc/skel	30.2			
			Hepatic	30.2			
			Renal	30.2			
39	Rat	8 wk (F)	Cardio			26 (degeneration)	Grice et al. 1969
40	Rat (Sprague-Dawley)	24 wk (F)	Cardio			8.4 M (Left ventricular hypertrophy and impaired ventricular function)	Haga et al. 1996 Sulfate

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
41	Rat	4 mo (G)	Resp	18			Holly 1955 Chloride
			Cardio	18			
			Gastro	18			
			Hemato		18[b] (erythrocytosis)		
			Hepatic	18			
			Renal			18 (tubular necrosis)	
42	Rat	7 mo 6 d/wk (GW)	Hemato	0.05	0.5[b] (increased RBC, hemoglobin)		Krasovskii and Fridlyand 1971
			Hepatic	2.5			
43	Rat CFY	3 wk (G)	Cardio			12.4 M (Incipient, multifocal myocytolysis, with degeneration of myofibrilles)	Morvai et al. 1993 Chloride
			Bd Wt		12.4 M (Decreased body weight 8%)		

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
44	Rat	150 d 5 d/wk (GW)	Hemato		10[b] (increased hemoglobin)		Murdock 1959 Chloride
			Hepatic		10 (increased weight 17%)		
			Renal			10 (necrosis of tubular lining cells)	
			Bd Wt	10			
45	Rat (Sprague-Dawley)	8 wk	Hemato	8.4 M			Pehrsson et al. 1991 Sulfate
			Bd Wt			8.4 M (>20% decrease from appropriate control)	
46	Rat (Sprague-Dawley)	12-16 d (W)	Bd Wt	10.6 M			Saker et al. 1998 Chloride
			Metab		10.6 M (Decreased serum glucose levels in diabetic rats, but not control rats)		

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
47	Rat	6 wk 7 d/wk (C)	Hemato	0.6	2.5[b] (polycythemia)		Stanley et al. 1947 Chloride
48	Rat (Long- Evans)	3 d (F)	Bd Wt	20 M	100 M (<20% reduction of body weights)		Wellman et al. 1984 Chloride
49	Mouse Parkes	45 d (W)	Endocr			26 F (Necrosis and inflammation of thyroid)	Shrivastava et al. 1996 Chloride
50	Gn Pig	5 wk (F)	Cardio			20 (cardiomyopathy)	Mohiuddin et al. 1970
			Bd Wt	20			
51	Dog	4 wk 7 d/wk (F)	Hemato		5[b] (polycythemia)		Brewer 1940
	Immuno/ Lymphoret						
52	Rat (Sprague-Dawley)	4 wk (F)				3.79 M (Atrophy of the thymus)	Chetty et al. 1979 Chloride

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
53	Rat	7 mo 6 d/wk (GW)		0.05	0.5	(decreased phagocytic ability)			Krasovskii and Fridlyand 1971 Chloride
	Neurological								
54	Rat (Sprague-Dawley)	57 d (W)			20 M	(Increased latency during retention testing)			Bourg et al. 1985 Chloride
55	Rat	57 d (W)			20	(increased reactivity)			Bourg et al. 1985 Chloride
56	Rat	7 mo 6 d/wk (GW)		0.05	0.5	(mildly increased latent reflex)	2.5	(pronounced increase in latent reflex)	Krasovskii and Fridlyand 1971 Chloride
57	Rat (Wistar)	30 d (W)			4.96 M	(Alterations in sympathetically-induced contractility of vas deferens)			Mutafova-Yambolieva et al. 1994 Chloride
58	Rat	69 d (F)		5	20	(changes in schedule training, conditioned suppression, and mixed schedule training tests)			Nation et al. 1983

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
59	Rat (Wistar)	30 d (W)			6.44 M (Alterations in cholinergic sensitivity)		Vassilev et al. 1993 Nitrate
60	Rat (Long- Evans)	3 d (F)		20 M	100 M (Saccharin and food aversion)		Wellman et al. 1984 Chloride
	Reproductive						
61	Rat (Sprague-Dawley)	98 days (F)				20 M Pronounced histologic alteration of seminiferous tubules	Corrier et al. 1985 Chloride
62	Rat (Sprague-Dawley)	90 d (W)			30.2 M 26% decrease in testicular weight		Domingo et al. 1984 Chloride
63	Rat	98 d 7 d/wk (F)				13.25 (testicular degeneration)	Mollenhauer et al. 1985
64	Rat	69 d (F)		5		20 M (testicular atrophy)	Nation et al. 1983 Chloride

Table 3-2 Levels of Significant Exposure to Cobalt - 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)	
65	Mouse (CD-1)	13 wk (W)					43.4 M (Irreversible testicular degeneration)	Anderson et al. 1992 Chloride
66	Mouse (CD-1)	13 wk (W)					43.4 M (Testicular degeneration)	Anderson et al. 1993 Chloride
67	Mouse	13 wk (W)			23 (reversible testicular degeneration)			Pedigo et al. 1988 Chloride
68	Mouse (B6C3F1)	10 wk (W)					58.9 M (Reduced pregnant females and pups per litter; reduced fertility)	Pedigo et al. 1993 Chloride
	Developmental							
69	Human	90 d (C)		0.6				Holly 1955 Chloride

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
70	Rat	Gd 14- Ld 21 (G)				5.4 (stunted pup growth)	Domingo et al. 1985 Chloride

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

[b] An increase in hemoglobin or red blood cells is not necessarily considered an adverse effect.

[c] Used to derive an intermediate oral MRL; concentration was divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability), resulting in an MRL of 0.01 mg/kg/day.

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = female; (G) = gavage; Gd = gestation day; (GO) = gavage oil; (GW) = gavage-water, Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); Ld = lactation day; LD50 = dose producing 50% death; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; mo = month(s); NOAEL = no observed-adverse-effect level; NS = not specified; (W) = drinking water; wk = week(s); x = times.

Figure 3-2. Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral

Acute (≤14 days)

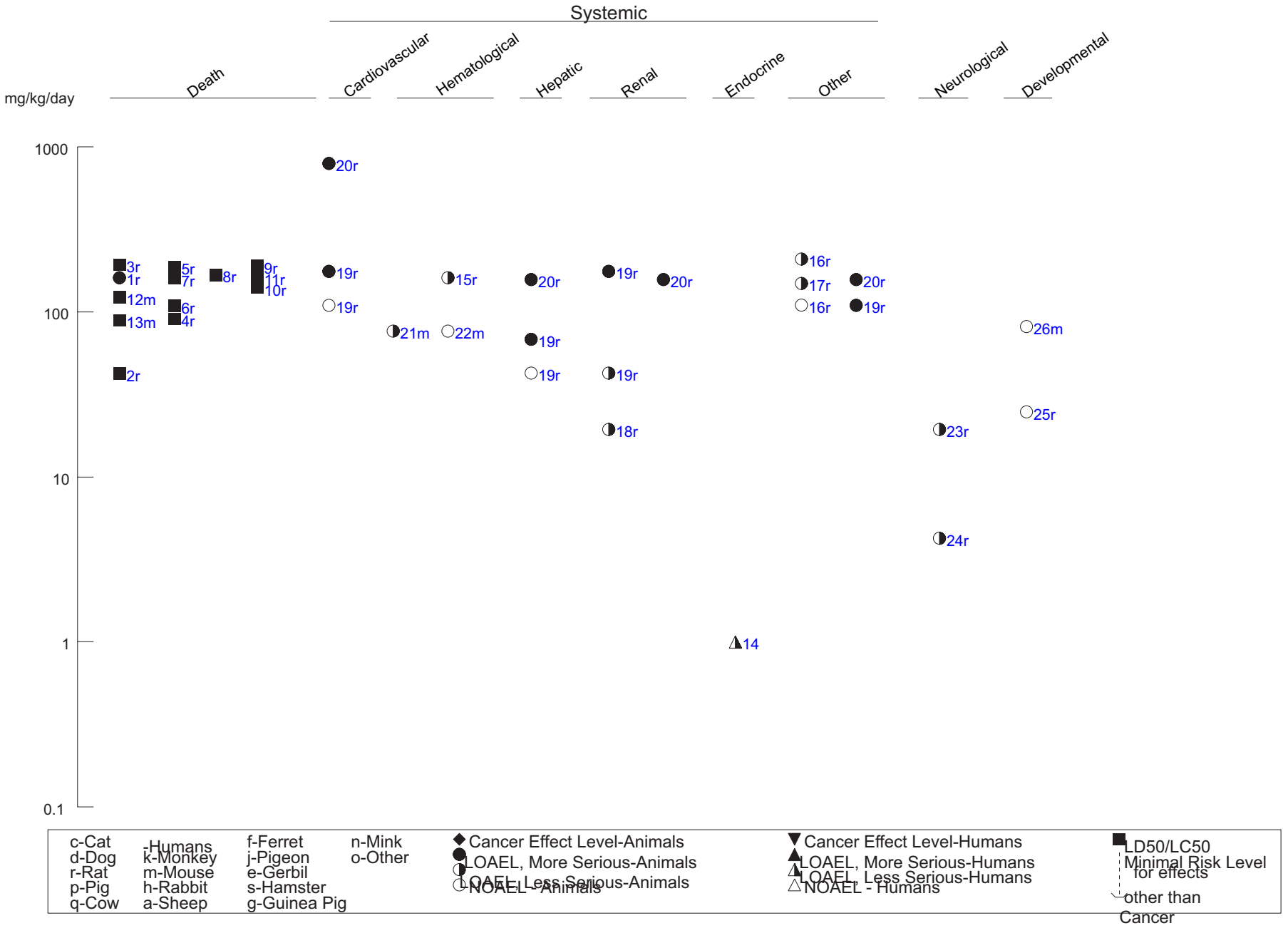


Figure 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (*Continued*)

Intermediate (15-364 days)

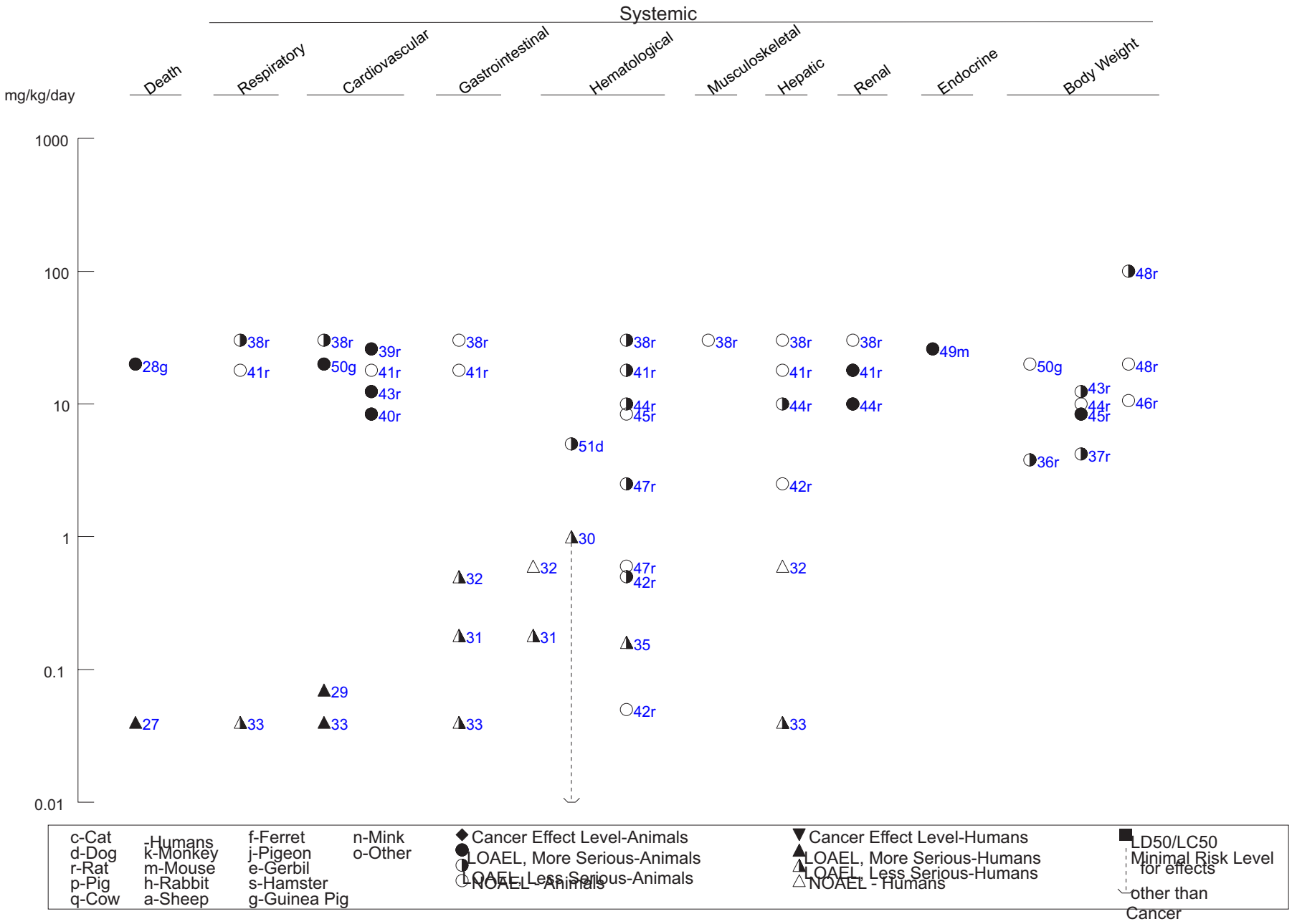
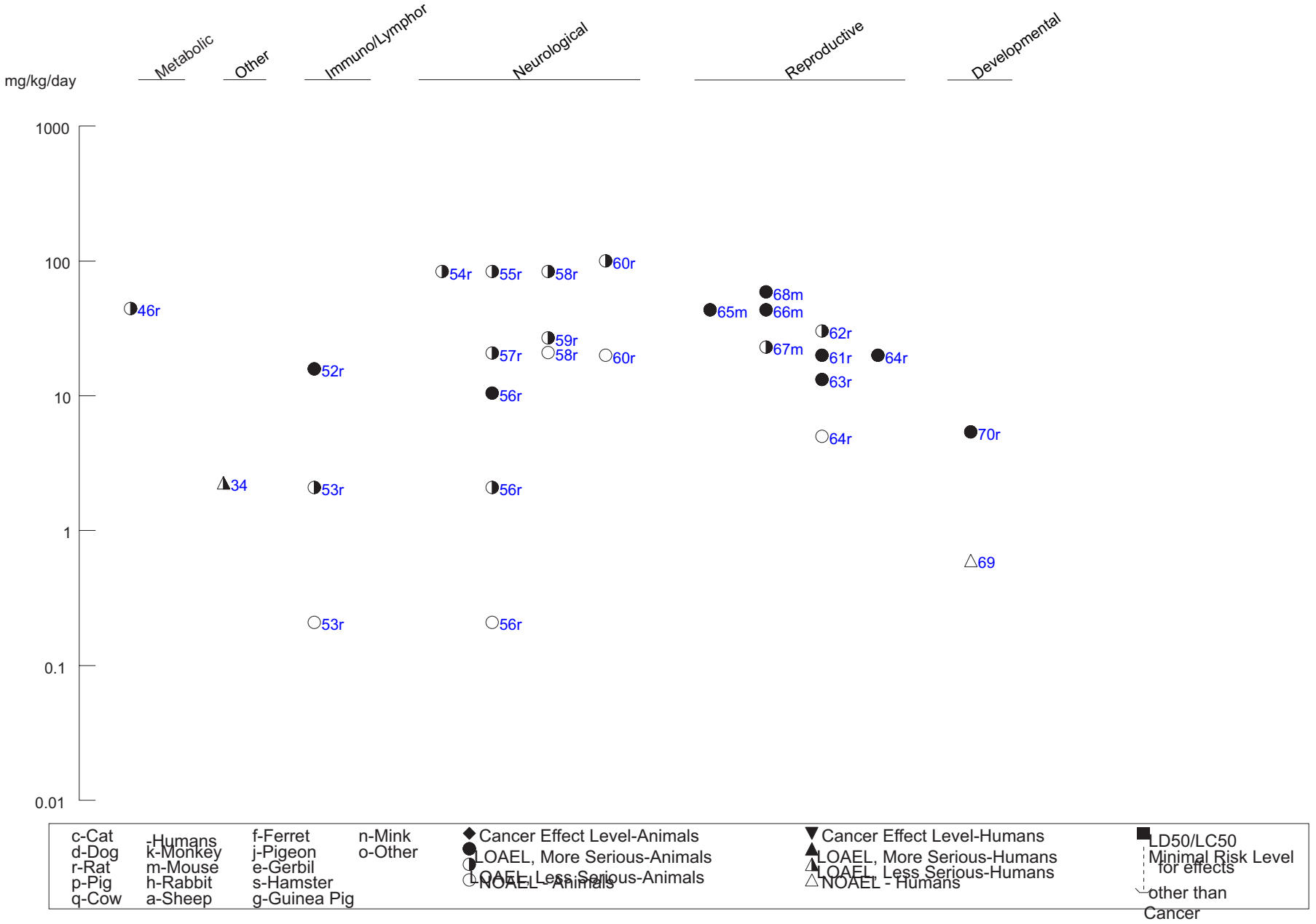


Figure 3-2 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Oral (*Continued*)

Intermediate (15-364 days)



A significant increase in the weight of the lungs, without morphological or histological changes, was found in rats that received 30.2 mg cobalt/kg/day as cobalt chloride in drinking water for 3 months, as compared with controls (Domingo et al. 1984). No morphological changes were seen in the lungs of rats treated with 18 mg cobalt/kg/day for 4 months (Holly 1955).

Cardiovascular Effects. Beer-cobalt cardiomyopathy was observed in people who heavily consumed beer containing cobalt sulfate as a foam stabilizer (Alexander 1969, 1972; Bonenfant et al. 1969; Kesteloot et al. 1968; Morin et al. 1967, 1971; Sullivan et al. 1969). The beer drinkers ingested an average of 0.04 mg cobalt/kg/day (Morin et al. 1971, n=50) to 0.14 mg cobalt/kg/day for a period of years (Alexander 1969, 1972, n=28). The cardiomyopathy was characterized by sinus tachycardia, left ventricular failure, cardiogenic shock, diminished myocardial compliance, absence of a myocardial response to exercise or catecholamine, enlarged heart, pericardial effusion, and extensive intracellular changes (changes in the myofibers, mitochondria, glycogen, and lipids). The beer-cobalt cardiomyopathy appeared to be similar to alcoholic cardiomyopathy and beriberi, but the onset of beer-cobalt cardiomyopathy was very abrupt. It should be noted, however, that the cardiomyopathy may have also been due to the fact that the beer-drinkers had protein-poor diets and may have had prior cardiac damage from alcohol abuse. Treatment of both pregnant and nonpregnant anemic patients for 90 days with doses of cobalt (0.6–1 mg/kg/day as cobalt chloride) that were much higher than the doses in the beer did not result in effects on the heart (Davis and Fields 1958; Holly 1955).

Approximately 40–50% of the patients admitted to the hospital with cardiomyopathy died within several years of diagnosis. In a followup study of four different sites, 0–43% of the survivors, depending on the site, showed a residual cardiac disability and 23–41% had abnormal electrocardiograms (Alexander 1972).

In an experiment designed to simulate conditions leading to beer-cobalt cardiomyopathy in humans, guinea pigs were given 20 mg cobalt/kg/day as cobalt sulfate by gavage either alone or in combination with ethanol (as part of a liquid diet) for 5 weeks (Mohiuddin et al. 1970). The experiment resulted in cardiomyopathy, which was characterized by abnormal EKGs; increased heart weights; lesions involving the pericardium, myocardium, and endocardium; and disfigured mitochondria. Alcohol did not intensify the cardiac effects. Myocardia changes (proliferative interstitial tissue, swollen muscle fibers, and focal degeneration) were also found in rats following a single dose of 176.6 mg cobalt/kg administered by

gavage as cobalt fluoride or a single dose of 795 mg cobalt/kg administered as cobalt oxide (Speijers et al. 1982).

Three weeks of exposure to 12.4 mg cobalt/kg/day as cobalt chloride in male rats resulted in cardiac damage, presenting as incipient, multifocal myocytolysis, with degeneration of myofibrilles (Morvai et al. 1993). After longer-term exposure (2–3 months) of rats to 26–30.2 mg cobalt/kg/day as cobalt sulfate in the diet or as cobalt chloride in the drinking water, degenerative heart lesions (Grice et al. 1969) and an increase in heart weight were found (Domingo et al. 1984). Exposure of rats to 8.4 mg cobalt/kg/day as cobalt sulfate resulted in left ventricular hypertrophy and impaired left ventricular systolic and diastolic functions in an isolated working rat heart model (Haga et al. 1996). Clyne et al. (2001) reported that exposure of rats to 8.4 mg cobalt/kg/day, as cobalt sulfate, in the diet for 24 weeks resulted in significant reductions in a number of enzymes in cardiac tissues, including manganese-superoxide dismutase, succinate-cytochrome c oxidase, NADH-cytochrome c reductase, and cytochrome c oxidase, as well as reducing the mitochondrial ATP production rate.

Gastrointestinal Effects. The first signs of the beer-cobalt cardiomyopathy syndrome were gastrointestinal effects and included nausea, vomiting, and diarrhea (Morin et al. 1971). Signs of heart failure subsequently appeared. These individuals had ingested an average of 0.04 mg cobalt/kg/day for a period of years during which cobalt sulfate was added to beer as a foam stabilizer; however, it is likely that alcohol consumption was also a factor.

In pregnant women given cobalt supplements (alone or combined with iron) to prevent the decrease in hematocrit and hemoglobin levels commonly found during pregnancy (n=78), a small percentage of those treated complained of gastric intolerance (Holly 1955). The women were treated with 0.5–0.6 mg cobalt/kg/day as cobalt chloride for 90 days. Nausea was reported in one anemic patient following treatment with 0.18 mg cobalt/kg/day as cobalt chloride (Duckham and Lee 1976b).

No morphological changes in the gastrointestinal system were observed following exposure of 20 male rats for 3 months to 30.2 mg cobalt/kg/day as cobalt chloride in the drinking water (Domingo et al. 1984) or exposure for 4 months to 18 mg cobalt/kg/day as cobalt chloride by gavage (Holly 1955).

Hematological Effects. Cobalt has been shown to stimulate the production of red blood cells in humans. Davis and Fields (1958) exposed six apparently normal men, ages 20–47, to a daily dose of

cobalt chloride, administered as a 2% solution diluted in either water or milk, for up to 22 days. Five of the six received 150 mg cobalt chloride per day for the entire exposure period, while the sixth was started on 120 mg/day and later increased to 150 mg/day. Blood samples were obtained daily from free-flowing punctures of fingertips at least 2 hours after eating, and at least 15 hours after the last dosage of cobalt. Blood was analyzed for red blood cell counts, hemoglobin percentage, leukocyte counts, reticulocyte percentages, and thrombocyte counts. Exposure to cobalt resulted in the development of polycythemia in all six subjects, with increases in red blood cell numbers ranging from 0.5 to 1.19 million (~16–20% increase above pretreatment levels). Polycythemic erythrocyte counts returned to normal 9–15 days after cessation of cobalt administration. Hemoglobin levels were also increased by cobalt treatment, though to a lesser extent than the erythrocyte values, with increases of 6–11% over pretreatment values. In five of the six subjects, reticulocyte levels were elevated, reaching at least twice the pre-experiment values. Thrombocyte and total leukocyte counts did not deviate significantly from pretreatment values. From the LOAEL of 1 mg/kg-day identified by this study, an intermediate-duration oral MRL of $1x10^{-2}$ mg/kg-day was derived (for derivation, see Section 2.3 and Appendix A).

Increased levels of erythrocytes were also found following oral treatment of anephric patients (with resulting anemia) with 0.16–1.0 mg cobalt/kg/day daily as cobalt chloride for 3–32 weeks (Duckham and Lee 1976b; Taylor et al. 1977). The increase in hemoglobin resulted in a decreased need for blood transfusions. Treatment of pregnant women for 90 days with 0.5–0.6 mg cobalt/kg/day as cobalt chloride, however, did not prevent the reduction in hematocrit and hemoglobin levels often found during pregnancy (Holly 1955).

Significantly increased erythrocyte (polycythemia), hematocrit, and hemoglobin levels were found in animals treated orally with cobalt chloride as a single dose of 161 mg cobalt/kg (Domingo and Llobet 1984) or with longer-term exposure (3 weeks to 2 months) to ≥0.5 mg/kg/day (Brewer 1940; Davis 1937; Domingo et al. 1984; Holly 1955; Krasovskii and Fridlyand 1971; Murdock 1959; Stanley et al. 1947). Of particular note is an 8-week study in rats (Stanley et al. 1947), which reported dose- and time-related increases in erythrocyte number following oral administration of cobalt chloride, with an apparent NOAEL of 0.6 mg cobalt/kg/day and a LOAEL of 2.5 mg cobalt/kg/day. Changes in the levels of other blood proteins (transferrin, several haptoglobulins, and ceruloplasmin) were noted in male Swiss mice following 4, 24, and 48 hours of treatment with 76.4 mg cobalt/kg as cobalt chloride in the drinking water (Bryan and Bright 1973). Exposure for 3 weeks or 3 months to 76.4 mg cobalt/kg as cobalt chloride in the drinking water resulted in no alterations in serum proteins examined.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to cobalt.

No morphological changes were found in the skeletal muscle of rats exposed to 30.2 mg cobalt/kg/day as cobalt chloride in the drinking water for 3 months (Domingo et al. 1984). This NOAEL in rats for intermediate-duration exposure is reported in Table 3-2 and plotted in Figure 3-2.

Hepatic Effects. Liver injury was evident in patients with beer-cobalt cardiomyopathy, characterized by central hepatic necrosis accompanied by increased levels of serum bilirubin and serum enzymes (serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], lactate dehydrogenase [LDH]), creatine phosphokinase, ornithine carbamyl transferase, isocitric dehydrogenase, aldolase) (Alexander 1972; Morin et al. 1971). The hepatic injury may have resulted from ischemia, secondary to the cardiac effects of cobalt, and/or from excessive alcohol consumption. The cardiomyopathy resulted from the ingestion of beer containing 0.04 mg cobalt/kg/day as cobalt sulfate that had been added as a foam stabilizer (Morin et al. 1971). Liver function tests were found to be normal in pregnant women receiving up to 0.6 mg cobalt/kg/day as cobalt chloride for 90 days for treatment of the decreases in hematocrit and hemoglobin levels commonly found during pregnancy (Holly 1955).

Data from animals have also indicated that cobalt has hepatic effects. Hyperemia of the liver and cytoplasmic changes in hepatocytes (clumpy cytoplasm located along the cell membrane) were found in rats administered a single dose of 68.2 mg cobalt/kg as cobalt fluoride or a single dose of 157.3 mg cobalt/kg as cobalt oxide (Speijers et al. 1982).

Increased liver weight (17%) was found in rats exposed to 10 mg cobalt/kg/day (as cobalt chloride) for 5 months (Murdock 1959). No morphological or enzymatic changes were found in the livers of rats exposed to 2.5–30.2 mg cobalt/kg as cobalt chloride by gavage or as cobalt chloride in the drinking water for 3–7 months (Domingo et al. 1984; Holly 1955; Krasovskii and Fridlyand 1971).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to cobalt.

Acute and prolonged exposure to cobalt results in renal tubular degeneration in rats. Renal injury, evidenced by histologic alteration of the proximal tubules, was observed in rats after a single oral exposure to 42 mg cobalt/kg as cobalt fluoride (Speijers et al. 1982) and after exposure to 10–18 mg cobalt/kg/day as cobalt chloride for 4–5 months (Holly 1955; Murdock 1959). A slightly decreased urinary output was observed in rats exposed to 19.4 mg cobalt/kg as cobalt sulfate, but not in rats exposed to 4.25 mg cobalt/kg as cobalt chloride (Singh and Junnarker 1991).

Endocrine Effects. Roy et al. (1968) reported on 20 Québécois patients who died of beer drinkers' myocardosis. Of these, 14 thyroids were available for examination. Three of those were normal, and the other 11 formed the basis of the study. "Abnormal" thyroids did not show gross changes, but upon histologic examination, they showed irregular follicle morphology and decreased follicular size.

Kriss et al. (1955) reported on five patients who had been receiving cobalt therapy for sickle-cell anemia or renal amyloidosis. Three of five developed goiter, one severe, while four of five showed microscopic alterations of the thyroid gland. Two of the patients died from non-cobalt-related causes, while the other three recovered once cobalt treatment was removed. A similar study was reported by Gross et al. (1955) in which stable cobalt was used therapeutically in four cases of sickle-cell anemia. Treatment with cobalt resulted in an enlargement of the thyroid gland, which was reversible upon cessation of cobalt therapy. Similar effects on the thyroid, including enlargement, hyperplasia, and an increased firmness, have been reported in several other cases where cobalt therapy for anemia was used (Chamberlain 1961; Little and Sunico 1958; Soderholm et al. 1968; Washburn and Kaplan 1964). No other studies examining the endocrine effects of stable cobalt in humans were located.

NTP (1998; Bucher et al. 1999) reported increased incidence of pheochromocytoma, a tumor of the adrenal medulla, in female rats exposed to 1.14 mg cobalt/m^3 for 2 years, but did not measure any other endocrine effects. Female mice exposed to 26 mg cobalt/kg-day in the drinking water for up to 45 days showed histopathological changes to the thyroid gland (Shrivastava et al. 1996). Cobalt significantly stimulated serum testosterone in mice treated orally with 23 mg cobalt/kg as cobalt chloride, though no dose-response relationship was present (Pedigo et al. 1988).

Dermal Effects. Allergic dermatitis has been reported in some cobalt-sensitized people following oral challenge with cobalt. Several patients with eczema of the hands were challenged orally with 1 mg cobalt as cobalt sulfate given in tablet form once per week for 3 weeks (0.014 mg/kg/day). A flaring of the

eczema was considered to be a positive allergic response to cobalt (Veien et al. 1987). No other studies were located regarding dermal effects in humans or animals after oral exposure to cobalt.

Ocular Effects. Severe visual disturbances (optic atrophy, impaired choroidal perfusion) developed in a man who was treated with cobalt chloride for pancytopenia and hypercellular bone marrow (Licht et al. 1972). He received 1.3 mg cobalt/kg daily for four series of treatments with a total duration of 6 weeks. However, no other cases of visual disturbances due to therapeutic administration of cobalt have been reported, and no such effects have been observed in animals.

Body Weight Effects. No effects on body weight in animals were found following longer-term (1–5 months) exposure of rats to 10–30.2 mg cobalt/kg/day as cobalt chloride (Bourg et al. 1985; Domingo et al. 1984; Murdock 1959) or of guinea pigs to 20 mg cobalt/kg/day as cobalt sulfate (Mohiuddin et al. 1970). A significant decrease (33%) in body weight gain was observed following 8 weeks of exposure of rats to 4.2 mg cobalt/kg/day as cobalt sulfate (Clyne et al. 1988).

Metabolic Effects. Treatment of rats with 10.6 mg Co/kg/day as $CoCl_2$ in the drinking water for 12–16 days resulted in a significant decrease in serum glucose levels in diabetic rats, but not in control rats (Saker et al. 1998).

Other Systemic Effects. Hypothermia occurred in rats following a single oral dose of 157 mg cobalt/kg given as cobalt oxide or a single oral dose of 110 mg cobalt/kg given as cobalt fluoride (Speijers et al. 1982). The hypothermia was time- and dose-related. Hypothermia was reported as an effect during LD_{50} studies with other cobalt compounds, but the exact dose for the onset of hypothermia with these compounds was not reported (Speijers et al. 1982). Other physiological signs noted in LD_{50} studies include decreased activity, ataxia, diarrhea, and salivation (FDRL 1984a, 1984b).

3.2.2.3 Immunological and Lymphoreticular Effects

Cobalt is known to function as a hapten, resulting in the generation of antibodies against cobalt-protein complexes. Allergic dermatitis has been reported in some cobalt-sensitized people following oral challenge with cobalt. Several patients with eczema of the hands were challenged orally with 1 mg cobalt as cobalt sulfate given in tablet form once per week for 3 weeks (0.014 mg/kg/day). A flaring of the

eczema was considered to be a positive allergic response to cobalt (Veien et al. 1987). Using both the oral challenge test and dermal patch tests, it was determined that the cobalt allergy was systemically induced. The exposure level associated with sensitization to cobalt was not established. After sensitization, allergic reactivity may be independent of dose. Cobalt has been found to be a sensitizer following inhalation exposure (Section 3.2.1.3). This LOAEL value was not reported in Table 3-2 because sensitized individuals only represent a small percent of the population.

A case report of a 6-year-old boy who had ingested approximately 1.7 mg of cobalt chloride reported neutropenia by 7 hours post-exposure (Mucklow et al. 1990).

Thymic atrophy was reported in male Sprague-Dawley rats exposed to 3.79 mg cobalt/kg/day as cobalt chloride in the feed for 4 weeks (Chetty et al. 1979). A deterioration in immunological reactivity, manifested by a decline in phagocytic activity, was reported in rats following 6–7 months of treatment with 0.5 mg cobalt/kg or greater as cobalt chloride (Krasovskii and Fridlyand 1971). This value is presented in Table 3-2 and Figure 3-2.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to stable cobalt.

Several rodent studies have identified neurological effects following cobalt exposure. In Wistar rats, a single gavage dose of 4.25 mg cobalt/kg as cobalt chloride resulted in a moderate reduction in spontaneous activity, muscle tone, touch response, and respiration, while 19.4 mg cobalt/kg as cobalt sulfate caused a mild reduction the same parameters (Singh and Junnarkar 1991). In rats exposed to 4.96 mg cobalt/kg/day as cobalt chloride for 30 days in the drinking water, cobalt led to changes in sympathetically mediated contractile activity of isolated rat vas deferens (Mutafova-Yambolieva et al. 1994). Rats exposed to 6.44 mg cobalt/kg/day as cobalt nitrate in the drinking water showed an increased sensitivity and decreased maximal response to a cholinergic agonist (Vassilev et al. 1993). In rats exposed to 20 mg cobalt/kg/day as cobalt chloride for 57 days in the drinking water, cobalt enhanced behavioral reactivity to stress (the animals were less likely to descend from a safe platform to an electrified grid) (Bourg et al. 1985). Rats exposed to the same dose in the diet for 69 days showed a slower rate of lever pressing than controls, but no change in behavioral reactivity to stress (Nation et al.

1983). Longer-term exposure of rats to cobalt chloride (7 months) resulted in a significant increase in the latent reflex period at ≥0.5 mg cobalt/kg as cobalt chloride and a pronounced neurotropic effect (disturbed conditioned reflexes) at 2.5 mg cobalt/kg (Krasovskii and Fridlyand 1971).

The NOAEL value and the LOAEL value for rats for intermediate duration are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to stable cobalt.

Testicular degeneration and atrophy have been reported in rats exposed to 13.3–58.9 mg cobalt/kg/day as cobalt chloride for 2–3 months in the diet or drinking water (Corrier et al. 1985; Domingo et al. 1984; Mollenhauer et al. 1985; Nation et al. 1983; Pedigo and Vernon 1993; Pedigo et al. 1988), or in mice exposed to 43.4 mg cobalt/kg/day as cobalt chloride for 13 weeks in the drinking water (Anderson et al. 1992, 1993).

The highest NOAEL and all reliable LOAEL values for rats in the intermediate-duration category are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No developmental effects on human fetuses were observed following treatment of pregnant women with cobalt chloride to raise hematocrit and hemoglobin levels that are often depressed during pregnancy. Dosages up to 0.6 mg cobalt/kg/day for 90 days were given (Holly 1955). Examination of the fetuses, however, was limited to the reporting of obvious birth defects, and exposure only occurred in the final trimester.

Oral exposure of female rats to cobalt chloride at 5.4 or 21.8 mg cobalt/kg/day from gestation day 14 through lactation day 21 has been shown to result in stunted growth and decreased survival, respectively, of newborn pups (Domingo et al. 1985b). The effects on the offspring occurred at levels

that also caused maternal toxicity (reduced body weight and food consumption, and altered hematological measurements) and might therefore have been an indirect effect of maternal toxicity rather than a direct effect of cobalt on the fetus (Domingo et al. 1985b). Teratogenic effects were not observed.

Szakmary et al. (2001) reported that exposure of pregnant rats to 0–38 mg Co/kg-day as cobalt sulfate did not result in changes in fetal death rates, maternal body weigh gain, average litter size, or average fetal or placental weights; however, a dose-related trend was seen for the percent of fetuses with retarded body weights. In contrast, no effects on fetal growth or survival were found following exposure of rats to 24.8 mg cobalt/kg/day as cobalt chloride during gestation days 6–15 (Paternian et al. 1988). In mice, exposure to 81.7 mg cobalt/kg/day as cobalt chloride during gestation days 8–12 was reported to have no effect on fetal growth or mortality in mice (Seidenberg et al. 1986). In a later mouse study that exposed pregnant mice to 19 mg Co/kg-day as cobalt sulfate, no changes in litter size, postimplantation loss, or average fetal or placental weights were seen; the only difference seen was an increase in the percent of fetuses with retarded body weights (Szakmary et al. 2001). The same study reported that rabbits exposed to ≥ 38 mg Co/kg-day, as cobalt sulfate, showed nearly complete maternal lethality, and complete fetal loss. Rabbits exposed to 7.6 mg Co/kg, as cobalt sulfate, showed significant increases in mortality and fetal resorption, as well as an increase in fetuses with retarded body weight (Szakmary et al. 2001). The highest NOAEL and all reliable LOAEL values for each species and duration category are reported in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

In a survey assessing the correlation between cancer mortality and trace metals in water supplies (10 basins) throughout the United States, no correlation was found between cancer mortality and the level of cobalt in the water (Berg and Burbank 1972). Cobalt levels of 1–19 µg/L, with resulting human intakes ranging from 0.03 to 0.54 µg/kg/day, were reported.

No studies were located regarding carcinogenic effects in animals after oral exposure to stable cobalt.

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding lethal effects in humans after dermal exposure to cobalt.

No mortality was observed in guinea pigs dermally exposed to 51.75 mg cobalt/kg for 5 days/week as dicobalt octacarbonyl for a total of 18 applications (Kincaid et al. 1954).

3.2.3.2 Systemic Effects

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

Dermal Effects. Dermatitis is a common result of dermal exposure to cobalt in humans that has been verified in a large number of studies (Alomar et al. 1985; Bedello et al. 1984; Dooms-Goossens et al. 1980; Fischer and Rystedt 1983; Goossens et al. 2001; Kanerva et al. 1988, 1998; Kiec-Swierczyńska and Krecisz 2002; Marcussen 1963; Minamoto et al. 2002; Pryce and King 1990; Swennen et al. 1993; Romaguera et al. 1982; Valer et al. 1967). Using patch tests and intradermal injections, it has been demonstrated that the dermatitis is probably caused by an allergic reaction to cobalt. Contact allergy was reported in 22 of 223 (9.9%) nurses who were tested with a patch test of 1.0% cobalt chloride (Kieć-Świerczyńska and Kręcisz 2000), as well as 16 of 79 (20.3%) of examined dentists (Kieć-Świerczyńska and Kręcisz 2002). Persons with body piercings showed an increased prevalence of allergy to cobalt, with the incidence of contact allergy being proportional to number of piercings (Ehrlich et al. 2001). The prevalence of sensitivity to cobalt following exposure to cobalt as a component of metal implants is low, with only 3.8% of patients developing a new sensitivity to cobalt following insertion of the implant (Swiontkowski et al. 2001). Exposure levels associated with the development of dermatitis have not been identified. It appears that the allergic properties of cobalt result mainly from exposure to the metal itself, rather than a salt, as Nielsen et al. (2000) demonstrated that daily repeated exposure to aqueous cobalt salts did not result in hand eczema in patients known to have cobalt allergy.

In animals, scabs and denuded areas were found after six doses of 51.75 mg cobalt/kg (5 days/week) as dicobalt octacarbonyl were applied to the shaved abdomens (uncovered area of approximately 50 cm^2) of guinea pigs (Kincaid et al. 1954). By the 11^{th} dose, the lesions disappeared. No adverse effects were observed in vehicle controls (methyl ethyl ketone). It is not known whether or not a similar reaction would result from metallic or inorganic forms of cobalt. This LOAEL value is reported in Table 3-3.

3.2.3.3 Immunological and Lymphoreticular Effects

Cobalt-induced dermatitis is well documented in the literature, and the studies indicate that cobalt is a sensitizer (Alomar et al. 1985; Dooms-Goossens et al. 1980; Fischer and Rystedt 1983; Goh et al. 1986; Kanerva et al. 1988; Marcussen 1963; Valer et al. 1967). Patch testing and intradermal injections were performed, but exposure levels of cobalt were not reported. Interrelationships exist between nickel and cobalt sensitization (Bencko et al. 1983; Rystedt and Fisher 1983); however, the extent of any potential interactions between the two metals on immunologic end points is not well understood. In guinea pigs, nickel and cobalt sensitization appear to be interrelated and mutually enhancing (Lammintausta et al. 1985), though cross-reactivity was not reported to occur.

Single or multiple dermal exposures of BALB/c mice to $CoCl_2$ in dimethylsulfoxide or in ethanol resulted in an increased cellular proliferation in the local lymph node assay in a concentration-dependant manner (Ikarashi et al. 1992a). The effect of three consecutive exposures to varying concentrations of $CoCl_2$ in DMSO on lymph node proliferation was measured in rats, mice, and guinea pigs (Ikarashi et al. 1992b). Stimulation Indices of 3 or greater, indicated by the authors as a significant response, were reported for mice exposed to 1, 2.5, or 5% $CoCl_2$, rats exposed to 2.5 or 5% $CoCl_2$, and guinea pigs exposed to 5% $CoCl_2$; these treatments resulted in dose levels of 10.8, 27, or 54.1 mg cobalt/kg/day for mice, 9.60 or 19.2 mg cobalt/kg/day for rats, and 14.7 mg cobalt/kg/day for guinea pigs.

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

Table 3-3 Levels of Significant Exposure to Cobalt - Chemical Toxicity - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference Chemical Form
				Less Serious		Serious	
ACUTE EXPOSURE							
Immuno/ Lymphoret							
Rat (Fischer- 344)	1x/d 3d		3.84 F mg/kg/day	9.6 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992b Chloride
Mouse (BALB/c)	1x or 1x/d for 3 d			10.8 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992a Chloride
Mouse CBA/N	1x/d 3 d		5.4 F mg/kg/day	10.8 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992b Chloride
Gn Pig (Hartley)	1x/d 3 d		7.39 F mg/kg/day	14.7 F mg/kg/day	(Increased proliferation of lymphatic cells)		Ikarashi et al. 1992b Chloride
INTERMEDIATE EXPOSURE							
Systemic							
Gn Pig (NS)	18 d 5 d/wk	Dermal		51.75 mg/kg/day	(skin lesions (scabs and denuded areas) at application site)		Kincaid et al. 1954

d =day(s); F = female; LOAEL = lowest-observed-adverse-effect level; NOAEL = no observed-adverse-effect level; wk = week(s); x = times.

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to cobalt.

3.2.4 Other Routes of Exposure

Endocrine Effects. Patients (n=12) injected with a single diagnostic dose of radioactive iodine, and then treated 48 hours later with 1 mg cobalt/kg/day as cobalt chloride for 2 weeks, resulted in a greatly reduced uptake of radioactive iodine by the thyroid in 1 week, with uptake nearing 0 by the second week (Roche and Layrisse 1956). When the cobalt treatment ended, the uptake values returned to normal. The decrease of radioactive iodine uptake found in patients administered 0.54 mg cobalt/kg/day for 10–25 days prior to iodine injection was found to result from cobalt blocking the organic binding of iodine (Paley et al. 1958).

In various species of animals, parenteral administration of cobalt resulted in cytotoxic effects on the alpha cells of the pancreas (Beskid 1963; Goldner et al. 1952; Hakanson et al. 1974; Lacy and Cardeza 1958; Lazarus et al. 1953; Van Campenhout 1955). Because this effect has never been reported in humans or animals following inhalation, oral, or dermal exposure to cobalt, the relevance of the effect to humans is not known.

Moger (1983) exposed primary cultures of mouse Leydig cells to 0–2.5 mM cobalt as cobalt for 3 hours, and measured the effects on androgen production. Cobalt exposure caused a dose-related decrease in both basal and LH-stimulated androgen production, with no effects on protein synthesis. The author suggested that these effects are the result of cobalt inhibition of calcium influx across the plasma membrane.

3.3 DISCUSSION OF HEALTH EFFECTS OF RADIOACTIVE COBALT BY ROUTE OF EXPOSURE

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

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

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

3.3.1 Inhalation Exposure

No studies were located regarding the following health effects in humans or animals after inhalation exposure to radioactive cobalt:

3.3.1.1 Death

3.3.1.2 Systemic Effects

3.3.1.3 Immunological and Lymphoreticular Effects

3.3.1.4 Neurological Effects

3.3.1.5 Reproductive Effects

3.3.1.6 Developmental Effects

3.3.1.7 Cancer

3.3.2 Oral Exposure

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

3.3.2.1 Death

3.3.2.2 Systemic Effects

3.3.2.3 Immunological and Lymphoreticular Effects

3.3.2.4 Neurological Effects

3.3.2.5 Reproductive Effects

3.3.2.6 Developmental Effects

3.3.2.7 Cancer

3.3.3 External Exposure

This section contains information regarding health effects related to external exposure to radioactive cobalt sources. Radionuclides of cobalt may emit beta particles and/or gamma rays, which may be a health hazard in living organisms because they ionize the atoms that they hit while passing through the tissues of the body (see Table 3-4 and Figure 3-3). Beta particles can travel appreciable distances in air, but travel only a few millimeters in solids. External exposure to beta particles may result in damage to skin and superficial body tissues at sufficiently high doses. Beta radiation is only a threat to internal organs if the radiation source is internalized. Gamma radiation, on the other hand, can easily pass completely through the human body and cause ionization of atoms in its path. For most radionuclides of public interest, the fraction of gamma rays that actually deposits energy and contributes to the radiation

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL			Reference Chemical Form
					Less Serious (rad)	Serious (rad)		
	ACUTE EXPOSURE							
	Death							
1	Human					2250 M	(Death)	Stavem et al. 1985
2	Mouse (BALB/c)					627	(30-day LD50 value, single exposure)	Darwezah et al. 1988
3	Mouse CBA/Ca.Lac.C	1x				1420 M	(Death)	Down et al. 1986
	Systemic							
4	Human	(occup)	Gastro	12.7				House et al. 1992
			Hemato	12.7				
5	Human		Dermal			159 M	(Severe alterations to skin of left hand)	Klener et al. 1986
			Ocular			159 M	(Progressive occlusion of vision of left eye)	

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL			Reference Chemical Form
					Less Serious (rad)		Serious (rad)	
6	Human		Cardio				2250 M (left ventricular hypertrophy)	Stavem et al. 1985
			Gastro				2250 M (Pronounced atrophy in intestines; less severe in stomach)	
			Hemato				2250 M (>35% decrease in hemogolbin and >90% decrease in thrombocytes)	
			Renal		2250 M	(Enlarged kidneys)		
7	Monkey (Rhesus)	30 min	Cardio		1000 M	(Minor changes: increased heart rate; decreased blood pressure; variable cardiac output and total peripheral resistance)		Bruner 1977
8	Monkey (Rhesus)	1 hr	Cardio				10000 M (Pronounced decreases in mean arterial blood pressure and blood flow to the brain)	Cockerham et al. 1986
9	Rat (Wistar)		Cardio		2500 M	(Increased brain uptake index)		Bezek et al. 1990

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
10	Rat (Sprague-Dawley)	1x	Resp			1500 M (Severe inflammation, pulmonary histopathology, fibrosis)	Lafuma et al. 1987
11	Mouse (Swiss-Webster)		Gastro		1000 M (Intestinal crypt cell damage, including necrosis and altered mitotic figures)		Devi et al. 1979
12	Mouse CBA/Ca.Lac.C	1x	Resp		1330 M (Increased breathing rate)		Down et al. 1986
			Dermal		1800 M (Mild epilation)		
13	Mouse (Swiss-Webster)	24 hr	Hepatic		1000 M (Transient decrease in total liver protein)		Mazur et al. 1991
14	Dog (Mongrel)	198 d	Cardio			4355 (Cardiac arrhythmia)	Dick et al. 1979
15	Dog (Beagle)	10.44 min	Gastro		800 (Repeated emesis)		Gomez-de-Segura et al. 1998

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL				Reference Chemical Form
					Less Serious (rad)		Serious (rad)		
16	Rabbit (New Zealand)	1x	Dermal		1730 M	(Alopecia)			Cox et al. 1981
17	Pig Large White	1x	Resp		900 F	(Reversible decrease in ventilation capacity)	1090 F	(Irreversible decrease in ventilation capacity, histopathology, pulmonary atrophy)	Rezvani et al. 1989
18	Pig Large White	1x	Renal				874 F	(50% loss in effective renal plasma flow)	Robbins et al. 1989a
19	Pig Large White	1x	Hemato		780 F	(Slight decreases in erythrocytes, hemoglobin, and hematocrit)	1190 F	(Severe decreases in erythrocytes, hemoglobin, and hematocrit)	Robbins et al. 1989b
			Renal		780 F	(Reversible changes in effective renal plasma flow and glomerular filtration rate)	980 F	(Persistent changes in effective renal plasma flow and glomerular filtration rate)	
20	Pig Large White	1x	Renal				557 F	(50% loss in effective renal plasma flow)	Robbins et al. 1989c

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
21	Pig Large White	1x	Renal			980 F (Progressive inflammatory and degenerative changes in the glomerulus)	Robbins et al. 1991
22	Baboon	3-4 wk, 1x/wk	Resp			3000 (Severe pulmonary fibrosis)	Collins et al. 1978
23	Ferret	2 hr	Gastro	49 M	77 M (Emesis with wretching)		King 1988
	Immuno/ Lymphoret						
24	Human	(occup)		12.7			House et al. 1992
25	Human				159 M (Minor reduction in white cell counts)		Klener et al. 1986
26	Human					2250 M (Pronounced decrease in lymphocytes and granulocytes)	Stavem et al. 1985

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
27	Mouse (Swiss-Webster)	24 hr			1000 M (>50% decrease in spleen weight and protein; increased spleen acid phosphatase)		Mazur et al. 1991
	Neurological						
28	Rat (CD)	140 d		150 M	450 M (Reversible deficits in fixed-ratio behavior parameters)		Mele et al. 1988
29	Mouse (Swiss-Webster)	97 d		300 M	500 M (Reversible decreases in aggressive behavior)		Maier and Landauer 1989
30	Rabbit Burgundy fawn	12 hr			450 M (Altered firing rates and patterns of hippocampal neurons)		Bassant and Court 1978
	Reproductive						
31	Rat (Sprague-Dawley)	1x			330 M (Decreased testis weight and altered spermatogenesis, with some evidence of recovery)		Cunningham and Huckins 1978
32	Rat (Wistar)	1x			80 M (Reversible decrease in testicular weight)		Laporte et al. 1985

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
	Developmental						
33	Monkey Squirrel	1x				100 (Developmental retardation, neurobehavioral deficits)	Brizzee et al. 1978
34	Rat (Sprague-Dawley)	1x				50 F (Defective eye development and spinal curvature)	Bruni et al. 1994
35	Rat	1x				260 (Testicular trophy; adrenal atrophy)	Inano et al. 1989
36	Rat (Wistar)	1x			260 M (Reduced NADPH cytochrome p450 reductase)		Inano et al. 1990
37	Rat (Wistar)	4d or 6d		11	16 (slightly decreased (2.6%) brain weight in offspring)	560 (decreased (13.1%) brain weight in offspring)	Reyners et al. 1992
38	Rat (Wistar)	1x				210 M (Testicular atrophy)	Suzuki et al. 1990

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL				Reference Chemical Form
					Less Serious (rad)		Serious (rad)		
39	Mouse (Swiss-Webster)	1x		5	10	(Decreased brain weight 3-4%, significantly increased microphthalmia)	50	(Increased fetal mortality and growth retardation)	Devi et al. 1994
40	Mouse (Swiss-Webster)	1x			25	(Decreased body weight 5%, liver weight 5%, and spleen weight 12%. Decreased spleen cellularity.)			Devi et al. 1998
41	Mouse (B6C3F1)	1x					100 M	(Increased number of tumor-bearing animals after in utero exposure)	Nitta et al. 1992
42	Mouse (Swiss-Webster)	1x					200	(Atrophy or lack of development of corpus callosum)	Schmidt and Lent 1987
43	Mouse	6d					20 F	(Altered neurobehavioral parameters, growth retardation)	Want et al. 1993

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)		LOAEL Serious (rad)		Reference Chemical Form
44	Mouse LACA	1x					50	(Delayed development, altered hindlimb splay)	Zhong et al. 1996
45	Hamster (Golden Syrian)	1x					200 F	(Severe developmental abnormalities of multiple organ systems, embryo death)	Harvey et al. 1962
46	Dog (Beagle)	1x					83	(Increased risk of thyroid neoplasia)	Benjamin et al. 1997
47	Dog (Beagle)	1x					15.6	(Increased cancer-related mortality - multiple tumor types)	Benjamin et al. 1998b
48	Dog (Beagle)	1x		16	83	(Hypodontia)			Lee et al. 1989
49	Dog (Beagle)	1x					96	(Optic atrophy/degeneration)	Schweitzer et al. 1987

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL				Reference Chemical Form
					Less Serious (rad)		Serious (rad)		
	Cancer								
50	Dog (Beagle)	1x					15.6	(Increased cancer-related mortality)	Benjamin et al. 1998b
	INTERMEDIATE EXPOSURE								
	Death								
51	Human						7500 F	(Death)	Roscher and Woodard 1969
	Systemic								
52	Human		Ocular				4800 F	(Progressive visual impairment and blindness)	Fishman et al. 1976
53	Human	22 - 35 d teletherapy	Cardio				4623	(Persistent pericarditis)	Martin et al. 1975
54	Human	18 d	Gastro		3600	(Loose bowel movements, impaired absorption of vitamin B12)			McBrien 1973
55	Human	17 d	Dermal		4056 F	(Comedones, which were resolved with treatment)			Myskowski and Safai 1981

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
56	Human		Gastro			7500 F (Severe gastrointestinal necrosis and fibrosis)	Roscher and Woodard 1969
57	Human	3 yr	Other	2400			Thibadoux et al. 1980
58	Human	7 wk	Dermal		4700 (Reversible changes in skin pigmentation)		van Oort et al. 1984
59	Rat (albino)	10 wk	Other	2400 M	4800 M (Transient alterations in incisor histopathology)	7200 M (Lasting alterations in incisor histopathology)	Sweeney et al. 1977
60	Dog (Beagle)	150-300 d	Hemato			1125 M (Aplastic anemia)	Seed et al. 1989
	Immuno/ Lymphoret						
61	Dog (Beagle)	150-300 d				1125 M (Dose- and time-related reduction in granulocytes, monocytes, and lymphocytes)	Seed et al. 1989

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL			Reference Chemical Form
					Less Serious (rad)	Serious (rad)		
	Neurological							
62	Human					4800 F	(Optic nerve damage, resulting in visual impairment and blindness)	Fishman et al. 1976
63	Human	9 mo				13150 F	(Neural necrosis and gliosis)	Llena et al. 1976
64	Human					5500 M	(Partial paralysis secondary to radiation myelopathy)	Sanyal et al. 1979
						5000[b] F	(Partial paralysis secondary to radiation myelopathy)	
	Reproductive							
65	Human	47 d				6600 M	(Calcification of the prostate)	Keys and Reed 1980
66	Mouse	32 wk				1282 F	(Decreased offspring per litter and sterility)	Searle et al. 1980
	Cancer							
67	Human	NS				1800 F	(Basal cell carcinoma)	Garcia-Silva et al. 1996
68	Human	8 mo				25150 M	(Multiple basal cell carcinomas)	Wollenberg et al. 1995

Table 3-4 Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL			Reference Chemical Form
					Less Serious (rad)	Serious (rad)		
	CHRONIC EXPOSURE							
	Systemic							
69	Human	3 yr	Cardio			13150 F	(Endothelial hyperplasia, dysplasia, and fibrosis)	Llena et al. 1976

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

[b] Differences in levels of health and cancer effects between males and females are not indicated in Figure 3-3. Where such differences exits, only the levels of effect for the most sensitive gender are represented.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; min = minute(s); mo = month(s); NOAEL = no observed-adverse-effect level; NS = not specified; (occup) = occupational; Resp = respiratory; wk = week(s); yr = year(s).

Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation

Acute (≤14 days)

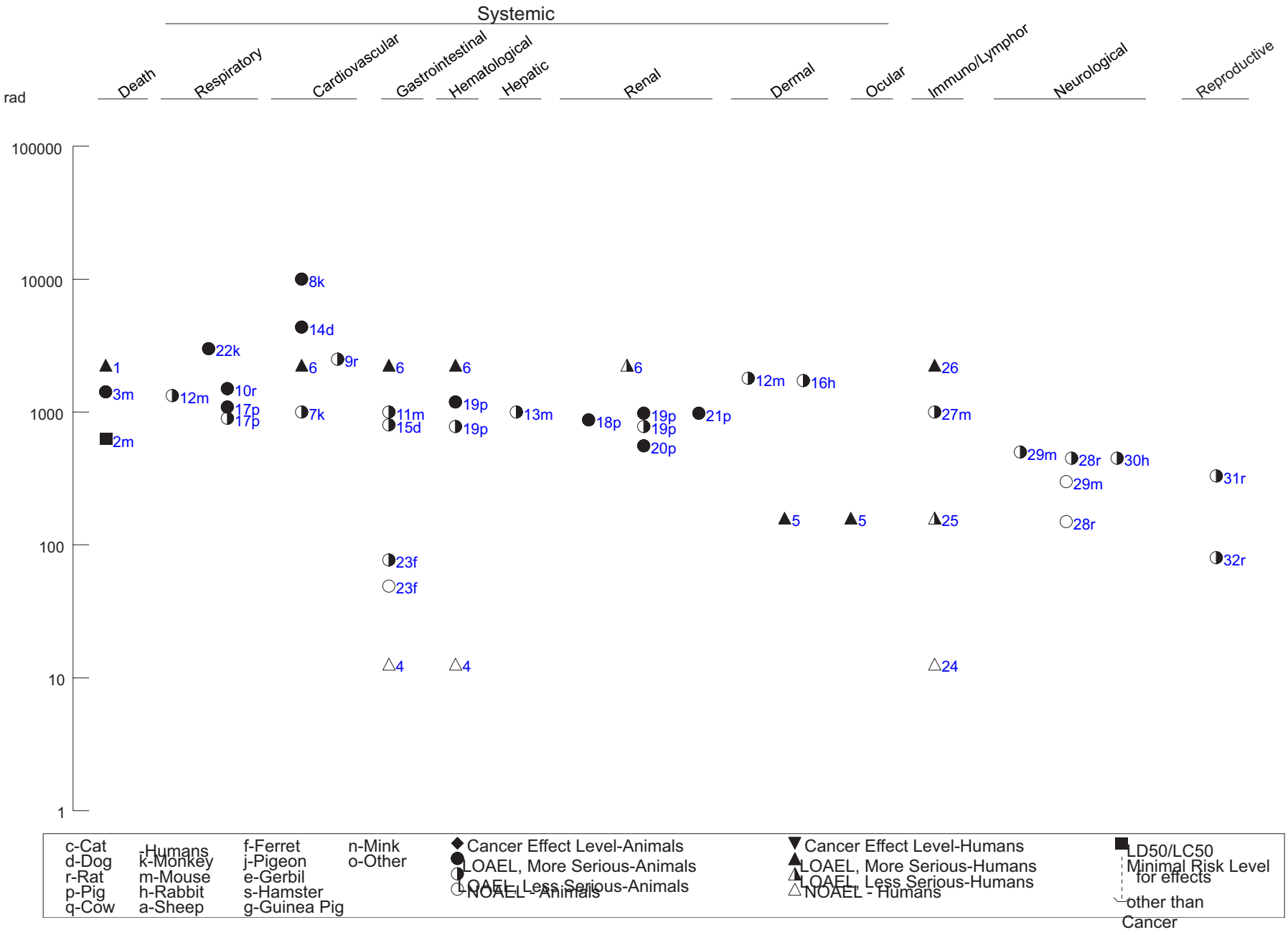


Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (*Continued*)

Acute (≤14 days)

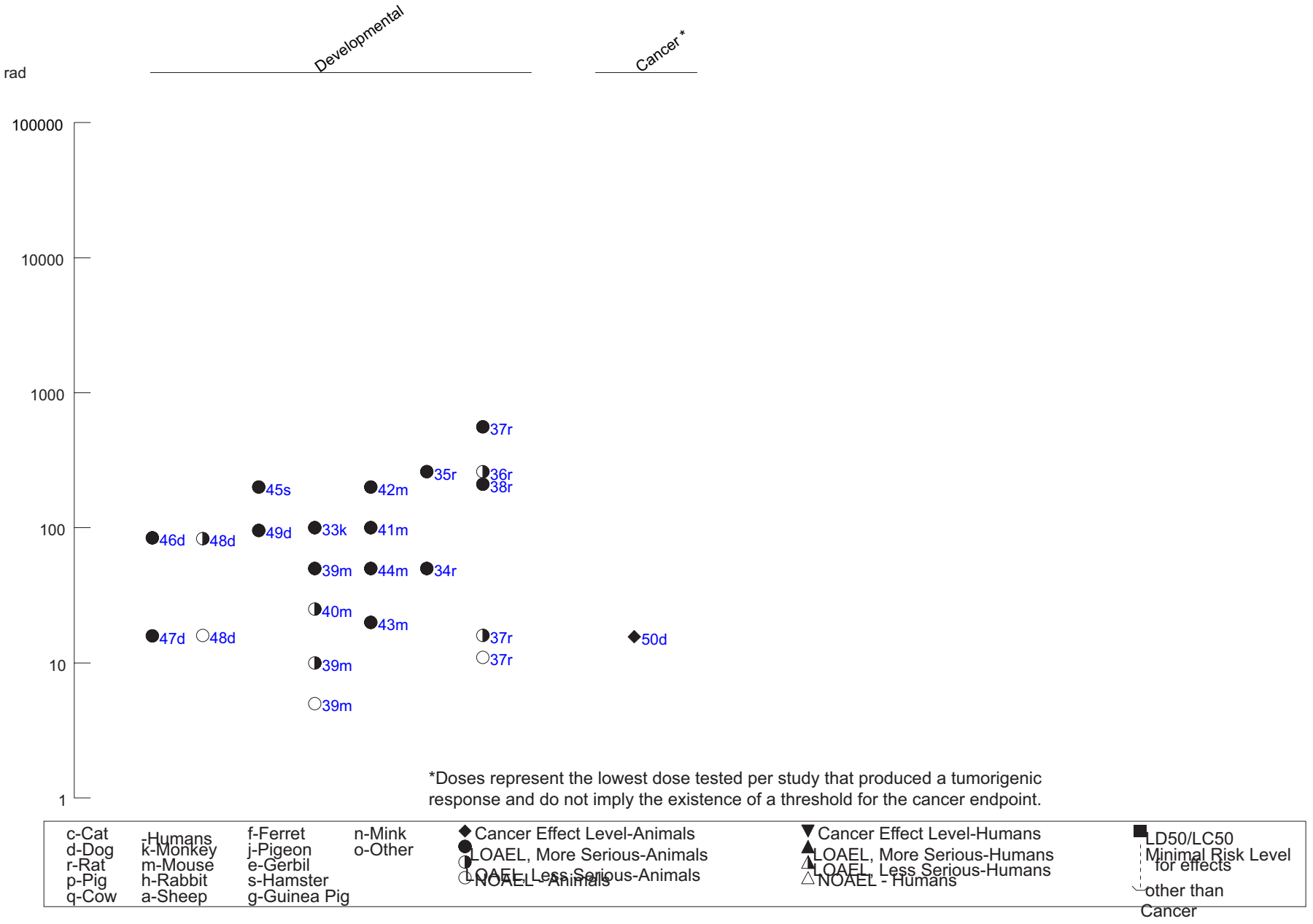


Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (*Continued*)

Intermediate (15-364 days)

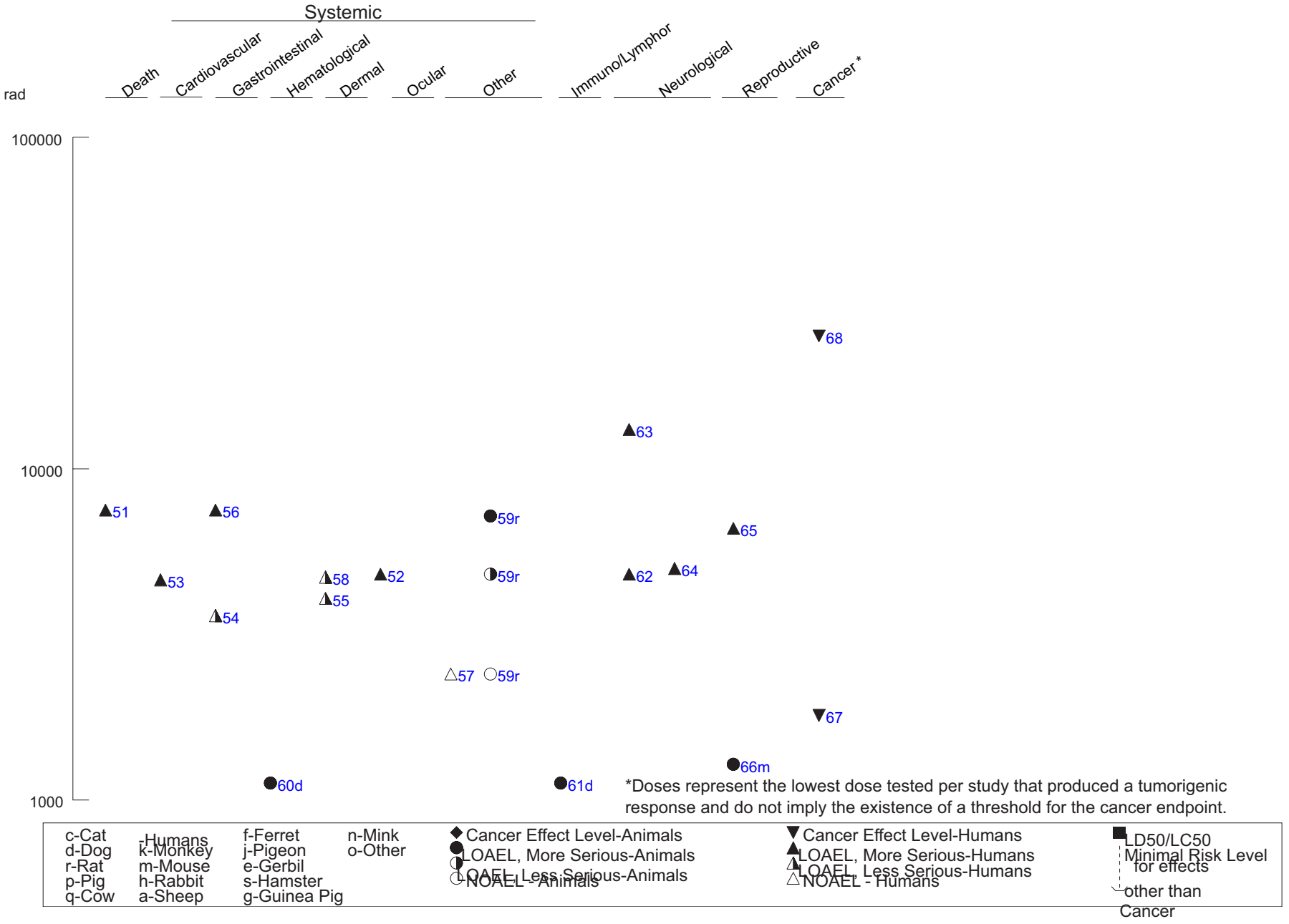
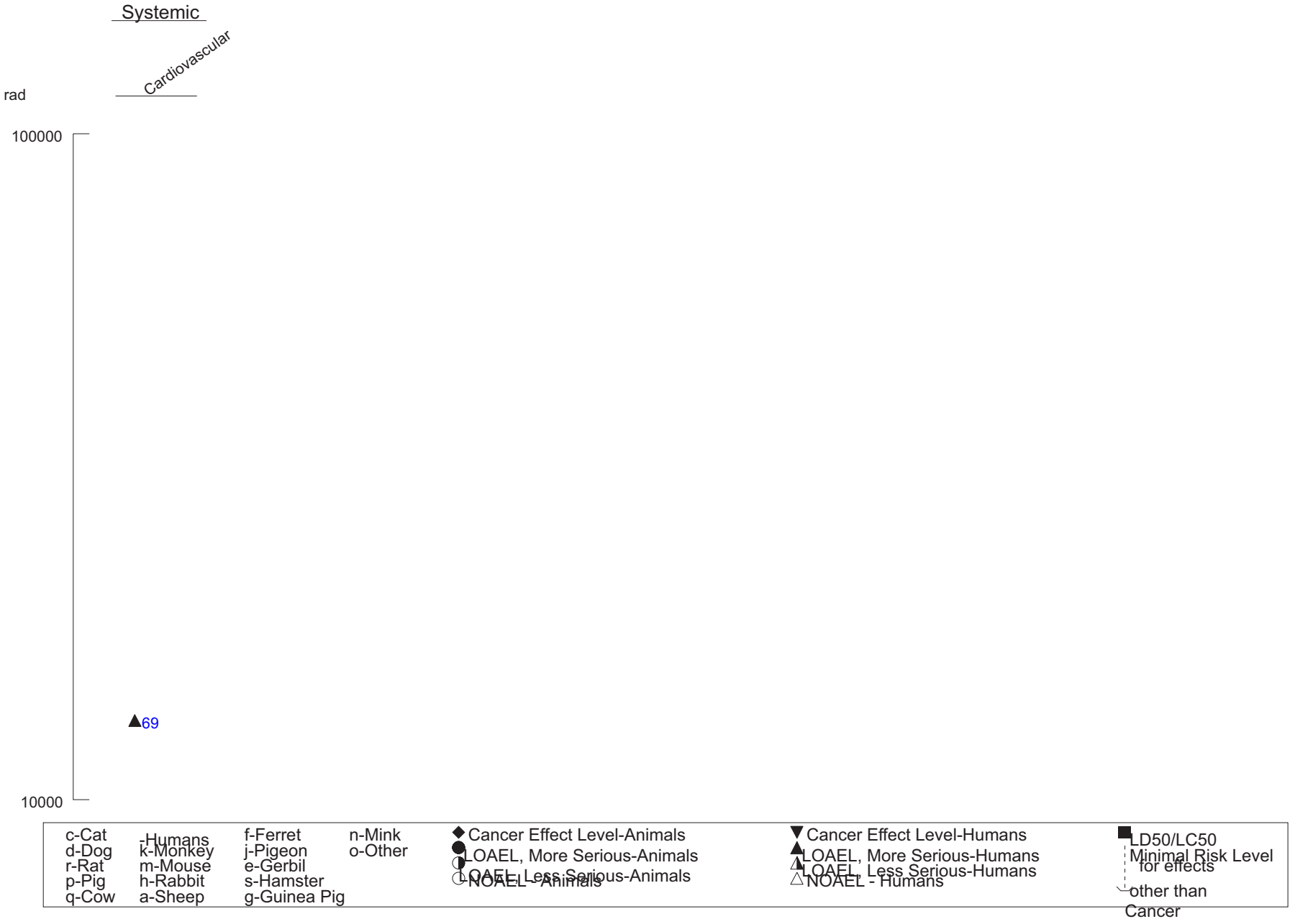


Figure 3-3. Levels of Significant Exposure to Cobalt - Radiation Toxicity - External Radiation (*Continued*)

Chronic (≥365 days)



dose increases with tissue density (resulting in a higher dose to bone than soft tissue) and decreases with energy. Several feet of concrete or a few inches of lead are typical shield thicknesses for protection from gamma rays. Because it is so highly penetrating, gamma radiation released by radionuclides such as cobalt may be a radiation hazard to internal organs (Agency for Toxic Substances and Disease Registry 1999; EPA 1997b). ^{60}Co gamma rays are commonly used for human radiotherapy. The purpose of this section is to provide information regarding health effects associated with external exposure to a radioactive cobalt source. These health effects are not specific to cobalt, but apply to any radionuclide delivering the same beta and gamma radiation dose at a comparable dose rate. Refer to Agency for Toxic Substances and Disease Registry (1999) for a detailed description of health effects from external exposure to ionizing radiation in general.

3.3.3.1 Death

Exposure to high levels of external radiation, including radiation from cobalt radionuclides, may result in mortality when the whole body dose exceeds 300 rads. Stavem et al. (1985) reported a case in which a worker was exposed to 2,250 rad (22.5 Gy) within a few minutes time, resulting in death due to acute radiation sickness (depressed leukocyte counts, vomiting, diarrhea, etc.). Complications resulting from cobalt radiotherapy resulted in the death of a patient from severe gastrointestinal complications (Roschler and Woodard 1969).

Norris and Poole (1969) reported on the mortality of dogs exposed to ^{60}Co gamma rays at a rate of 35 rad (0.35 Gy) per day for 40 days, resulting in a cumulative exposure of 1,400 rad (14 Gy). Twelve of 40 animals died prior to termination of the 40-day exposure period, 13 of 40 died within the 23-day post-exposure observation period, and 15 survived to the end of the study period, indicating an LD_{50} of <1,400 rad at 35 rad/day. Darwezah et al. (1988) reported single, whole-body exposure LD_{50} values in mice of 913 rad (9.13 Gy) and 627 rad (6.27 Gy) at 6 and 30 days post-irradiation, respectfully. Down et al. (1986) reported a slightly higher LD_{50} of 1,400–1,450 rad (14–14.5 Gy) for ^{60}Co thoracic irradiation in mice at 26 days postirradiation. Several studies have demonstrated that decreasing the dose rate or the portion of the body exposed will increase the LD_{50} for ^{60}Co gamma rays (Darwezah et al. 1988; Down et al. 1986; Hanks et al. 1966; Page et al. 1968).

3.3.3.2 Systemic Effects

Respiratory Effects. Ionizing radiation is known to exert dramatic effects on the tissue of the lung (Agency for Toxic Substances and Disease Registry 1999; Davis et al. 1992; Libshitz 1993; Roswit and White 1977), particularly at the high doses used in radiotherapy. The first phase of damage usually consists of radiation pneumonitis, which occurs between 3 and 13 weeks after irradiation and is characterized by low-grade fever, mild exertional dyspnea, congestion, and unproductive cough. The second phase is characterized by radiation-induced lung fibrosis, emphysema, and pleural thickening. Patients receiving radiotherapy treatment regimens of ≥4,000 rad (40 Gy) to the chest region almost always develop radiographic changes in the lung (Davis et al. 1992), whereas lower therapeutic doses (2,500–3,000 rad, 25–30 Gy) generally result in a lower risk of adverse pulmonary symptoms (Davis et al. 1992; Roswit and White 1977). Prophylactic protective measures may be taken, and these symptoms may be treated later if detected early enough in their progression (Roswit and White 1977).

At similar doses, studies in animals, including rats, mice, baboons, and pigs, using ^{60}Co radiation have also shown radiation pneumonitis and fibrosis, similar to effects seen in humans (Collins et al. 1978; Down et al. 1986; Lafuma et al. 1987; Rezvani et al. 1989). Other respiratory changes seen in animal experiments included an increased breathing rate, effects on the surfactant system, edema, increased pleural fluid content, pulmonary atrophy, and histologic alterations of the lung parenchyma (Bellet-Barthas et al. 1980; Collins et al. 1978; Down et al. 1986; Lafuma et al. 1987).

Cardiovascular Effects. Martin et al. (1975) reported that 24 of 81 patients who underwent ^{60}Co teletherapy for Hodgkin's disease, using an upper mantle treatment regimen of 4,000 rad (40 Gy) over 22–35 days, developed radiation-related pericarditis. In 14 of these patients, the condition was transient, while it persisted in the other 10 patients. Llena et al. (1976) presented a case wherein a 51-year-old woman who had received a localized dose of 13,150 rad (131.5 Gy) of ^{60}Co radiation between the nasopharynx and cervical lymph nodes as part of radiotherapy developed severe alterations in the endothelial cells of the brain, including proliferation, increased cytoplasmic organelles, and infoldings of the plasma membrane.

Whole-body exposure of Rhesus monkeys to 10,000 rad (100 Gy) over a 90-second period resulted in dramatic decreases in mean systemic arterial blood pressure, as well as in mean blood flow in the pons and pre-central gyrus, beginning at 10 minutes post-irradiation and persisting throughout the 60-minute

observation period (Cockerham et al. 1986). Bruner (1977) examined cardiovascular parameters in Rhesus monkeys exposed to 1,000 rad (10 Gy) at rates of 129–164 rad/minute (1.29–1.64 Gy/minute). Heart rate was elevated post-exposure, blood pressure was reduced near the end of exposure and thereafter, cardiac output increased at the end of exposure, but thereafter fell to below control levels, and total peripheral resistance to blood flow decreased at early times post-exposure, but thereafter rose to above control levels. Ten of 12 dogs irradiated with 4,355–5,655 rad (43.6–56.6 Gy), focused on the interatrial septum of the heart, developed cardiac arrhythmias (Dick et al. 1979). The permeability of the blood-brain barrier was significantly increased, particularly for hydrophillic compounds, in rats exposed to 2,500 rad (25 Gy) from a ^{60}Co source (Bezek et al. 1990).

Gastrointestinal Effects. A worker accidentally exposed to an acute whole-body dose of 2,250 rad (22.5 Gy) showed slight atrophy of the stomach glands, marked atrophy in the small intestine, and total atrophy of the glands in the large intestine (Stavem et al. 1985). Two years after a woman received ^{60}Co radiation therapy amounting to 4,000 rad (40 Gy) anteriorly and 3,500 rad (35 Gy) posteriorly over a 6-week period, she reported severe gastrointestinal difficulties, including epigastric pain, vomiting, bloody stools, and weight loss (Roschler and Woodard 1969), eventually resulting in death. Autopsy revealed dense fibrous layers around the sacrum, with severe fibrosis confirmed by microscopic examination. Cobalt radiotherapy for carcinoma of the bladder (~3,100–3,600 rad, 31–36 Gy, over 18 days) resulted in loose bowel movements and a decreased absorption of vitamin B12 following oral exposure in 8 of 14 patients (McBrien 1973). No gastrointestinal symptoms were reported in three workers who were accidentally exposed to much lower exposure levels, ranging from 2.24 to 12.7 rad (0.022–0.127 Gy) (House et al. 1992).

Exposure of male Sprague-Dawley rats to 850 rad (8.5 Gy) of ^{60}Co gamma radiation resulted in marked alterations in drug absorption, primarily due to a decrease in gastric emptying rate (Brady and Hayton 1977b). Exposure of young adult beagle dogs to 800 rad (8 Gy) of ^{60}Co radiation at a rate of 177.5 rad/minute (1.775 Gy/minute) resulted in a 100% emesis rate within 10 hours post-irradiation, with an average of 2.4 episodes per animal and an average time to emesis of 82 minutes (Gomez-d-Segura et al. 1998). King (1988a) reported a NOAEL of 49 rad (0.49 Gy) and an EC_{50} of 77 rad (0.77 Gy) for emesis and wretching following exposure of male ferrets to ^{60}Co gamma radiation. Exposure of male Swiss mice to 1,000 rad (10 Gy) of ^{60}Co radiation resulted in necrosis of the intestinal crypt cells (Devi et al. 1979).

Hematological Effects. No changes in hematologic parameters were reported in three workers who were accidentally exposed to levels ranging from 2.24 to 12.7 rad (0.022–0.127 Gy) (House et al. 1992). Hashimoto and Mitsuyasu (1967) reported that in 50 of 58 patients receiving local radiotherapy, irradiated bone marrow was more hypoplastic in the hematopoietic elements than in non-irradiated marrow in the same individual. A male worker exposed to 159 rad (1.59 Gy) showed minor reductions in leukocytes, neutrophils, and lymphocytes (Klener et al. 1986). Stavem et al. (1985) reported that a male worker exposed to 2,250 rad (22.5 Gy) showed a progressive decrease in hemoglobin and circulating thrombocytes prior to death. Autopsy showed a pronounced hypocellularity of the bone marrow.

Seed et al. (1989) exposed male Beagle dogs to 7.5 rad/day (0.075 Gy/day) gamma radiation for 150–700 days from a ^{60}Co source. The irradiated dogs initially showed a significant suppression, compared with levels from the control animals, of the five circulating types of cells studied (granulocytes, monocytes, platelets, erythrocytes, and lymphocytes), which lasted ~250 days; this was followed by a recovery phase for the remainder of the study period. Hashimoto and Mitsuyasu (1967) exposed guinea pigs to whole-body ^{60}Co radiation, and reported an initial hypoplasia of the bone marrow followed by recovery of hematopoietic activity by 3 weeks post-irradiation. Robbins et al. (1989b) reported significant reductions in erythrocyte count, hematocrit, and hemoglobin levels within 6–8 weeks of irradiation of the kidneys of female pigs with 980–1,400 rad (9.8–14 Gy) of ^{60}Co gamma rays.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals following external exposure to ^{60}Co radiation. These tissues are among the most radioresistant in both humans and animals.

Hepatic Effects. No studies were located regarding hepatic effects in humans following external exposure to ^{60}Co radiation.

No changes in liver weight were seen in male Swiss mice exposed to 1,000 rad (10 Gy) of ^{60}Co radiation and examined every 4 hours for 24 hours post-irradiation (Mazur et al. 1991). Andrzejewski et al. (1980) reported increased respiration rates in rat liver mitochondria after whole-body exposure to 1,000 or 3,000 rad (10 or 30 Gy) of ^{60}Co radiation; the increase was greater and more persistent at the higher dose level.

Renal Effects. Stavem et al. (1985) reported that a 64-year-old man who accidentally received a fatal dose (2,250 rad) of cobalt radiation developed enlarged kidneys. No other studies were located regarding renal effects in humans after external exposure to cobalt radiation.

Robbins et al. (1989a, 1989b, 1989c, 1991a, 1991b) performed a series of studies in female White pigs wherein the kidneys of the animals were exposed to single doses of 780–1,400 rad (7.8–14 Gy) of ^{60}Co radiation and examined for periods up to 24 weeks postirradiation. Irradiation resulted in an initial increase in glomerular filtration rate (GFR), followed by a dose-related decrease in the GFR, beginning at 4 weeks postexposure. Effective renal plasma flow (ERPF) was also decreased in a dose-related manner beginning at 4 weeks postexposure, but did not show the initial increase seen in GFR. Some recovery of GFR and ERPF occurred by 24 weeks postirradiation, though values were still significantly reduced below controls in all groups but the 780 rad (7.8 Gy) group. Histology was performed on animals exposed to 980 rad (9.8 Gy) and killed between 2 and 24 weeks after exposure. Beginning at 2 weeks postirradiation, increased numbers of inflammatory cells were present within the glomerulus, and there was an increase in mesangial matrix and number of mesangial cells. The glomerular changes continued to progress in severity throughout the observation period, with generalized thickening of the capillary walls, extensive duplication of the basement membrane, and progressive inflammation. Tubular changes appeared to be maximal at 6 weeks, including focal degeneration and necrosis, with partial recovery at later timepoints.

Endocrine Effects. Prager et al. (1972) reported that 5 of 23 patients receiving cobalt radiotherapy (3,900–4,600 rad, 39–46 Gy) for Hodgkin's disease developed hypothyroidism, with substantial decreases in levels of T4 relative to patients with normal thyroids. Chang et al. (2001) examined the residents of ^{60}Co-contaminated buildings for effects on the thyroid. There was an increased prevalence of goiter in males of all ages and females <15 years of age, as well as a dose-related increase in the prevalence of thyroid cysts in females of all ages, and elevated tri-iodothyronine levels in males <15 years of age. No other studies examining the endocrine effects of radioactive cobalt exposure, either internal or external, in humans were located.

Whole-body acute exposure of rats to 330 rad (3.3 Gy) did not affect FSH, LH, or testosterone levels (Cunningham and Huckins 1978). Similarly, male Wistar rats exposed to a single dose of 80 rad (0.8 Gy) of testicular radiation showed no changes in FSH, LH, prolactin, or testosterone (Laporte et al. 1985). No

other studies examining the endocrine effects of radioactive cobalt exposure, either internal or external, in animals were located.

Dermal Effects. Several studies in humans have demonstrated that high-dose exposure to cobalt radiation can result in damage to the skin. Klener et al. (1986) described the accidental irradiation of a worker who was attempting to bring under control a sealed ^{60}Co source. The patient's left palm (the patient was left-handed) developed an irregular oval defect 3x4 cm with whitish edges and bleeding, as well as superficial lesions on the third and fourth finger. Considerable spontaneous pain required the administration of analgesics. The lesions showed no tendency to heal, instead spreading to the adjacent digits. After several failed skin graft attempts, the condition worsened, necessitating the amputation of fingers five through two. Walter (1980) reported that a patient who had undergone ^{60}Co radiotherapy (dose not reported) of the forehead and scalp developed a pronounced acneform reaction, characterized primarily by alopecia with multiple open comedones on the scalp and forehead, and hair loss. With treatment, the comedones were 80% cleared at 9 months post-diagnosis (13 months post-treatment), but no hair regrowth was noted. Myskowski and Safai (1981) have likewise reported localized comedones in a patient following 4,056 rad (40.6 Gy) of ^{60}Co radiotherapy. Van Oort et al. (1984) reported that patients receiving 4,700–6,000 rad (47–60 Gy) of ^{60}Co radiotherapy over a 7-week period showed significant differences in baseline color of the skin, primarily erythema, and pigmentation, beginning the third week of exposure and persisting throughout the fifth week postirradiation (study week 12). Johansson et al. (2000) reported that 86% of women who had been treated with 5,400–5,700 rad (54–57 Gy) after a radical mastectomy developed fibrosis of the skin of the treated area.

Cox et al. (1981) reported a dose-related loss of hair in rabbits exposed to 1,730–3,210 rad (17.3–32.1 Gy) ^{60}Co gamma rays, targeted at the skin near the eyes or of the ears, with recovery initially noted in animals exposed to 2,140 rad (<21.4 Gy) by day 200 postirradiation. Beginning at day 500 postirradiation, a substantial loss of hair again was seen, persisting throughout the end of the study. Mice exposed to 1,800 rad (18 Gy) of ^{60}Co radiation showed a slight increase in epilation score (Down et al. 1986).

Ocular Effects. Exposure to high-dose radiation from cobalt sources has been shown to result in effects on the eye, in particular the development of cataracts. Augsburger and Shields (1985) described 13 patients who developed cataracts following ^{60}Co plaque radiotherapy; estimated doses to the eyes ranged from 2,000 to 10,000 rad (20–100 Gy). Fishman et al. (1976) reported on two patients who

received head-only 60Co radiotherapy, in combination with chemotherapy, for the treatment of acute lymphocytic leukemia. Both patients, who received 2,400 rad (24 Gy) over an initial 16-day course of treatment followed later by either 2,400 or 2,500 rad (24 or 25 Gy) in followup therapy, developed progressively severe vision disorders, resulting in partial or total blindness. Exposure of a male worker to a whole-body dose of 159 rad (1.59 Gy) of ^{60}Co radiation resulted in a progressive deterioration of visual acuity, due to cataract development, in the left eye (which was more exposed than the right) over time (Klener et al. 1986). Chen et al. (2001) evaluated subjects that had been exposed to 120–194 mSv (range: 1.11–1493.4 mSv) for an undisclosed period of time for lenticular opacities. Subjects <20 years old showed a dose-dependent increase in the numbers of focal lens defects, while for those aged 20–40 and >40, no such statistical correlation was seen.

Other Systemic Effects. Thibadoux et al. (1980) reported that of 61 children receiving a course of 2,400 rad (24 Gy) of cranial radiotherapy, none developed significant reductions in hearing levels by the end of the third year after irradiation.

Taiwanese children (48 boys, 37 girls) who were raised in apartments contaminated with ^{60}Co were compared to 21,898 age- and sex-matched nonexposed children from a nationwide surveillance program (Wang et al. 2001). After adjusting for effects from parental heights and body mass index, clear dose-related decreases in height percentile (HP) and age-specific relative height differences (RHD) were seen in exposed boys, but not in exposed girls. Average cumulative doses were 120.8 and 129.9 mSv for the boys and girls, respectively.

Sweeney et al. (1977) examined the effects of 60Co radiation on the teeth of rats exposed to 0, 2,400, 4,800, or 7,200 rad (0, 24, 48, or 72 Gy). Animals exposed to 4,800 rad (48 Gy) showed transient effects on the incisors only, while at 7,200 rad (72 Gy), the effects lasted throughout the 10-week study period.

3.3.3.3 Immunological and Lymphoreticular Effects

A worker accidentally exposed to an acute dose of 2,250 rad (22.5 Gy) showed a rapid fall in circulating lymphocytes and granulocytes prior to death (Stavem et al. 1985). Chronic exposure to low amounts of ^{60}Co radiation in people living in a contaminated building significantly reduced the numbers of circulating CD4+ lymphocytes in the blood (Chang et al. 1997, 1999b); mean total radiation dose was estimated to be

0.169 Gy (16.9 rad) over a 2–13-year period. Similarly, children chronically-exposed to low levels (estimated dose of 0.002–0.085 Gy [0.2–8.5 rad]) of ^{60}Co radiation in a contaminated kindergarten building showed significant decreases in total leucocytes and neutrophils, but an increase in eosinophils, 5–7 years after exposure had ceased (Chang et al. 1999a).

In male Swiss mice exposed to 1,000 rad (10 Gy) of ^{60}Co radiation, significant decreases in weight of the spleen were seen as early as 1 hour post-exposure and persisted throughout the following 24 hours (Mazur et al. 1991). Spleen acid phosphatase activity, expressed as activity per gram of protein, was significantly increased in irradiated animals beginning at 13 hours post-exposure.

3.3.3.4 Neurological Effects

Exposure of both humans and animals to high doses of cobalt radiation has been shown to result in damage to nervous tissue, particularly peripheral nerves. Llena et al. (1976) presented a case wherein a 51-year-old woman who had received 13,150 rad (131.5 Gy) of 60Co radiation between the nasopharynx and cervical lymph nodes as part of radiotherapy developed focal necrosis of the brain in the frontal lobe, as confirmed by gross and microscopic examination. Fishman et al. (1976) reported on two patients who received head-only ^{60}Co radiotherapy, in combination with chemotherapy, for the treatment of acute lymphocytic leukemia. Both patients, who received 2,400 rad (24 Gy) over an initial 16-day course of treatment followed later by either 2,400 or 2,500 rad (24 or 25 Gy) in followup therapy, developed progressively severe vision disorders, resulting in partial or total blindness. Histopathology from one patient demonstrated severe alterations in the optic nerve, including severe atrophy, terminal beading, lack of myelin, and calcification. Sanyal et al. (1979) reported on five patients who received doses of 4,500–6,000 rad (45–60 Gy) ^{60}Co radiation as radiotherapy, who developed varying degrees of myelopathy, resulting in minimal to mild paralysis. In patients that had been treated with ^{60}Co radiation (total dose of 54–57 Gy, or 5,400–5,700 rad) following mastectomy, 63% developed brachial plexus neuropathy and 5% developed vocal chord paresis over the 30-year period reported by the study (Johansson et al. 2000).

Mele et al. (1988) exposed male rats to 50, 150, or 450 rad (0.5, 1.5, or 4.5 Gy) 3 times, at 43-day intervals, and examined them for changes in behavior daily for 30 days following each exposure. Rats exposed to 450 rad (4.5 Gy), but not those exposed to 150 rad (1.5 Gy) or 50 rad (0.5 Gy), showed

significant deficits in fixed-ratio response rates and running rates after each exposure, beginning the day after exposure and persisting for 4–5 days, after which both rates returned to normal. After the third exposure, all rats were exposed to 650 rad (6.5 Gy), which resulted in similar performance decrements as were seen in the 450 rad (4.5 Gy) animals, again beginning 24 hours after exposure, with previous exposure resulting in no differences in behavioral parameters. Maier and Landauer (1989) reported significant decreases in offensive behavior in mice acutely exposed to whole-body doses of 500 or 700 rad (5 or 7 Gy), but not those exposed to 300 rad (3 Gy), with changes occurring in the second week postirradiation and responses returning to normal by day 19 postirradiation. Rabin et al. (1998) reported that exposure of rats to ^{60}Co radiation (up to 30 Gy or 3,000 rad) showed a dose-related decrease in the acquisition of controlled taste aversion behavior. Bassant and Court (1978) reported that rabbits exposed to 450 rad (4.5 Gy) of ^{60}Co radiation whole-body showed an altered activity of hippocampal cells, with a slowed mean discharge rate and increased interspike variability persisting for at least 12 hours postirradiation.

3.3.3.5 Reproductive Effects

Ionizing radiation in general, and gamma-emitting isotopes in particular, is known to have profound effects on reproductive tissues, with effects seen primarily in rapidly-dividing germ cells resulting in temporary or permanent sterility in both sexes, as well as other effects (Agency for Toxic Substances and Disease Registry 1999). These effects are usually observed only at high radiation doses. Keys and Reed (1980) reported a case of a man who, as treatment for a prostate tumor, received an estimated dose of 6,600 rad (66 Gy) to the prostate over a 47-day period, and who later developed a severe prostatic calcification necessitating surgical correction.

^{60}Co radiation at high doses has been shown to elicit profound decrements in reproductive ability in animal species. Whole-body acute exposure of rats to 330 rad (3.3 Gy) decreased testicular weights beginning at 22 days postirradiation, with recovery of testicular weight beginning about day 65 (Cunningham and Huckins 1978). Histologic examination of the testes revealed destruction of the spermatogonial population, with a slow recovery as the spermatogonial population was rebuilt from the surviving stem cells. Searl et al. (1976) reported that exposure of male mice to 1,128 rad (11.3 Gy) over a 28-week period resulted in significant reductions of testis mass and epididymal sperm count. Male Wistar rats exposed to a single dose of 80 rad (0.8 Gy) to the testes showed increased tubular fluid production

and decreased testicular weight at 30 and 45 days postirradiation, but not at later time points (Laporte et al. 1985). Single doses of >100 rad (1 Gy) of ^{60}Co radiation caused decreased fertility in exposed female mice (Philippe 1975). Continuous exposure of female mice to an average daily dose of 8 or 16 rad/day (0.08 or 0.16 Gy/day) caused a decreased number of offspring per litter and decreased reproductive performance, with 100% sterility occurring at 32 weeks of exposure at 8 rad/day (0.08 Gy/day) or 20 weeks of exposure at 16 rad/day (0.16 Gy/day) (Searl et al. 1980). Female rabbits exposed to 400 rad (4 Gy) prior to implantation showed dramatic decreases in implantation (Chang et al. 1963).

3.3.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after external exposure to cobalt radiation.

In utero exposure to cobalt radiation has been extensively studied in animal species, and may elicit substantial effects across many organ systems of the developing organism. Effects have been noted following single-dose exposures as low as 10 rad (0.10 Gy) in mice (Devi et al. 1994; Wang et al. 1993), 50 rad (0.5 Gy) in rats (Bruni et al. 1994), 200 rad (2 Gy) in hamsters (Harvey and Chang 1962), 250 rad in rabbits (Chang et al. 1963), 15.6 rad (0.16 Gy) in dogs (Benjamin et al. 1998a, 1998b), and 100 rad (1 Gy) in monkeys (Brizzee et al. 1978). Organs known to be affected include the brain (Brizzee et al. 1978; Bruni et al. 1994; Devi et al. 1994; Hamilton et al. 1989; Reyners et al. 1992; Schmidt and Lent 1987), eyes (Brizzee et al. 1978; Bruni et al. 1994; Schweitzer et al. 1987), hair (Hirobe 1994; Hirobe and Zhou 1990), kidney (Benjamin et al. 1998a; Brizzee et al. 1978), liver (Devi et al. 1998), ovaries (Inano et al. 1989), pituitary (Brizzee et al. 1978), skeleton (including cleft palate, shortened digits, fused digits, and other gross abnormalities) (Bruni et al. 1994; Chang et al. 1963; Harvey and Chang 1962), spleen (Devi et al. 1998), teeth (Lee et al. 1989), testes (Inano et al. 1989; Suzuki et al. 1990), and thyroid (Benjamin et al. 1997). ^{60}Co radiation *in utero* has also shown to cause functional alterations, including postnatal growth retardation (Wang et al. 1993; Zhong et al. 1996), neurobehavioral changes (Brizzee et al. 1978; Wang et al. 1993), hormonal production (Brizzee et al. 1978; Inano et al. 1989; Suzuki et al. 1990), alterations in hepatic enzymes (Inano et al. 1990), and diabetes mellitus (Benjamin et al. 1998a). *In utero* irradiation with cobalt also leads to increased tumor incidence later in life (Benjamin et al. 1991, 1997, 1998b; Nitta et al. 1992).

Devi et al. (1994) exposed pregnant mice to a single dose of 0–50 rad (0–0.50 Gy) of ^{60}Co radiation on day 11.5 of gestation. A significant decrease in pup brain weight and an increase in the incidence of microphthalmia was seen at 10 rad (0.10 Gy), with decreases in head width, head length, body length, and body weight occurring at higher doses. A later study (Devi et al. 1998) found decreases in body weight, liver weight, and spleen weight in pups 72 hours after irradiation with 25 rad (0.25 Gy) of ^{60}Co radiation on day 17 of gestation. Male offspring, but not female offspring, of mice exposed to 50 rad (0.5 Gy) on gestation day 9 showed decreased body weights on postnatal days 0, 3, and 7, while offspring of both sexes showed delays in pinna detachment, incisor eruption, eye opening, and testes descent (Zhong et al. 1996). Wang et al. (1993) reported that mice exposed to a cumulative *in utero* dose of 10 rad (0.10 Gy) showed alterations in visual placing reflex tests, while those exposed to 20 or 40 rad (0.20 or 0.40 Gy) showed decreased mean body weight, delayed eye opening, and alterations in the air righting reflex.

Rats exposed to 50 rad (0.50 Gy) of ^{60}Co radiation on gestational day 9.5 showed histologic damage to the neuro-epithelium 4 hours post-exposure, with abnormal flexion of the embryo and abnormal flexion of the head at 48 hours post-exposure (Bruni et al. 1994). At birth, rats showed increased incidence of defective eye development, spinal curvature, and visceral anomalies. Reyners et al. (1992) reported decreased brain weight in 3-month-old rats that had been exposed to cumulative doses of 160 rad (1.6 Gy) over gestation days 12–16 or 170 rad (1.7 Gy) over gestation days 14–20. Male rats exposed to 210 rad (2.1 Gy) on day 20 of gestation showed atrophy of the testes, prostates, and seminal vesicles, as well as a complete disappearance of germinal cells within the testes, on postnatal day 70 (Suzuki et al. 1990). Inano et al. (1989) exposed rats on gestation day 20 to 260 rad (2.6 Gy) of ^{60}Co radiation. Seminiferous tubules of male offspring and ovaries of female offspring showed pronounced atrophy, and steroid hormone production was significantly altered.

Benjamin et al. (1997, 1998a, 1998b) exposed groups of pregnant Beagle dogs to 15.6–17.5 or 80.8–88.3 rad (0.15–0.175 or 0.8–0.88 Gy) of ^{60}Co radiation on day 8, 28, or 55 post-breeding. Animals were allowed to live their full life span and were observed for radiation-related illnesses and cause of death. No change in the mean age at death was seen as a result of exposure. Males exposed to either exposure level at day 55 post-breeding, but not females at any time or males exposed at days 8 or 28, showed an increase in deaths due to renal disease. High-dose females exposed on days 28 or 55 showed an increase in the frequency of diabetes mellitus. Both sexes showed an increase in malignant neoplasias in general when exposed to radiation at 8 or 55 days postcoitus, but not at 28 days, while females exposed on day 55 also showed an increase in lymphoid neoplasia. A similar exposure on day 28 or 55 postcoitus

also resulted in a dose-dependent decrease in brain weight (Hamilton et al. 1989). *In utero* radiation of dogs to higher doses (100–380 rad [1–3.8 Gy]) resulted in retinal dysplasia and atrophy (Schweitzer et al. 1987).

3.3.3.7 Cancer

The carcinogenic effects of high doses of ionizing radiation have been well documented (Agency for Toxic Substances and Disease Registry 1999), though the effects of lower doses are less clearly defined. Duncan et al. (1977) reported on a cohort of patients who had received radiotherapy for carcinoma of the cervix. Eight of 2,674 patients developed bladder tumors within 6 months to 20 years following irradiation; the incidence rate was over 57 times greater than the general female population. All eight patients had received high (therapeutic) doses of ^{60}Co irradiation, though five of the eight also received radium therapy in conjunction with ^{60}Co irradiation. Wollenberg et al. (1995) presented a case of a 55-year-old farmer who received a total of 25,150 rad (251.5 Gy) distributed over six areas of the body over an 8-month period as a ^{60}Co teletherapy treatment regimen. Twenty years after irradiation, the patient developed a total of 43 basal cell carcinomas of the skin over the treated areas, all of which were successfully removed with cryosurgery. A 2-year-old girl exposed to 1,800 rad (18 Gy) of ^{60}Co radiation as part of a treatment regimen for acute lymphoblastic leukemia L1 developed, at age 12, a basal cell carcinoma of the scalp (Garcia-Silva et al. 1996). Three patients receiving cobalt irradiation as part of a chemotherapy/radiation treatment developed basal cell carcinoma of the scalp 8–15 years after treatment in the area of radiation treatment (Dinehart et al. 1991).

3.3.4 Other Routes of Exposure

This section includes injection and *in vitro* studies that provide evidence for the biological basis of toxicity of stable and radioactive cobalt in humans and animals. Since these studies are not directly relevant to general population exposure conditions, no LSE tables have been created for this section.

3.4 GENOTOXICITY

Stable Cobalt. No studies were located regarding genotoxic effects in humans following oral or dermal exposure to cobalt. No studies were located regarding genotoxic effects in animals following inhalation exposure to cobalt.

Gennart et al. (1993) examined a cohort of 26 male workers who had been occupationally-exposed to cobalt, chromium, nickel, and iron. Analysis of variance on sister-chromatid exchange rank values revealed that exposure status (exposed vs. controls) and smoking habits had statistically significant effects. De Boeck et al. (2000) reported no significant change in the comet assay on lymphocytes from nonsmoking workers who had been occupationally exposed to cobalt or hard metal dusts; a positive association was found between hard metal exposure and increased micronucleus formation in smokers only.

Single oral exposure of male Swiss mice to 0, 4.96, 9.92, or 19.8 mg cobalt/kg as cobalt chloride resulted in significantly increased percentages of both chromosomal breaks and chromosomal aberrations in bone marrow cells, with significant linear trends toward increasing aberrations with increased exposure (Palit et al. 1991a, 1991b, 1991c, 1991d).

Results of genetic testing of cobalt are presented in Table 3-5. Several different forms of cobalt, including cobalt chloride and cobalt sulfide, were tested. No profound differences were found among the various forms.

Cobalt was found to be generally nonmutagenic in bacteria (*Salmonella typhimurium*, *Escherichia coli*) and yeast when compounds with a valence state of II were tested (Arlauskas et al. 1985; Fukunaga et al. 1982; Kanematsu et al. 1980; Kharab and Singh 1985; Ogawa et al. 1986; Singh 1983; Tso and Fung 1981). A very weak mutagenic response was found with *Bacillus subtilis* (Kanematsu et al. 1980). A mutagenic response to cobalt was found, however, when compounds with a valence state of III were tested in *S. typhimurium* and *E. coli* (Schultz et al. 1982). The authors suggested that this may be due to the formation of cobalt(III) complexes that are inert to ligand substitution, allowing optimal interaction of cobalt with genetic material (Schultz et al. 1982). Other studies have shown cobalt to be a comutagen in combination with 4-substituted pyridines in *S. typhimurium* (Ogawa et al. 1988). It has been reported that cobalt acts as an antimutagen in bacterial (*S. typhimurium*, *B. subtilis*, *E. coli*) and yeast test systems

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

Species (test system)	End point	Results		Reference	Valence state
		With activation	Without activation		
Stable Cobalt					
Prokaryotic organisms:					
Salmonella typhimurium (plate incorporation)	Gene mutations	No data	–	Tso and Fung 1981	II
S. typhimurium (plate incorporation)	Gene mutations	No data	–	Arlauskas et al. 1985	II
S. typhimurium (plate incorporation)	Gene mutations	No data	–	Ogawa et al. 1986	II
S. typhimurium (plate incorporation)	Gene mutations	No data	+	Schultz et al. 1982	III
Bacillus subtilis (rec assay)	Gene mutations	No data	(+)	Kanematsu et al. 1980	II
Escherichia coli (reversion assay)	Gene mutations	No data	–	Kanematsu et al. 1980	II
E. coli (repair assay)	DNA damage	No data	+	Schultz et al. 1982	III
Eukaryotic organisms:					
Fungi:					
Saccharomyces cerevisiae (plate assay)	Reversion	No data	–	Kharab and Singh 1985	II
S. cerevisiae (plate assay)	Reversion	No data	–	Fukunaga et al. 1982	II
S. cerevisiae (plate assay)	Reversion	No data	–	Singh 1983	II
S. cerevisiae (plate assay)	Conversion	No data	+	Kharab and Singh 1985	II
S. cerevisiae (plate assay)	Conversion	No data	+	Fukunaga et al. 1982	II
S. cerevisiae (plate assay)	Conversion	No data	+	Singh 1983	II
Mammalian cells:					
Hamster ovary cells	Clastogenic effects	No data	+	Hamilton-Koch et al. 1986	II
Hamster embryo cells	Transformation	No data	+	Costa et al. 1982	II
Human lymphocytes	Sister chromatid exchange	No data	+	Andersen 1983	II
Human HeLa cells	Inhibition of DNA synthesis	No data	+	Painter and Howard 1982	II
Human diploid fibroblasts	DNA damage	No data	+	Hamilton-Koch et al. 1986	II

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

Species (test system)	End point	Results		Reference	Valence state
		With activation	Without activation		
Radioactive Cobalt					
Mammalian cells:					
Chinese hamster ovary cells	DNA amplification	No data	+	Luecke-Huhle et al. 1986	N/A
Hamster embryo cells	DNA amplification	No data	+	Luecke-Huhle et al. 1990	N/A
Mouse lymphosarcoma cells	Chromosomal aberrations	No data	+	Juraskova and Drasil 1987	N/A
Mouse lymphosarcoma cells	Sister-chromatid exchanges	No data	+	Juraskova and Drasil 1987	N/A
Human lymphocytes	Chromosomal aberrations	No data	+	Koksal et al. 1995	N/A
Human lymphocytes	Micronucleus formation	No data	+	Koksal et al. 1996	N/A
Human leukocytes	DNA strand breaks	No data	+	Rueff et al. 1993	N/A
Human leukocytes	Chromosomal aberrations	No data	+	Rueff et al. 1993	N/A
Human leukocytes	Chromosome breaks	No data	+	Lindahl-Kiessling et al. 1970	N/A
Human fibroblasts	Transformation	No data	+	Namba et al. 1981	N/A
Human fibroblasts	Transformation	No data	+	Namba et al. 1985	N/A
Human fibroblasts	DNA strand breaks	No data	+	Coquerelle et al. 1987	N/A
Human fibroblasts	Transformation	No data	+	Namba et al. 1988	N/A
Human fibroblasts	Retinoblastoma gene alterations	No data	+	Endo et al. 1993	N/A
Human fibroblasts	DNA strand breaks	No data	+	Dolling et al. 1998	N/A
Human kidney cells	DNA strand breaks	No data	+	Feinendegen et al. 1977	N/A
Human kidney cells	DNA strand breaks	No data	+	Feinendegen et al. 1978	N/A

DNA = deoxyribonucleic acid; + = positive results; – = negative results; (+) = weakly positive results

(*Saccharomyces cerevisiae*) (Inoue et al. 1981; Kada et al. 1986; Kuroda and Inoue 1988). A possible explanation was that cobalt acts by correcting the error-proneness of deoxyribonucleic acid (DNA) replicating enzymes by improving their performance in DNA synthesis (Inoue et al. 1981; Kada et al. 1986; Kuroda and Inoue 1988). However, cobalt has also been shown to increase the frequency of genetic conversions in *S. cerevisiae* (Kharab and Singh 1985; Singh 1983). The reasons for this apparent dichotomy in yeast cells is not known.

In contrast to the results seen in bacteria, stable cobalt compounds were generally found to be genotoxic or mutagenic in mammalian assay systems. Exposure to cobalt compounds (metal, salts, or hard metal) has been shown to produce clastogenic effects in mammalian cells, including human lymphocytes (Anard et al. 1997; Hamilton-Koch et al. 1986; Painter and Howard 1982); transformation in hamster cells (Costa et al. 1982); sister chromatid exchanges in human lymphocytes (Andersen 1983); and micronucleus formation in mouse bone marrow cells (Suzuki et al. 1993) and human lymphocytes (Capomazza and Botta 1991; Olivero et al. 1995; Van Goethem et al. 1997). Hard metal is generally more genotoxic in *in vitro* tests than other cobalt compounds. Cobalt ions are also thought to inhibit DNA repair in mammalian cells by interaction with zinc-finger proteins involved in DNA excision repair (Asmuß et al. 2000; De Boeck et al. 1998; Hartwig et al. 1991; Kasten et al. 1997; Sarkar 1995).

Thirty hours following single intraperitoneal injection of cobalt(II) chloride in BALB/c mice, an increase in micronucleus formation was seen at 12.4 or 22.3 mg cobalt/kg (as cobalt chloride), but not at 6.19 mg/kg (Suzuki et al. 1993). Single injection of mg cobalt/kg (as cobalt chloride) resulted in significantly increased micronucleus formation at 24 hours post-injection, but not at 12, 48, 72, or 96 hours. Two or 10 days following intraperitoneal injection of male and female F344 rats with 3 or 6 mg cobalt/kg, increased levels of oxidatively-damaged DNA bases were noted in the liver, kidney, and to a lesser extent, the lung (Kasprzak et al. 1994).

Radioactive Cobalt. The ability of ionizing radiation to induce genotoxic damage is well-documented (Agency for Toxic Substances and Disease Registry 1999). Chang et al. (1999c) reported increased micronucleus frequency, both of single and multiple nucleates, in 48 people who had been exposed to 12–1,600 rad (0.12–16 Gy) over a 2–10-year period as a result of a building contaminated with ^{60}Co-containing steel. Subjects who had left the building showed a decrease in micronucleus formation that correlated with time since cessation of exposure. Three workers accidentally exposed to 2.2–12.7 rad (0.022–0.127 Gy) showed no elevation in frequency of chromosome alterations (House et al. 1992). Ten

children who received chemotherapy and 1,725–2,405 rad (17.25–24.05 Gy) as cobalt radiotherapy for acute lymphatic leukemia showed no clastogenic changes after chemotherapy but before irradiation. After radiotherapy, significant dose-related increases in chromosomal aberrations were seen (Rauscher and Bauchinger 1983).

Radiation from cobalt isotopes has been shown to induce numerous genetic changes, including translocations (Gilot-Delhalle et al. 1988; Grahn and Carnes 1988; Grahn et al. 1983; Searl et al. 1976), decreased DNA synthesis (Lohmann et al. 1966), dominant lethal mutations (Grahn et al. 1988; Searl et al. 1976; Zhou et al. 1986), chromosome deletions (Brooks et al. 1971b, 1974), polycentrics (Brooks et al. 1971a, 1974), and aberrations (Brooks et al. 1971a, 1971b) in exposed animals.

Radiation from cobalt isotopes was genotoxic in several assay systems in mammalian cells: DNA amplification in hamster cells (Lucke-Huhle et al. 1986, 1990); chromosomal aberrations and sister-chromatid exchanges in mouse lymphosarcoma cells (Juraskova and Drasil 1987); chromosomal aberrations and micronucleus formation in human lymphocytes (Koksal et al. 1995, 1996; Schmid et al. 2002); DNA breakage in human leukocytes (Lindahl-Kiessling et al. 1970; Reuff et al. 1993), kidney cells (Feinendegen et al. 1977), and fibroblasts (Coquerelle et al. 1987; Dolling et al. 1998); chromosomal aberrations in human leukocytes (Reuff et al. 1993); transformation of human fibroblasts (Namba et al. 1981, 1985, 1988); and retinoblastoma gene alterations in human fibroblasts (Endo et al. 1993).

3.5 TOXICOKINETICS

3.5.1 Absorption

3.5.1.1 Inhalation Exposure

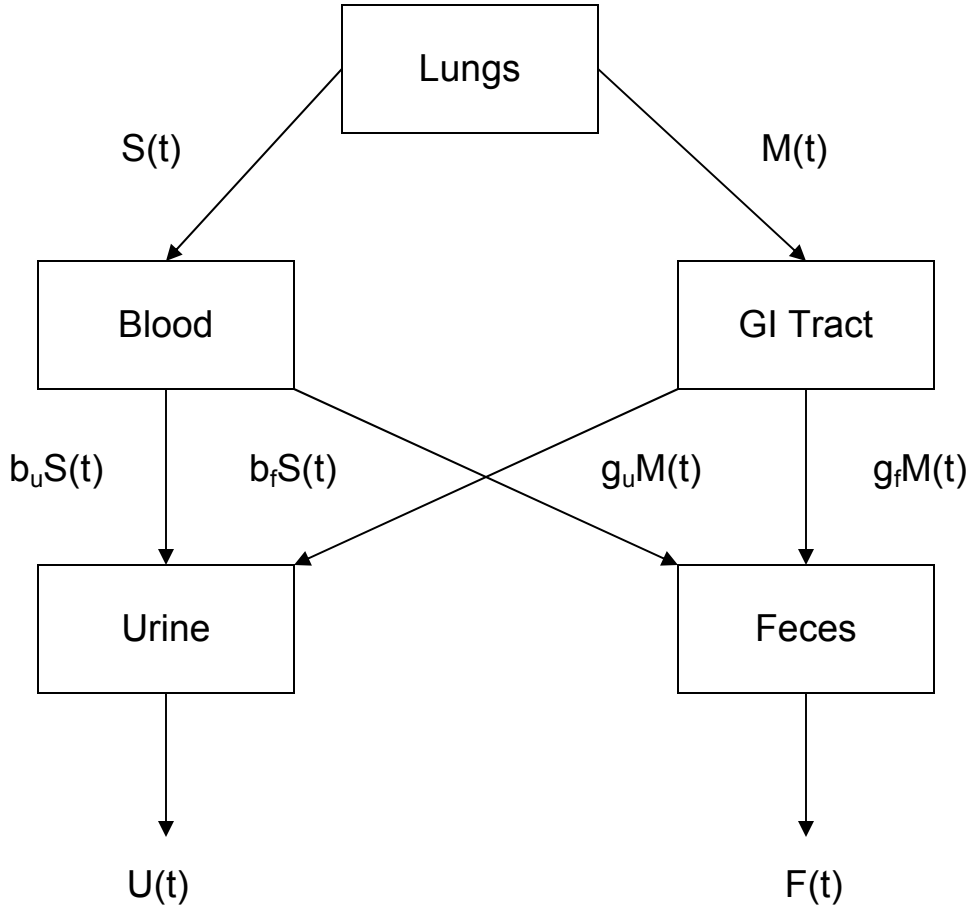
Inhaled cobalt particles are deposited in the upper and lower respiratory tract and cobalt is subsequently absorbed by several mechanisms (Casarett and Doull 1986); however, two of these mechanisms in particular appear to be most relevant. The deposition pattern in the respiratory tract is related to particle size, which determines the degree to which particles are affected by inertial impaction, sedimentation, diffusion, and electrostatic precipitation. Large particles (diameter >2 μm) tend to deposit in the upper respiratory tract where high airstream velocities and airway geometry promote inertial impaction of larger particles. Smaller particles escape inertial impaction and enter the lower respiratory tract where lower

airstream velocities and airway geometry favor the process of sedimentation, diffusion, and electrostatic precipitation of small particles. Fractional deposition can be expected to vary considerably with age, particle size, and breathing patterns (see Table 3-10). Fractional deposition of inhaled cobalt oxide particles in humans varied from approximately 50% of the inhaled dose for particles with a geometric mean diameter of 0.8 μm to approximately 75% of the inhaled dose for particles with a geometric mean diameter of 1.7 μm (Foster et al. 1989).

The transfer pathways of cobalt oxide (^{57}Co used as a tracer) from the lungs in humans and animals are shown in Figure 3-4. Particles of cobalt deposited in the respiratory tract can be absorbed into the blood after dissolution (S(t)) or mechanically transferred to the gastrointestinal tract by mucociliary action of the respiratory tract and swallowing action (M(t)). Only a portion (probably <50%) of the cobalt that enters the gastrointestinal tract will be absorbed into the body. The relative magnitude of the translocation and mechanical clearance pathways depends on the size and solubility of the cobalt particles that are inhaled. Large particles (>2 μm) will tend to deposit in the middle and upper airways where mechanical clearance mechanisms predominate over translocation. Smaller particles that enter the lower respiratory tract will tend to remain until dissolved or phagocytized by macrophages and translocation occurs. The sum of the activities of translocation and mechanical clearance determine the kinetics of absorption of inhaled cobalt. In humans, the ratio of translocation (S(t)) to mechanical clearance (M(t)) is approximately 5–1 for particle sizes ranging from 0.8 to 1.7 μm (mean geometric diameter) (Foster et al. 1989).

Data on retention of cobalt oxide (^{57}Co used as a tracer) in the respiratory tracts of humans and several animal species are summarized in Table 3-6. Considerable variability exists among species. In humans, almost one-half of the original lung burden persisted 6 months after exposure; in rats, clearance of cobalt from the lungs was nearly complete after 6 months. The elimination half-time for cobalt in the human lung increased with increasing time after exposure (Foster et al. 1989; Sedlet et al. 1958). This may reflect slower clearance of cobalt that is bound to cellular components in the lung (Kreyling et al. 1985, 1986).

Figure 3-4. Transfer Parameters for Cobalt Following Inhalation of Cobalt Oxide* (CO_3O_4) Particles, Showing the Fractions of the Lung Content, L(t), and Time, t, Cleared Per Day by Each Route**



GI tract = gastrointestinal tract;
$b_fS(t)$ = fraction of cobalt excreted in the feces after translocation;
$b_uS(t)$ = fraction of cobalt excreted in the urine after translocation;
F(t) = fecal excretion rate;
$g_fM(t)$ = fraction of cobalt excreted in the feces after mechanic clearance to the gastrointestinal tract;
$g_uM(t)$ = fraction of cobalt excreted in the urine after mechanic clearance to the gastrointestinal tract;
M(t) = rate of mechanical transport of cobalt particles from the lungs to the gastrointestinal tract;
S(t) = rate of translocation of cobalt from the lungs to the blood;
U(t) = urinary excretion rate

*Cobalt-57 tracer used
**Derived from Bailey et al. 1989

Table 3-6. Initial (Day 3) Lung Deposits of Cobalt Oxide and Summary of Lung Retention at 90 and 180 Days[a,b]

	Mean initial ^{57}Co activity in lung L(3) (kBq)		Lung retention L(90)/L(3) (%)		Lung retention L(180)/L(3) (%)	
Species (strain)	0.8 μm	1.7 μm	0.8 μm	1.7 μm	0.8 μm	1.7 μm
Human	53	42	64	75	45	56
Baboon	2,100	1,700	55	55	26	37
Beagle dog	1,150	1,450	27	45	5.5	12
Guinea pig (Harwell)	8.4	1.4	49	46	8.3	15
Rat (HMT, 1985)	10.8	4.7	5.2	20	1.3	8.0
Rat (HMT, 1986)	3.2	0.7	5.3	18	1.2	9.2
Rat (F344, SPF)	8.8	4.4	14	25	4.7	9.2
Rat (Sprague-Dawley)	0.9	0.10	8	39	1	15
Syrian hamster	4.0	1.2	21	35	3.4	12
Mouse (CBA/H)	1.8	No data	15	No data	2.8	No data

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer

3.5.1.2 Oral Exposure

Gastrointestinal absorption of cobalt in humans varies considerably (18–97% of the given dose) based on the type and dose of cobalt compound given and the nutritional status of the subjects (Harp and Scoular 1952; Smith et al. 1972; Sorbie et al. 1971; Valberg et al. 1969). More cobalt was absorbed through the gastrointestinal tract of humans when the body was deficient in iron (31–71% in iron deficiency; 18–44% in controls) (Sorbie et al. 1971; Valberg et al. 1969). One study in humans has shown that oral exposure to cobalt chloride resulted in significantly higher urinary excretion in females relative to males (Christensen et al. 1993).

In animal studies, many factors have been shown to influence the absorption of cobalt compounds following oral exposure. In several studies in rats (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Schade et al. 1970; Taylor 1962), soluble cobalt chloride was absorbed in the range of 13–34%, whereas physiologically insoluble cobalt oxide particles have been shown to be poorly absorbed, in the range of 1–3% (Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989). The particle size of the given dose of cobalt oxide had no significant effect on gastrointestinal absorption (Table 3-7). Administration of cobalt chloride labeled with radioactive 58Co and complexed with histidine, lysine, glycylglycine, ethylenediaminetetraacetic acid (EDTA), casein, or glycine resulted in decreased gastrointestinal absorption of cobalt; administration of cobalt chloride (with 58Co tracer) in cows' milk permitted a significantly greater (about 40%) absorption through the gastrointestinal tract (Taylor 1962). The same study found that while there was no difference in the chlorides of cobalt(II) and cobalt(III), a cobalt(II) glycine complex was absorbed in greater quantities than a cobalt(III) glycine complex. Other studies have also demonstrated that the chemical form of the cobalt compound can affect the absorption of cobalt following oral exposure (Deka et al. 1981; Firriolo et al. 1999; Inaba et al. 1980; Kinoshita and Fujita 1972), with more water-soluble compounds generally showing greater absorption.

Iron deficiency led to increased absorption of cobalt from the gastrointestinal tract, and simultaneous administration of cobalt and iron reduced the amount of cobalt absorbed (Reuber et al. 1994; Schade et al. 1970). Increasing oral doses of cobalt resulted in decreased fractional absorption (Houk et al. 1946; Kirchgessner et al. 1994; Taylor 1962), and more soluble forms of cobalt were better absorbed than less soluble compounds (Kreyling et al. 1986). Absorption is 3- to 15-fold greater in younger animals (rats and guinea pigs examined from days 1–60 of life) than in adult (200 days of age) animals (Naylor and

Table 3-7. Summary of Measurements of Retention and Excretion After Intragastric Administration of Cobalt Oxide (Co_3O_4) Particles (Mean Percentage of Recovered Activity at 7 Days After Administration)[a,b]

Species (strain)	Cumulative fecal excretion		Whole body retention		Cumulative urinary excretion		Absorption	
	0.8 µm	1.7 µm	0.8 µm	1.7 µm	0.8 µm	1.7 µm	0.8 µm	1.7 µm
Baboon	97.8	98.4	0.12	0.20	2.0	1.4	2.6	1.9
Guinea pig	98.7	97.6	0.16	0.66	1.1	1.9	1.3	2.3
Rat (HMT)	96.3	99.4	0.09	0.02	2.8	0.6	3.9	1.0
Rat (F-344)	99.6	99.7	0.04	0.03	0.4	0.3	0.4	0.3
Hamster	96.0	96.3	0.50	0.18	3.5	3.5	5.1	5.1
Mouse (CBA/H)	99.1	No data	0.3	No data	0.6	No data	0.8	No data

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer

Harrison 1995). Species differences in absorption of cobalt oxide do not appear to exist (Bailey et al. 1989), but absorption of soluble cobalt compounds is greater in rats (13–34%) than in dairy cows (1–2%) and guinea pigs (4–5%) following oral exposure (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Naylor and Harrison 1995; Schade et al. 1970; Taylor 1962; van Bruwaene et al. 1984).

3.5.1.3 Dermal Exposure

Four humans who placed their right hands into a box filled with hard metal dust (~5–15% cobalt metal, 95–85% tungsten carbide) for 90 minutes showed an increase in urinary cobalt levels by an order of magnitude in the post-exposure samples, remaining elevated for as long as 48–60 hours (Scansetti et al. 1994). Similarly, cobalt was detected in the fingernails of three volunteers who placed their fingers in cobalt solution 10 minutes/day for 7 days (Nielsen et al. 2000), even after the cessation of exposure. These findings demonstrate that cobalt from these metal dusts can be absorbed through the skin. The absorption of $2.2x10^{-5}$ mg ^{60}Co/kg as cobalt chloride in 1.4N HCl through 1 cm^2 of intact or abraded skin of guinea pigs was examined by Inaba and Suzuki-Yasumoto (1979). Absorption through intact skin was very small (<1%), while absorption through abraded skin was almost 80% 3 hours after exposure. A study in hamsters (Lacy et al. 1996) also reported a low amount of absorption of cobalt through unabraded skin.

3.5.1.4 Other Routes of Exposure

No studies were located regarding absorption of cobalt in humans or animals after other routes of exposure.

3.5.2 Distribution

As a component of vitamin B_{12}, cobalt is an essential element and, therefore, is found in most body tissues. It has been identified in liver, muscle, lung, lymph nodes, heart, skin, bone, hair, stomach, brain, pancreatic juice, kidneys, plasma, and urinary bladder of nonexposed subjects, with the highest cobalt concentration found in the liver (Collecchi et al. 1986; Forbes et al. 1954; Hewitt 1988; Ishihara et al.

1987; Muramatsu and Parr 1988; Teraoka 1981; Yamagata et al. 1962; Yukawa et al. 1980) (see Chapter 6 for more information). Tissue levels reflected exposure from all routes. The total body content of cobalt has been estimated at 1.1–1.5 mg (ICRP 1979; Yamagata et al. 1962); about 0.11 mg was found in the liver (ICRP 1979).

In patients with laryngeal carcinoma, levels of cobalt in the tumor were significantly higher ($p<0.001$) than levels in the nonmalignant tissues around the tumor (68.7 ng/g tissue versus 39.6 ng/g) (Collecchi et al. 1986). The mean cobalt concentrations in plasma (18.3 ng/mL) were also significantly higher in these patients than in the comparison population (0.73 ng/mL). The clinical significance of these findings is not known.

3.5.2.1 Inhalation Exposure

In workers occupationally exposed to airborne cobalt, increased cobalt levels were found in tissues at death. Significant increases in cobalt in the lung have been found in copper smelter and metal workers and coal miners occupationally exposed to cobalt (Gerhardsson et al. 1984; Hewitt 1988; Hillerdal and Hartung 1983; Teraoka 1981). No increase in liver or kidney cobalt levels were found in the copper smelter workers as compared to controls (Gerhardsson et al. 1984). In metal workers, increased cobalt levels were also found in the lymph nodes, liver, spleen, and kidneys (Hillerdal and Hartung 1983; Teraoka 1981).

The tissue distribution of cobalt in animals is similar to that in humans, with marked increases in the concentration of cobalt in the lungs following inhalation exposure (Barnes et al. 1976; Brune et al. 1980; Collier et al. 1991; Kreyling et al. 1986; Kyono et al. 1992; Patrick et al. 1989; Talbot and Morgan 1989). Histologically, the particles of cobalt in the lung are found in macrophages within the bronchial wall or in the interstitium close to the terminal bronchioli (Brune et al. 1980). Significant concentrations of cobalt have been found in the liver, kidney, trachea, spleen, bones, and heart (Barnes et al. 1976; Brune et al. 1980; Kerfoot 1975; Kreyling et al. 1986; Wehner and Craig 1972), with the greatest concentrations in the liver and the kidney (Kerfoot 1975; Wehner and Craig 1972).

3.5.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to cobalt.

In animals, the cobalt absorbed through the gastrointestinal tract was primarily retained in the liver (Ayala-Fierro et al. 1999; Greenberg et al. 1943; Simesen 1939). Appreciable levels were also found in the kidneys, heart, stomach, and intestines (Ayala-Fierro et al. 1999; Persson et al. 1992; Simesen 1939). Following a single oral dose of cobalt napthenate, appreciable levels of cobalt were found in the heart, liver, and kidney, but not in the spleen or testes (Firriolo et al. 1999). Following oral exposure to pregnant rats, a dose-dependent increase in cobalt levels in fetal blood and amniotic fluid was seen (Szakmary et al. 2001).

Following longer-term exposure (8 weeks) to cobalt sulfate in the diet, exposed rats showed a 30-fold increase in the cobalt concentration in the myocardium, a 26-fold increase in the concentration in the soleus muscle, and a 100-fold increase in the concentration in serum compared with nonexposed controls (Clyne et al. 1988; Pehrsson et al. 1991). Long-term oral exposure of rats to cobalt chloride resulted in significantly increased levels of cobalt in the liver, kidney, muscle, brain, and testes of treated rats (Barnaby et al. 1968; Bourg et al. 1985; Thomas et al. 1976).

3.5.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to cobalt.

3.5.2.4 Other Routes of Exposure

Following intravenous injection of cobalt chloride (as a combination of radioactive $^{55}CoCl_2$ and $^{56}CoCl_2$) in two humans, the liver and bladder contained the highest portions of cobalt (Jansen et al. 1996).

Distribution in animals after an intravenous dose appears to be similar to what we know of cobalt distribution in humans following injection of cobalt compounds. Two hours after intravenous injection of cobalt chloride (with a radioactive ^{57}Co tracer) in rats, accumulation was found in the liver (22.8% of the dose), kidneys (10.2%), and intestines (3.16%) (Gregus and Klaassen 1986). Similar results (29% liver,

10% kidneys, 4.6% intestines) were found following intracardiac injection of cobalt nitrate in rats (Patrick et al. 1989) or intravenous injection of a combination of radioactive $^{55}CoCl_2$ and $^{56}CoCl_2$ in rats (exact percentages were not provided) (Jansen et al. 1996). One hundred days after intravenous injection of $^{60}CoCl_2$ in rats, the greatest concentrations were found in spleen>heart>bone, while liver and kidney, initially the highest in cobalt, contained comparatively low amounts of cobalt (Thomas et al. 1976). Similar results were seen 132 days following an intraperitoneal injection of $^{60}CoCl_2$ in rats (Barnaby et al. 1968). Intramuscular injection of cobalt mesoporphyrin in rats yielded the greatest levels of cobalt in liver and blood, followed by kidney, lung, spleen, adrenal glands, and heart at 7 days post-injection and later (Feng et al. 1998). Four weeks after subcutaneous administration of cobalt protoporphyrin, the greatest tissue levels of cobalt occurred in the kidney, followed by spleen, liver, lung, thymus, and gonads (Rosenberg 1993). When cobalt (with a ^{57}Co tracer) encapsulated in liposomes was intravenously injected into rats, decreased distribution to the heart (40% less than animals receiving cobalt chloride), kidneys, and carcass, and increased distribution to the spleen and bones were found (Szebeni et al. 1989).

3.5.3 Metabolism

Cobalt is essential in the body because it is a component of cyanocobalamin (vitamin B_{12}) (Vouk 1986). Vitamin B_{12} acts as coenzyme in many enzymatic reactions, most notably a methyl transfer reaction that converts homocysteine to methionine and for a separate reaction that converts L-methylmalonylcoenzyme A (CoA) to succinyl-CoA (Institute of Medicine 2000). Vitamin B_{12} is also a part of some enzymes involved in hematopoiesis; deficiency can lead to pernicious anemia (Domingo 1989). No other essential function of cobalt has been reported. The Recommended Dietary Allowance (RDA) for vitamin B_{12} for adults is 2.4 μg/day, which contains 0.1 μg of cobalt (Institute of Medicine 2000).

3.5.4 Elimination and Excretion

3.5.4.1 Inhalation Exposure

No data are available on the clearance of soluble cobalt particles in humans. Following exposure of humans to physiologically insoluble cobalt compounds (cobalt metal, cobalt oxides), clearance from the body, assessed by both urinary/fecal clearance and a reduction in whole-body retention, appears to follow

three-phase kinetics. The first phase, likely representing mucociliary clearance of particles deposited in the tracheobronchial region, has a half-time on the order of 2–44 hours (Apostoli et al. 1994; Mosconi et al. 1994b). The second phase, with a half-time on the order of 10–78 days, may represent macrophage-mediated clearance of cobalt particles from the lung (Beleznay and Osvay 1994; Mosconi et al. 1994b). The third clearance phase, representing long-term clearance from the lungs, has a half-time on the order of years (Bailey et al. 1989; Beleznay and Osvay 1994; Mosconi et al. 1994b; Newton and Rundo 1971). Following a controlled aerosol exposure in humans, about 40% of the initial lung burden of inhaled cobalt oxide (with a 57Co tracer) was retained for a period of 6 months after exposure (Foster et al. 1989). Within the first week, about 17% of the initial lung burden was eliminated, with the majority (about 90%) mechanically cleared to the gastrointestinal tract and excreted in the feces (Foster et al. 1989). Six months after exposure, a cumulative elimination of 33% of the initial lung burden was found in the urine and 28% was found in the feces (Foster et al. 1989). The ratio of peak absorption rate to average mechanical clearance rate (Figure 3-4 and Table 3-8) was about 5 to 1. The elimination of cobalt following inhalation exposure was affected by the time after exposure (urinary excretion increases as time increases) and particle size (more cobalt is initially mechanically cleared to the gastrointestinal tract when the aerosol consists of bigger particles) (Bailey et al. 1989; Foster et al. 1989).

In animals, the solubility of the cobalt compound appears to greatly affect its long-term clearance. Studies with cobalt oxides have shown that the more soluble CoO is cleared from the lungs at a greater rate than the less soluble Co_3O_4 (Barnes et al. 1976; Kreyling 1984a). More soluble cobalt compounds are absorbed into the blood at a greater rate, and excreted in the urine and, to a lesser extent, the feces (Barnes et al. 1976). The rate of urinary excretion appears to correlate with the rate of translocation of cobalt from the lungs to the blood, and the rate of fecal clearance with the rate of mechanical clearance of cobalt from the lungs to the gastrointestinal tract (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kreyling et al. 1986, 1989; Patrick et al. 1989; Talbot and Morgan 1989). Following an initial high rate of fecal clearance, urinary excretion was the primary route of cobalt elimination after a single inhalation exposure (2 weeks of observation) (Palmes et al. 1959) or 3 months of exposure (Kerfoot 1975; Palmes et al. 1959). In several species of animals, most of the inhaled Co_3O_4 (with a ^{57}Co tracer) following a single exposure was cleared from the lungs by 6 months after exposure (Table 3-6) (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kreyling et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). The peak translocation and average mechanical clearance of cobalt from the lungs for different species are reported in Table 3-8, with the rate (high to low) following as mouse > rat > hamster > guinea pig > baboon, human > beagle dog.

Table 3-8. Peak Translocation and Average Mechanical Clearance Rates After Inhalation of Cobalt Oxide[a,b]

	Percent of lung content cleared per day				
	Translocation at peak				Average mechanical clearance[c]
Species (strain)	0.8 µm	Peak day	1.7 µm	Peak day	
Human	0.45	180	0.5	180	0.1
Baboon	0.6	180	0.2	d	0.1
Beagle dog	2.1	85	1.7	180	0.03
Guinea pig	2.1	180	1.0	75	0.3
Rat HMT	2.4	40	0.6	d	0.9
Rat (F-344)	1.1	10	0.4	d	1.0
Hamster	1.8	180	0.7	180	0.8
Mouse	1.7	180	No data	No data	1.05

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer
[c]Clearance rates were virtually identical in both particle size groups
[d]Constant value over 180 days

3.5.4.2 Oral Exposure

In humans orally exposed to cobalt, fecal elimination, which is the primary route of elimination, varies considerably (3–99% of the dose) and depends on the amount and type of cobalt given and on the nutritional status of the subjects (Section 3.5.1.2) (Harp and Scoular 1952; Paley et al. 1958; Smith et al. 1972; Sorbie et al. 1971; Valberg et al. 1969). Within days after oral exposure, 10 times more cobalt was excreted in feces than in the urine (Paley et al. 1958). Less cobalt was eliminated in the feces (more was absorbed) in subjects with an iron deficiency (Sorbie et al. 1971; Valberg et al. 1969).

Fecal elimination of cobalt is the primary route of elimination in animals following oral exposure and depends mainly upon the particle solubility (decreasing fecal clearance with increasing solubility) of the cobalt compound. The cumulative urinary and fecal elimination in several species following oral administration of Co_3O_4 (with a ^{57}Co tracer) is reported in Table 3-7 (Bailey et al. 1989). Following oral administration in several species, very little Co_3O_4 was absorbed through the gastrointestinal tract and most (>96%) was quickly eliminated in the feces. No significant differences in elimination of Co_3O_4 were found among species of animals (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). For the more soluble cobalt(II) chloride, reported fecal elimination levels have ranged from 70 to 83% of the administered dose for rats, with urinary excretion accounting for the majority of the remainder of the dose (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971). In lactating dairy cows, about 97% of an oral dose of cobalt chloride was recovered in the feces by day 70 post-exposure, while the urine and milk contained 0.26 and 0.012% of the dose, respectively (van Bruwaene et al. 1984). Following a single exposure in beagle dogs, more Co_3O_4 (physiologically insoluble) was eliminated in the feces (90% in the feces and 5% in the urine) than following an exposure to cobalt nitrate (soluble) (70% in the feces and 25% in the urine) (Kreyling et al. 1986).

As is the case for absorption of cobalt compounds, the iron status of the animal also appears to affect the elimination of cobalt compounds. Following oral exposure, iron-deficient rats eliminated less of a given dose in the feces than normal rats, while co-administration of iron compounds resulted in an increased fecal excretion of cobalt compounds (Reuber et al. 1994; Schade et al. 1970).

3.5.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to cobalt.

Lacy et al. (1996) reported that the majority of the absorbed dose of $CoCl_2$ was excreted in the urine 48 hours after a single dermal exposure in Syrian hamsters. No other studies were located regarding excretion in animals after dermal exposure to cobalt.

3.5.4.4 Other Routes of Exposure

Following intravenous injection of cobalt chloride in humans, about 30% of the dose was excreted in the urine within 24 hours (Smith et al. 1972), 56–73% was excreted within 48 hours (Paley et al. 1958), and 57% was excreted within 2 weeks (Kent and McCance 1941).

Following intravenous injection of cobalt nitrate (with a 57Co tracer) in various species of animals, most of the injected dose was excreted in the urine; about 80% of the given dose was excreted in the urine within 21 days (Table 3-9) (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). Other investigators have also found that the urine is the primary route of cobalt excretion following intravenous administration (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Gregus and Klaassen 1986; Kreyling et al. 1986; Onkelinx 1976; Thomas et al. 1976). Most of the remaining cobalt (5–30% of the total dose) after intravenous exposure was excreted in the feces, with the majority of studies reporting very little long-term retention. Excretion of cobalt (about 2–7% of the injected dose) in the bile was also reported (Cikrt and Tich 1981; Gregus and Klaasen 1986; Sheline et al. 1945). Elimination following intraperitoneal injection is similar to that seen following intravenous exposure, with urinary excretion being the major route of elimination, and fecal excretion accounting for the majority of the remainder of the dose (Barnaby et al. 1968; Hollins and McCullough 1971; Talbot and Morgan 1989), though long-term clearance may be more balanced between the two (Hollins and McCullough 1971). Following subcutaneous injection, both $CoCl_2$ and $Co(NO_3)_2$ were cleared rapidly from the body (Rosenberg 1993; Talbot and Morgan 1989), with the urine being the major route of clearance (Talbot and Morgan 1989).

Table 3-9. Summary of Measurements of Retention and Excretion of Cobalt Following Injection of Cobalt Nitrate $Co(NO_3)_2$ Solution (Mean Percent Recovery)[a,b]

Species (strain)	Whole body retention on day			Cumulative urinary excretion on day			Cumulative fecal excretion on day		
	1	7	21	1	7	21	1	7	21
Baboon	No data	No data	No data	57	74	80	5	17	20
Beagle dog	No data	No data	No data	71	86	87	3.4	4.4	4.9
Guinea pig	34	8	3.5	64	82	85	2.2	10	12
Rat (HMT)	18	4.2	1.9	64	72	74	18	24	24
Rat (F-344)	No data	No data	2.9	No data	No data	80	No data	No data	18
Hamster	27	4.3	1.9	55	68	69	17	28	29
Mouse	23	2.9	1.1	59	71	72	18	26	27

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer

Following injection, studies have shown that the chemical form of the cobalt compound can affect its elimination. Subcutaneous injection of cobalt protoporphyrin in rats, in which the cobalt atom is chelated within the porphyrin ring, resulted in a slower elimination from the body than cobalt chloride, with significant cobalt levels (~20% of initial injection) still present in the body 14 days after exposure (Rosenberg 1993). Likewise, intramuscular injection of cobalt mesoporphyrin resulted in primarily in fecal excretion, with a high systemic retention (Feng et al. 1998). It therefore appears that a greater solubility leads to fast elimination, mainly in the urine, while a less soluble compound will be retained for longer periods and eliminated to a greater extent in the feces.

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

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

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of

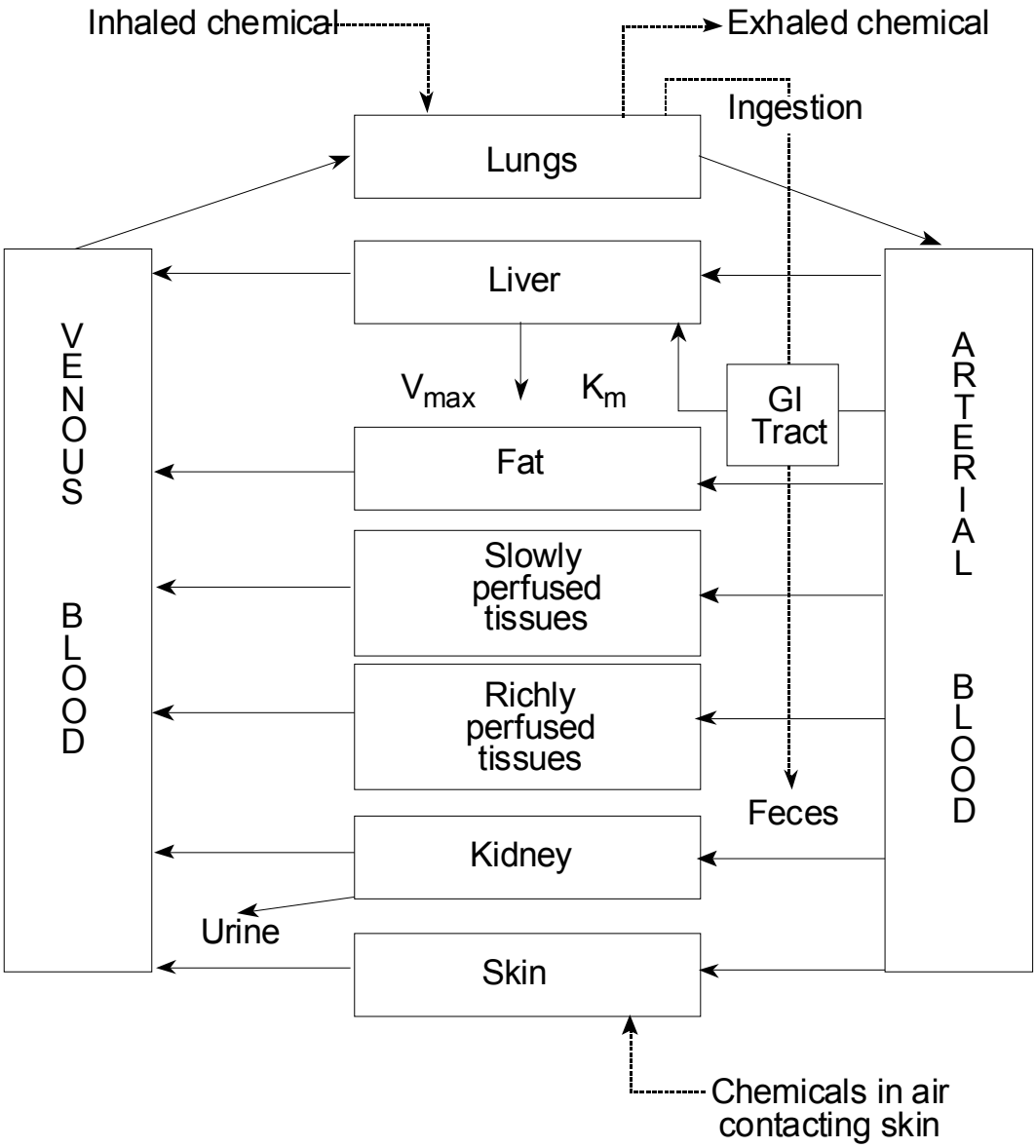
toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). Similar models have been developed for radionuclides. These PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model. Figures 3-6 through 3-9 show models for radionuclides in general or specifically for cobalt.

The ICRP (1995) developed a Human Respiratory Tract Model for Radiological Protection, which contains respiratory tract deposition and clearance compartmental models for inhalation exposure that may be applied to particulate aerosols of cobalt compounds. The ICRP (1993) also developed a 3-compartment biokinetic model for human oral exposure that applies to cobalt. EPA (1998) has adopted the ICRP (1993, 1995) models for assessment of radiologic cancer risks from cobalt exposures. 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

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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.

ICRP model for calculating doses 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 for cobalt

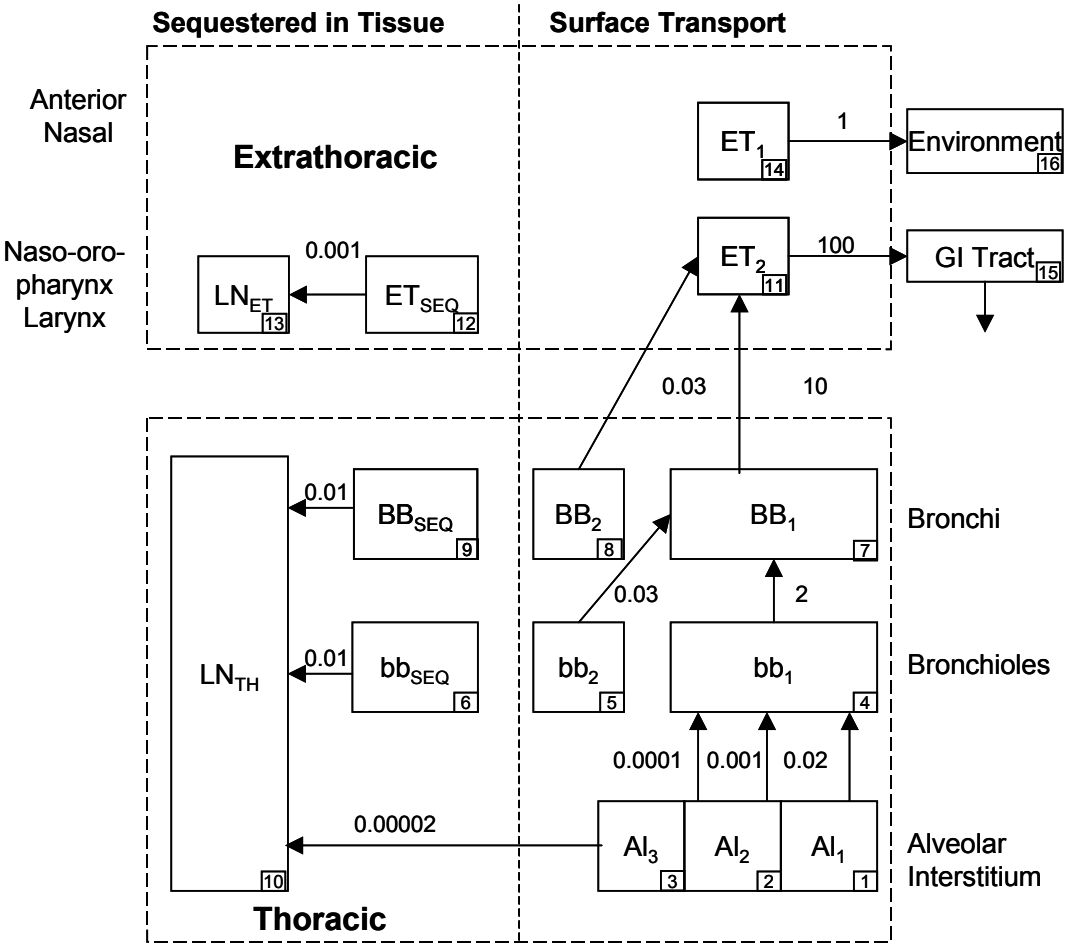
Human Respiratory Tract Model for Radiological Protection (ICRP 1994).

Respiratory Tract Deposition. The ICRP (1994) has developed a physiologically-based pharmacokinetic model for behavior of aerosols and vapors in the respiratory tract. ICRP (1994) provides inhalation dose coefficients that can be used to estimate the committed equivalent and the effective doses to organs and tissues throughout the body based on a unit intake of radioactive material and the anticipated distribution and retention of the material, its radioactive decay, and the energy of the radiationemitted from the material and absorbed by tissues. The model applies to three levels of particle solubility, a wide range of particle sizes (approximately 0.0005–100 μm in diameter), and parameter values that can be adjusted for various segments of the population (e.g., sex, age, level of physical exertion). This model also allows one to evaluate the bounds of uncertainty in deposition estimates. Uncertainties arise from natural biological variability among individuals and the need to interpret some experimental evidence that remains inconclusive. It is applicable to particulate aerosols containing cobalt, and was developed for a wide variety of radionuclides and their chemical forms.

The ICRP deposition model estimates the fraction of inhaled particle mass that initially deposits in each compartment (Figure 3-6). 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 of particles, the model uses experimental data, where deposition is related to particle size and airflow parameters, and scales deposition for women and children from adult male data. 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

Figure 3-6. Compartment Model to Represent Particle Deposition and Time-Dependent Particle Transport in the Respiratory Tract*



*Compartment numbers shown in lower right corners are used to define clearance pathways. The clearance rates, half-lives, and fractions by compartment, as well as the compartment abbreviations are presented in Table 3-11.

Source: ICRP 1994b

was used to interpret data and to predict deposition for compartments and subpopulations other than adult males. Table 3-10 provides reference respiratory values for the general Caucasian population under several levels of activity.

Deposition of inhaled gases and vapors is modeled as a partitioning process, which depends on the physiological parameters noted above as well as the solubility and reactivity of compound in the respiratory tract (Figure 3-7). The ICRP (1994) model defines three categories of solubility and reactivity: SR-0, SR-1, and SR-2:

- Type SR-0 compounds include insoluble and nonreactive gases (e.g., inert gases such as H2, He). These compounds do not significantly interact with the respiratory tract tissues and essentially all compound inhaled is exhaled. Radiation doses from inhalation of SR-0 compounds are assumed to result from the irradiation of the respiratory tract from the air spaces.

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

- Type SR-2 compounds include soluble and reactive gases and vapors that are completely retained in the extrathoracic regions of the respiratory tract. SR-2 type compounds include sulfur dioxide (SO2) and hydrogen fluoride (HF).

Respiratory Tract Mechanical (Particle) 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 chemical materials. The compartmental model is linked to the deposition model (see Figure 3-6) and to reference values presented in Table 3-11. This table provides deposition fractions and clearance rates for each compartment for insoluble particles. The table provides rates of insoluble particle transport for each of the compartments, expressed as a fraction of the deposit per day and also as clearance half-time. ICRP (1994) 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 deposited 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

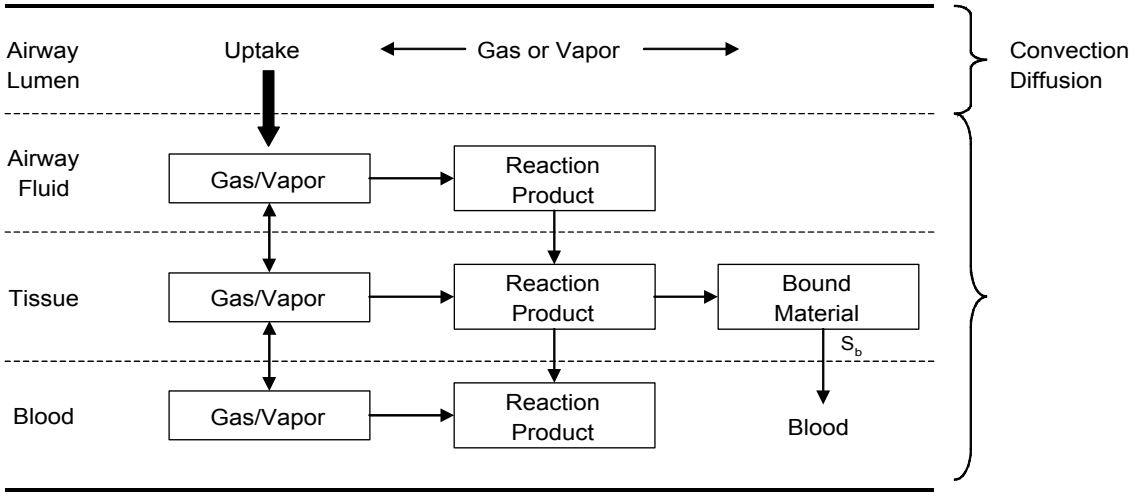
Table 3-10. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity[a]

Activity:		Resting (sleeping)			Sitting awake			Light exercise			Heavy exercise		
Maximal workload:		8%			12%			32%			64%		
Breathing parameters[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 months		0.04	0.09	38	N/A	N/A	N/A	0.07	0.19	48	N/A	N/A	N/A
1 year		0.07	0.15	34	0.1	0.22	36	0.13	0.35	46	N/A	N/A	N/A
5 years		0.17	0.24	23	0.21	0.32	25	0.24	0.57	39	N/A	N/A	N/A
10 years	Male:										0.841	2.22	44
	Female:										0.667	1.84	46
	Both:	0.3	0.31	17	0.33	0.38	19	0.58	1.12	32			
15 years	Male:	0.50	0.42	14	0.533	0.48	15	1.0	1.38	23	1.352	2.92	36
	Female:	0.42	0.35	14	0.417	0.40	16	0.903	1.30	24	1.127	2.57	38
Adult	Male:	0.63	0.45	12	0.750	0.54	12	1.25	1.5	20	1.923	3.0	26
	Female:	0.44	0.32	12	0.464	0.39	14	0.992	1.25	21	1.364	2.7	33

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

h = hour; L = liter(s); min = minute(s); N/A = not applicable

Figure 3-7. Reaction of Gases or Vapors at Various Levels of the Gas-Blood Interface



Source: ICRP 1994b

Table 3-11. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part A

Clearance rates for insoluble particles

Pathway	From	To	Rate (d^{-1})	Half-time[a]
$m_{1,4}$	AI_1	bb_1	0.02	35 days
$m_{2,4}$	AI_2	bb_1	0.001	700 days
$m_{3,4}$	AI_3	bb_1	0.0001	7,000 days
$m_{3,10}$	AI_3	LN_{TH}	0.00002	—
$m_{4,7}$	bb_1	BB_1	2	8 hours
$m_{5,7}$	bb_2	BB_1	0.03	23 days
$m_{6,10}$	bb_{seq}	LN_{TH}	0.01	70 days
$m_{7,11}$	BB_1	ET_2	10	100 minutes
$m_{8,11}$	BB_2	ET_2	0.03	23 days
$m_{9,10}$	BB_{seq}	LN_{TH}	0.01	70 days
$m_{11,15}$	ET_2	GI tract	100	10 minutes
$m_{12,13}$	ET_{seq}	LN_{ET}	0.001	700 days
$m_{14,16}$	ET_1	Environment	1	17 hours

See next page for Part B

Table 3-11. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part B

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

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

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

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

where:

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

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

Source: ICRP 1994

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 sub-compartments of different clearance rates within each region (e.g., BB_1, BB_2, BBseq), 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. The 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 (BB_2 and bb_2) is assumed to have fractions of the inhaled particles, depending on the particle size, deposited in BB_2 and bb_2; both have clearance half-times estimated at 20 days. A small fraction of particles deposited in the BB and bb regions is retained in the airway wall for even longer periods (BBseq and bbseq).

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

Particle clearance from the alveolar-interstitial region has been measured in human subjects. The ICRP model uses 2 half-times to represent clearance: about 30% of the particles have a 30-day half-time, and

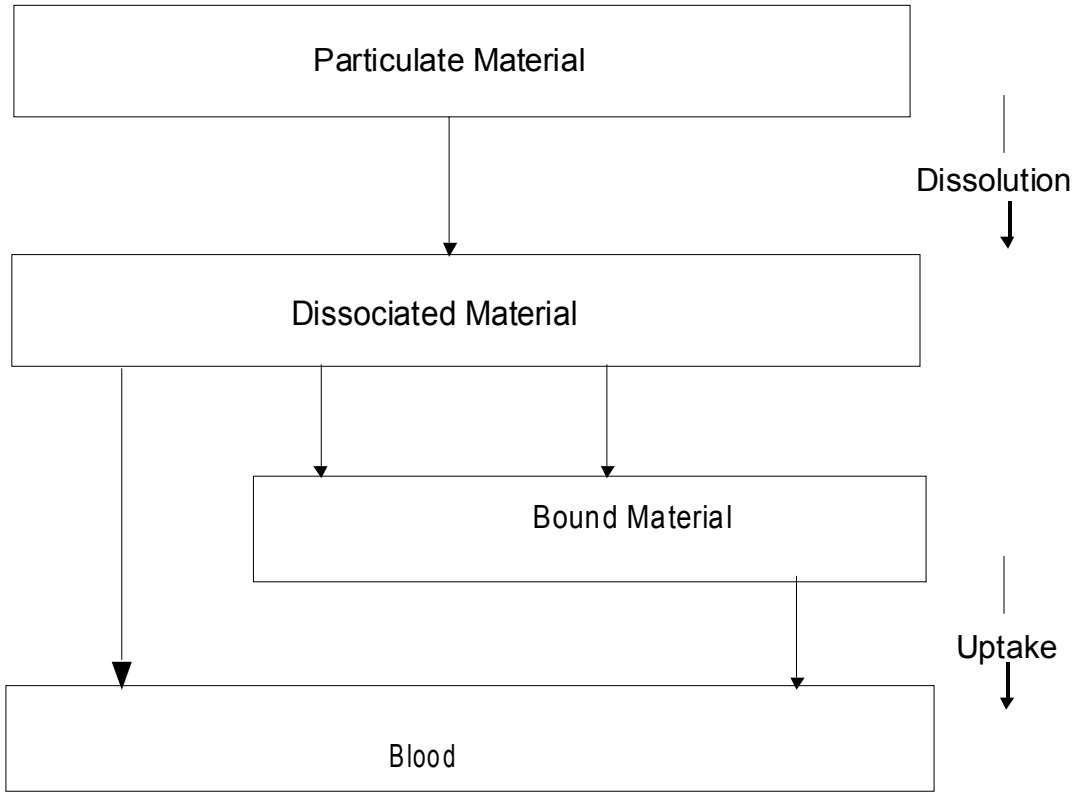
the remaining 70% are given a half-time of several hundred days. Over time, the AI particle transport rate falls and some compounds have been found in lungs 10–50 years after exposure.

Absorption into Blood. The ICRP model assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages (ET_1), where no absorption occurs. It is essentially a 2-stage process, as shown in Figure 3-8. 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 data for specific compounds, the model uses the following default absorption rate values for those compounds that are classified as Types F (fast), M (medium), S (slow), and V (instantaneous):

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

ICRP (1995) considers the experimental and human data to support the following classifications: cobalt chloride and nitrate, Type F; cobalt oxides, Type M or S; cobalt in fused aluminosilicate or polystyrene, Type S; cobalt in mineral dusts such as fly ash and volcanic ash, Type M; cobalt metal and metal alloys, M or S. ICRP (1995) recommends assigning all cobalt aerosols to Type M in the absence of specific information supporting an alternative classification.

Figure 3-8. The Human Respiratory Tract Model: Absorption into Blood



Source: ICRP 1994

ICRP (1993) Cobalt Biokinetics Model.

Description of the model.

ICRP (1979, 1993) developed a 3-compartment model of the kinetics of ingested cobalt in humans that is applicable to infants, children, adolescents, and adults. Absorption of ingested cobalt is assumed to be 60% in infants up to 3 months of age, 30% from 3 months to 15 years of age, and 10% after age 15 years. Absorbed cobalt is assumed to distribute as follows: 50% is excreted (urine and feces combined in a 6:1 ratio), 5% is transferred to the liver, and 45% is transferred to other tissues (Figure 3-9). Elimination from tissue compartments is described by three first order rate constants representing slow, medium, and fast elimination pools with half-times of 6, 60, and 800 days, respectively. The elimination half-times are assumed to be independent of age.

Validation of the model.

The extent to which the ICRP model has been validated is not described in ICRP (1993).

Risk assessment.

The model has been used to establish radiation dose equivalents (Sv/Bq) of ingested ^{57}Co, ^{58}Co, and ^{60}Co for ages 3 months to 70 years (ICRP 1993).

Target tissues.

The model can be used to estimate the radiation dose from cobalt radionuclides to all major organs and can be applied to environmental and occupational exposures.

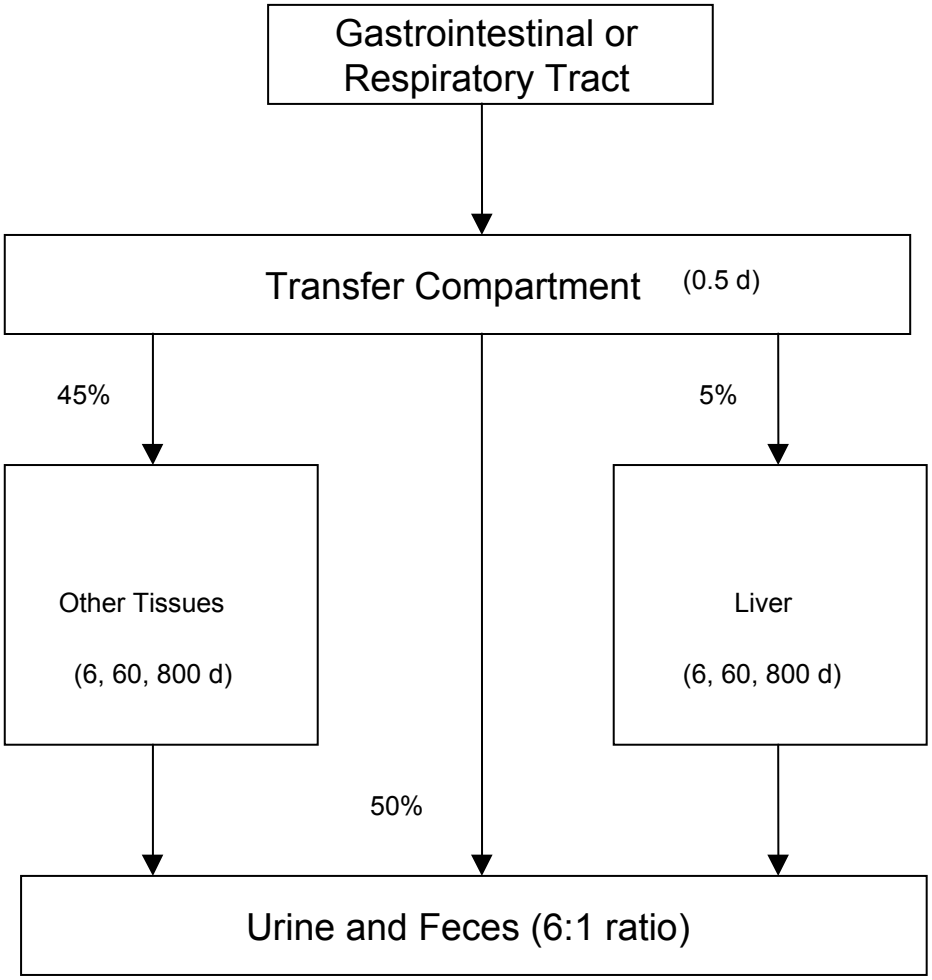
Species extrapolation.

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

*Inter*route extrapolation.

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

Figure 3-9. ICRP Biokinetics Model for Cobalt



Absorbed cobalt enters a virtual transfer compartment from which unidirectional transfer to tissues is assumed to occur. Percentages shown are of the initial amounts absorbed. Numbers in parentheses are elimination half-times to urine and feces combined (d=days. Liver other tissues are assumed to have fast, medium, and slow elimination pools.

3.6 MECHANISMS OF ACTION

3.6.1 Pharmacokinetic Mechanisms

Absorption. Following inhalation exposure, the absorption of deposited cobalt compounds seems to be related to their biological solubility. Cobalt compounds deposit in the lungs based on their aerosol characteristics. Physiologically insoluble cobalt particles are generally cleared by phagocytosis and/or mucociliary transport, and thus, have a low systemic absorption. To some extent, cobalt particles may be dissolved within alveolar macrophages (Kreyling et al. 1990). More soluble forms of cobalt may enter the bloodstream through the alveolar or bronchial walls.

Following oral exposure, the absorption of cobalt varies with the amount given, with a greater dose leading to 4- to 20-fold greater fractional absorption (Smith et al. 1972). Nutritional status also seems to be an important factor in cobalt absorption, with both overnight fasting and iron deficiency resulting in increased cobalt absorption (Smith et al. 1972; Sorbie et al. 1971; Valberg et al. 1969). It has been suggested that cobalt and iron share a common absorptive pathway in the intestines, though the cobalt absorption takes place without ferritin (Reuber et al. 1994; Schade et al. 1970; Thomson et al. 1971). Solubility of the cobalt compound is also an important factor regarding the absorption following oral exposure, with increasing solubility resulting in increasing absorption (Christensen et al. 1993). One study in humans showed that oral exposure to cobalt resulted in significantly higher urinary excretion in females relative to males (Christensen et al. 1993), but these results have not been verified by other studies. A complex, specific pathway exists for the absorption of vitamin B_{12}, whereby the molecule interacts with several factors in the stomach and intestine to facilitate absorption (for review, see Russel-Jones and Alpers 1999).

Dermal absorption of cobalt compounds depends greatly on whether the skin is intact or damaged. Absorption through intact skin is comparatively low, while absorption through damaged skin is much higher (Inaba and Suzuki-Yasumoto 1979; Lacy et al. 1996).

Distribution. As a component of vitamin B_{12}, cobalt is found in most body tissues. Absorbed cobalt is transported throughout the body in the blood, with greatest levels found in the liver, followed by the kidney (Ayala-Fierro et al. 1999; Greenberg et al. 1943; Gregus and Klaassen 1986; Patrick et al. 1989).

Following inhalation exposure, significant levels of cobalt are found in the lungs of exposed humans and animals (Barnes et al. 1976; Brune et al. 1980; Collier et al. 1991; Gerhardsson et al. 1984; Hewitt 1988; Hillerdal and Hartung 1983; Kreyling et al. 1986; Kyono et al. 1992; Patrick et al. 1989; Talbot and Morgan 1989; Teraoka 1981). Within the lung, physiologically insoluble cobalt particles tend to be located within macrophages within the bronchial wall or in the interstitium close to the terminal bronchioli (Brune et al. 1980).

Excretion. Following inhalation exposure, the rate of urinary excretion appears to correlate with the rate of translocation of cobalt from the lungs to the blood, and the rate of fecal clearance with the rate of mechanical clearance of cobalt from the lungs to the gastrointestinal tract (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kerfoot 1975; Kreyling et al. 1986, 1989; Palmes et al. 1959; Patrick et al. 1989; Talbot and Morgan 1989). Likewise, the majority of absorbed cobalt following oral exposure is rapidly removed from the body by excretion in the urine, and to a lesser extent in the bile and feces, with fecal elimination being the primary method of excretion for physiologically insoluble cobalt compounds in both humans and animals (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Harp and Scoular 1952; Paley et al. 1958; Patrick et al. 1989; Smith et al. 1972; Sorbie et al. 1971; Talbot and Morgan 1989; Valberg et al. 1969). The primary route for excretion following dermal exposure is the urine (Lacy et al. 1996; Scansetti et al. 1994).

3.6.2 Mechanisms of Toxicity

Stable Cobalt. The exact mechanisms by which cobalt exerts its effects on cells are not completely understood. However, a number of potential mechanisms have been identified. Several studies have demonstrated that hard metal, a metal alloy with a tungsten carbide and cobalt matrix, is considerably more toxic than either cobalt or tungsten carbide alone. A mechanism by which hard metal may exert its effects has been proposed by a group of Belgian researchers (Lasfargues et al. 1995; Lison et al. 1995, 1996). In this proposed mechanism, tungsten carbide, which is a very good conductor of electrons, facilitates the oxidation of cobalt metal to ionic cobalt (presumably Co^{2+}) by transferring electrons from the cobalt atom to molecular oxygen adjacent to the tungsten carbide molecule. The result is an increased solubility of cobalt, relative to cobalt metal alone, and the generation of active oxygen species. The cobalt ions formed may be absorbed into the blood and transported throughout the body, where they may elicit effects by the above mechanisms. *In vitro* evidence for this mechanism includes the ability of hard

metal particles, but neither cobalt nor tungsten carbide alone, to generate substantial levels of oxidant species and cause significant lipid peroxidation (Lison et al. 1995; Zanetti and Fubini 1997). Hard metal particles have also been shown to increase the levels of inducible nitric oxide synthase (iNOS), a gene responsive to oxidant stress (Rengasamy et al. 1999).

Another potential mechanism for cobalt toxicity is through oxidant-based and free radical-based processes. Exposure to soluble cobalt increases indices of oxidative stress, including diminished levels of reduced glutathione, increased levels of oxidized glutathione, activation of the hexose monophosphate shunt, and free-radical-induced DNA damage (Hoet et al. 2002; Kasprzak et al. 1994; Lewis et al. 1991; Zhang et al. 1998a); hydrogen peroxide appears to be a necessary cofactor for cobalt-induced oxidative DNA damage (Ivancsits et al. 2002). Cobalt has been shown to generate oxygen radicals, including superoxide, both *in vitro* and *in vivo* (Kadiiska et al. 1989; Kawanishi et al. 1994; Moorhouse et al. 1985), through what may be a Fenton-type mechanism (Lloyd et al. 1997). *In vivo* exposure to cobalt in rats and guinea pigs resulted in increased lipid peroxidation in the liver (Christova et al. 2001, 2002; Sunderman and Zaharia 1988), as well as changes in reduced glutathione and hepatic levels of superoxide dismutase, catalase, heme oxygenase, and glutathione peroxidase (Christova et al. 2001, 2002). Exposure to cobalt results in accumulation in cardiac tissues, and is thought to stimulate carotid-body chemoreceptors, mimicking the action of hypoxia (Di Giulio et al. 1990, 1991; Hatori et al. 1993; Morelli et al. 1994). Cobalt administration to a neuroblastoma/glioma cell line resulted in an upregulation of opioid delta receptors, through a mechanism similar to that of hypoxia (Mayfield et al. 1994). Exposure to cobalt also elicits effects on a number of genes known to be sensitive to oxidant status, including hypoxia-inducible factor 1, erythropoietin, vascular endothelial growth factor, catalase, and monooxygenase enzymes (Bunn et al. 1998; Daghman et al. 1999; Dalvi and Robbins 1978; Di Giulio et al. 1991; Goldberg et al. 1988, 1994; Ho and Bunn 1996; Hoet et al. 2002; Ladoux and Frelin 1994; Legrum et al. 1979; Semenza et al. 1994; Yasukochi et al. 1974), and may also lead, through these genes or other pathways, to the induction of apoptosis (Zou et al. 2001).

Soluble cobalt has also been shown to alter calcium influx into cells, functioning as a blocker of inorganic calcium channels (Henquin et al. 1983; Moger 1983; Yamatani et al. 1998). This mechanism has been linked to a reduction of steroidogenesis in isolated mouse Leydig cells (Moger 1983). Additionally, soluble cobalt has been shown to alter the inorganic calcium influx in liver cells after exposure to glucagon (Yamatani et al. 1998), and calcium influx into pancreatic β cells (Henquin et al. 1983) and

isolated rat islets (Henquin and Lambert 1975). Cobalt may also affect neuromuscular transmission though antagonism with calcium (Weakly 1973).

Another potential mechanism of cobalt toxicity is relevant to cobalt cardiomyopathy. As mentioned previously, cobalt accumulated in the heart of beer drinkers. Microscopic analysis revealed fragmentation and degeneration of myofibers and aggregates of abnormal mitochondria (Ferrans et al. 1964). These mitochondrial changes are indicative of disturbances in energy production or utilization possibly related to cobalt effects on lipoic acid. Cobalt irreversibly chelates lipoic acids under aerobic conditions (Webb 1982). Lipoic acid is a required cofactor for oxidative decarboxylation of pyruvate to acetyl CoA and of α-ketoglutarate to succinate (Lehninger 1982). In the myocadrium of rats treated with cobalt, oxidation of pyruvate or fatty acids is impaired (Wiberg 1968).

A number of investigators have reported that cobalt ions can result in increased damage to DNA when co-exposed with oxidants *in vitro*, such as UV radiation or H_2O_2 (De Boeck et al. 1998; Hartwig et al. 1991; Nackerdien et al. 1991). It is believed that cobalt acts by inhibition of DNA repair, particularly the incision and polymerization steps (Asmuß et al. 2000; Kasten et al. 1997), accomplishing this through interaction with zinc finger DNA repair proteins (Asmuß et al. 2000; Sarkar 1995).

Another potentially important mechanism by which cobalt may exert effects is through its effects on heme and heme-containing enzymes. Cobalt is thought to inhibit heme synthesis *in vivo* by acting upon at least two different sites in the biosynthetic pathway: synthesis of 5-aminolevulinate and conversion of 5-aminolevulinate into heme (de Matteis and Gibbs 1977). This inhibitory activity might result in the formation of cobalt protoporphyrin rather than heme (Sinclair et al. 1979). Cobalt treatment also stimulates heme oxidation in many organs, due to the induction of heme oxygenase (for review, see Sunderman 1987). Effects on heme synthesis may potentially affect a wide variety of heme-containing proteins, including monooxygenase enzymes (i.e., cytochromes P450) and catalase (Legrum et al. 1979; Yasukochi et al. 1974). Conversely, cobalt acts, through a mechanism believed to involve a heme-containing protein, to increase erythropoietin, which stimulates the production of red blood cells (Di Giulio et al. 1991; Goldberg et al. 1988; Smith and Fisher 1973). The regulatory mechanisms behind this apparent dichotomy have not been fully elucidated.

Another potential mechanism by which cobalt may exert its effects is through interactions with the immune system. Exposure of humans to cobalt by the inhalation and dermal routes have resulted in

sensitization to cobalt (Alomar et al. 1985; Bencko et al. 1983; Dooms-Goossens et al. 1980; Fischer and Rystedt 1983; Goh et al. 1986; Kanerva et al. 1988; Marcussen 1963; Shirakawa et al. 1988, 1989; Valer et al. 1967). Exposure to inhaled cobalt chloride aerosols can precipitate an asthmatic attack in sensitized individuals (Shirakawa et al. 1989), suggesting cobalt sensitization as one mechanism by which cobalt-induced asthma may be produced. IgE and IgA antibodies specific to cobalt have been reported in humans (Bencko et al. 1983; Shirakawa et al. 1988, 1989). There is evidence that cobalt sensitivity in humans may to be regulated by T-lymphocytes (Katsarou et al. 1997). A human helper T-lymphocyte cell line specific for cobalt (CoCl2) has been established (Löfström and Wigzell 1986). Cobalt may also interact directly with immunologic proteins, such as antibodies or Fc receptors, to result in immunosensitization (Cirla 1994). *In vitro*, cobalt(II) has been shown to reduce the proliferation of both B and T lymphocytes, as well as the release of the cytokines IL-2, IL-6, and IFN-Gamma (Wang et al. 1996). Interrelationships exist between nickel and cobalt sensitization (Bencko et al. 1983; Rystedt and Fisher 1983); however, the extent of any potential interactions between the two metals on immunologic end points is not well understood. In guinea pigs, nickel and cobalt sensitization appear to be interrelated and mutually enhancing (Lammintausta et al. 1985), though cross-reactivity was not reported to occur.

Cobalt has been shown to have a number of effects on glucose metabolism. Treatment of animals with cobalt results in a depression of serum (Eaton and Pommer 1973; Ybarra et al. 1997) or tissue (Wiberg 1968) glucose levels. In rats made diabetic by pretreatment with streptozotocin, this depression was persistent, whereas it was transient in normal rats (Ybarra et al. 1997). Many of the effects of cobalt on glucose metabolism are thought to result from alterations in the expression of the glut family of glucose transport proteins, a family of facilitative Na+-independent transport proteins thought to mediate non-insulin-dependent transport of glucose. Exposure to soluble cobalt results in increased expression of these genes, particularly GLUT1, in cells of the liver, kidney cortex, myocardium, skeletal muscle, and cerebrum (Behrooz and Ismail-Beigi 1997; Ybarra et al. 1997). Cobalt also reduces the amount of glucose produced in liver cells following stimulation with glucagon (Eaton and Pommer 1973; Yamatani et al. 1998), as well as reducing insulin release in isolated rat islets (Henquin and Lambert 1975).

Radioactive Cobalt. Due to the nature of its ionizing radiation, radioactive cobalt can present a health hazard. Highly-penetrating gamma emissions are the major source of damage to tissues and internal organs following external exposure to radioactive cobalt isotopes. If radioactive cobalt is internalized, nearby tissues are at highest risk for damage due to the release of beta particles. In either case, exposure to ionizing radiation results in an increased risk of cellular damage. Both beta and gamma radiations are

capable of producing ionization events when they hit cellular molecules, including DNA, RNA, or lipids. Ionized molecules within irradiated cells may be repaired quickly to prevent further damage. On the other hand, irreparable damage may be imposed on cellular materials, such as DNA, which might ultimately result in either cell death or the formation of cancerous tumors. Very large acute radiation doses can damage or kill enough cells to cause the disruption of organ systems, resulting in acute radiation syndrome or even death. Human and animal data indicate that sufficiently high exposures to cobalt radiation can result in adverse effects such as reduced fertility, abnormal development, genotoxicity, pulmonary fibrosis, gastrointestinal atrophy and fibrosis, hematological and lymphoreticular disorders, cancer, and death (Chang et al. 1999b; Davis et al. 1992; Dinehart et al. 1991; Hashimoto and Mitsuyasu 1967; Klener et al. 1986; Libshitz 1993; Myskowski and Safai 1981; Rauscher and Bauchinger 1983; Roschler and Woodard 1969; Roswit and White 1977; Stavem et al. 1985; Van Oort et al. 1984). For a more complete discussion of the mechanisms associated with the toxic effects of ionizing radiation, refer to Chapter 5 of the Toxicological Profile for Ionizing Radiation (Agency for Toxic Substances and Disease Registry 1999).

3.6.3 Animal-to-Human Extrapolations

Bailey et al. (1989) reported a wide variation across species, including man, in the retention and clearance of inhaled physiologically insoluble 57Co particles (see Table 3-8), noting that this variation illustrates the potential difficulty of extrapolating the results of animal lung retention experiments to human even qualitatively. Species differences in absorption of physiologically insoluble cobalt oxide following oral exposure do not appear to exist (Bailey et al. 1989), although humans were not examined. Absorption of soluble cobalt compounds is greater in rats (13–34%) than in dairy cows (1–2%) and guinea pigs (4–5%) following oral exposure (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Naylor and Harrison 1995; Schade et al. 1970; Taylor 1962; van Bruwaene et al. 1984).

3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate

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

The available human and animal data suggest that the endocrine system, particularly the thyroid gland, may be a target of stable and radioactive cobalt toxicity. These effects are discussed in Sections 3.2 and 3.3 under Systemic Effects.

3.8 CHILDREN'S SUSCEPTIBILITY

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

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

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

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

have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

Though human data are lacking, animal studies have suggested several differences in pharmacokinetic behavior of cobalt compounds between children and adults. Following inhalation exposure to Co_3O_4, deposition tended to increase with age, though no significant differences were reported (Collier et al. 1991). The youngest animals exposed (3 weeks postnatal) had the lowest fractional retention 182 days postexposure, though no differences were seen at day 7 or 83. The authors attributed this to a faster rate of translocation of cobalt from the lung to the blood, which could enhance subsequent excretion. Naylor and Harrison (1995) reported that in rats and guinea pigs, fractional absorption of cobalt following oral exposure was highest at 1 day after birth, and diminished rapidly with time thereafter. Collier et al. (1991) reported no difference in absorption of cobalt nitrate following oral exposure to animals aged 3–46 weeks, which is in agreement with the results of the later portion of the Naylor and Harrison (1995) study. No PBPK models specific for cobalt exposures to children were located. However, the ICRP Human Respiratory Tract Model is applicable to children, and may be used for children if the appropriate values for the parameters are used.

Once in the bloodstream, soluble cobalt compounds have been shown, in animal studies, to cross the placenta and enter the fetus. Twenty-four hours after intravenous injection of cobalt chloride in rats, 0.14% of the dose was found in the fetus, 0.19% in the chorioallantoic placenta, and 0.22% in the yolk sac (Zylicz et al. 1975). Several other rat studies (Nishimura et al. 1978; Zylicz et al. 1975, 1976) have demonstrated that the amount of cobalt crossing the placenta following intravenous injection is greater in later gestation stages, though the percent of the maternal dose reaching the fetus is still relatively low (in <1% of the maternal dose). The fetal uptake of cobalt following intravenous administration to the mother was increased when the cobalt was given as cyanocobalmin, relative to cobalt chloride (~5% of the maternal dose for cyanocobalmin, compared to <1% for cobalt chloride) (Nishimura et al. 1978), indicating that the form of the cobalt compound may affect its availability to the fetus.

Cobalt has been detected in human breast milk (Byczkowski et al. 1994; Kratchler et al. 1998). In general, physiological concentrations of cobalt in breast milk are very low, on the order of parts per billion (Byczkowski et al. 1994). Animal studies are in agreement with this observation. By day 70 post-exposure in lactating dairy cows orally exposed to cobalt chloride, the milk contained 0.012% of the dose (van Bruwaene et al. 1984). One to two percent of cobalt given intravenously to mother rats as cyanocobalmin was transferred to offspring via the breast milk (Nishimura et al. 1978).

Health Effects from Exposure to Stable Cobalt. Available data have not clearly defined whether children are at greater risk from exposure to stable cobalt than adults. Studies in adult humans have identified several health effects of cobalt compounds following inhalation, oral, or dermal exposure. Data on effects of cobalt in children following inhalation exposures are lacking. Jacobziner and Raybin (1961) reported on two cases of children who had accidentally ingested unknown amounts of cobalt chloride; a 19-month-old male died approximately 6.5 hours after ingestion, whereas a 3-year-old male was given medical treatment and showed no symptoms after ingestion. Several studies (Chamberlain 1961; Little and Sunico 1958; Sederholm et al. 1968; Washburn and Kaplan 1964) have reported enlarged thyroid glands in children given cobalt chloride for treatment of anemia; removal of cobalt therapy resulted in a return to normal thyroid size. Patch testing of children aged 4–14 years revealed a 13.3% dermal sensitization rate to cobalt chloride (Romaguera and Vilaplana 1998). More girls reacted positively than boys, which the authors attributed to the wearing of costume jewelry, which often contains cobalt, and the resulting exposure.

Offspring of mice intravenously injected with approximately 1.2 mg cobalt/kg at day 8 of gestation, but not at day 3, showed a significant increase in the number of skeletons with delayed ossification (Wilde 1984). Other studies, however, have not shown developmental effects of stable cobalt compounds, or have shown effects only at maternally toxic doses (Domingo et al. 1985b; Paternian et al. 1988; Seidenberg 1986).

Health Effects from Exposure to Radioactive Cobalt. Taiwanese children (48 boys, 37 girls) who were raised in apartments contaminated with ^{60}Co were compared to 21,898 age- and sex-matched non-exposed children from a nationwide surveillance program (Wang et al. 2001). After adjusting for effects from parental heights and body mass index, clear dose-related decreases in height percentile (HP) and age-specific relative height differences (RHD) were seen in exposed boys, but not in exposed girls. Average

cumulative exposures were 120.8 and 129.9 mSv (equivalent to ~12.1 or 13 rad) for the boys and girls, respectively.

No other studies of human children exposed to radioactive cobalt or cobalt radiation were located. As rapidly-dividing cells are more sensitive to radiation, the developing fetus and growing children are expected to be more sensitive to cobalt radiation than adults.

Animal studies have shown that exposures to external radiation from cobalt isotopes (as low as 10 rad [0.1 Gy] in mice) may have a dramatic effect on the developing fetus (see Section 3.2.4.6 and Agency for Toxic Substances and Disease Registry 1999). Exposure duration, gestational day, and dose all influence the effect of cobalt radiation on the developing organism. Radiation exposure to very young dogs (80 rad [0.8 Gy] on day 2 or 70 postpartum) has resulted in an increased incidence of diabetes mellitus, renal disease, and cancer (Benjamin et al. 1998a, 1998b).

3.9 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to cobalt are discussed in Section 3.9.1.

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

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

3.9.1 Biomarkers Used to Identify or Quantify Exposure to Cobalt

Biomonitoring data exist that demonstrate a positive correlation between occupational exposure levels of cobalt and the levels of cobalt in both the urine and blood (Table 3-12) (Alexandersson 1988; Ichikawa et al. 1985; Lison et al. 1994; Nemery et al. 1992; Scansetti et al. 1985). Available studies of unexposed humans have reported cobalt blood levels of 0.05–0.19 µg/dL and urinary cobalt levels of 0.04–2 µg/dL (Alexandersson 1988; Ichikawa et al. 1985). Figure 3-10 graphically presents the cobalt exposure data and cobalt in blood data presented in Table 3-12 (Ichikawa et al. 1985). The highest excretion rate of cobalt in urine occurs during the first 24 hours after short-term exposure; therefore, subjects should be tested quickly to assess whether cobalt exposure has occurred (Alexandersson 1988). Occupational exposure to 0.1 mg/m^3 cobalt resulted in blood levels of cobalt ranging (95% CI) from 0.57 to 0.79 µg/dL, compared to 0.19 µg/dL in unexposed workers, and urinary levels from 59 to 78 µg/L, compared to 2 µg/L in unexposed workers (Ichikawa et al. 1985). Correlations between recent exposure and cobalt levels in the blood or urine are more consistent for soluble cobalt compounds (metal, salts, and hard

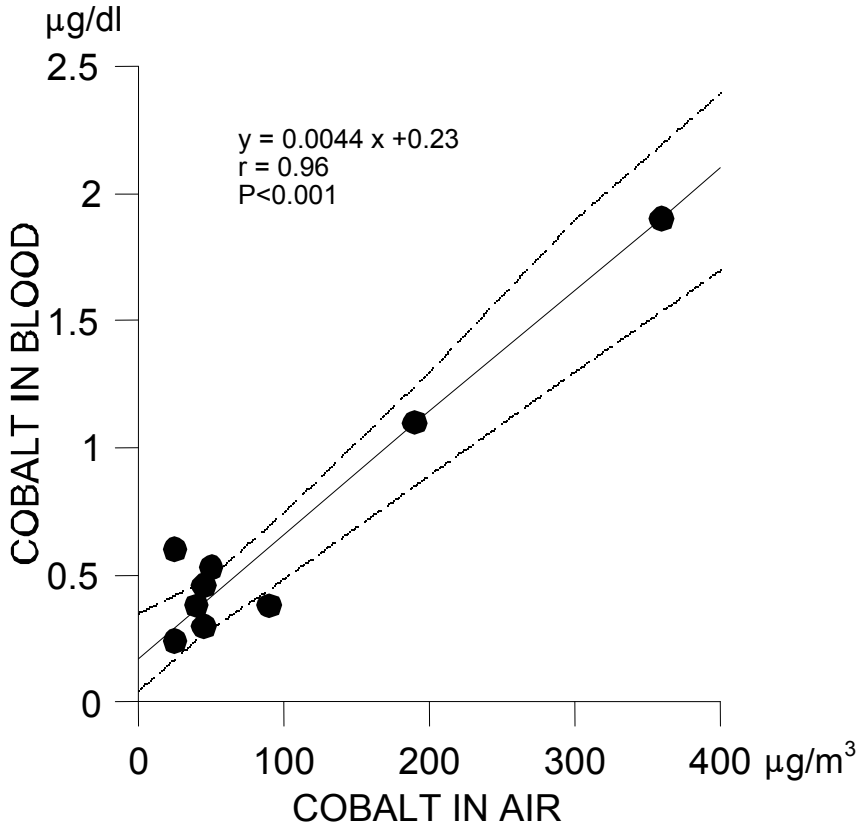
Table 3-12. Cobalt Exposure Concentrations and Amounts in the Blood and Urine of Subjects Examined[a]

Subjects	Number	Cobalt in air[b] mean±SD µg/m^3		Cobalt in blood[b] mean±SD µg/dL		Cobalt in urine[b] mean±SD µg/L	
Powder handlers	2	186±108	(110–262)	1.08±0.28	(0.88–1.28)	148±13	(138–158)
Rubber press operators	6	367±324	(92–859)	1.87±1.96	(0.40–5.30)	235±182	(41–392)
Automatic press operators	11	56±60	(9–210)	0.57±0.53	(0.10–0.95)	34±43	(4–73)
Shapers (lathing)	7	33±15	(15–62)	0.67±0.44	(0.14–1.34)	33±30	(11–95)
Shapers (sawing)	21	50±35	(8–144)	0.52±0.31	(0.15–1.15)	41±60	(6–266)
Sintering workers	21	28±30	(4–145)	0.26±0.10	(0.09–0.45)	10±10	(2–46)
Wet grinders							
A	27	44±48	(4–227)	0.42±0.31	(0.10–1.30)	35±34	(2–180)
B	18	45±50	(3–161)	0.33±0.10	(0.16–0.52)	19±15	(2–67)
C	12	92±92	(15–291)	0.43±0.39	(0.12–1.90)	68±87	(3–265)
D	25	44±54	(3–205)	0.35±0.20	(0.10–1.00)	17±16	(1–69)
Workers using respirators	25	317±307	(7–1,203)	0.65±0.86	(0.20–3.90)	26±30	(1–119)
Office workers	20	No data		0.19±0.11	(0.08–0.40)	2±1	(1–4)

[a]Adapted from Ichikawa et al. 1985
[b]The range of each value is given in parentheses.

SD = standard deviation

Figure 3-10. Relation Between Mean Cobalt Exposure and Mean Blood Concentration of Cobalt in Exposed Workers*



*Adapted from Ichikawa et al. 1985

metals), while blood and/or urinary cobalt levels are less reflective of recent exposure for less soluble compounds (cobalt oxides) (Lison et al. 1994).

Sensitive serum protein responses were found in animals exposed to cobalt at levels below those necessary to produce hematopoietic effects (Stokinger and Wagner 1958). These serum protein responses included an increase in alpha globulin fractions of serum proteins and associated serum neuraminic acid. The responses were observed in rabbits and dogs following both inhalation and injection of cobalt. The authors indicated that this increase was a unique response to cobalt exposure. The characteristics of the response were similar to those of the erythropoietic response found following exposure to higher levels of cobalt; the response is delayed, does not occur in all animals within a given exposure group, is not of great magnitude, and is not persistent (Stokinger and Wagner 1958).

Biomarkers specific for exposure to cobalt radioisotopes have not been reported.

3.9.2 Biomarkers Used to Characterize Effects Caused by Cobalt

Sensitization to cobalt results in cobalt-specific changes in serum antibodies (IgE and IgA) that may be monitored to determine if sensitization, or additional exposure, to cobalt has occurred (Bencko et al. 1983; Shirakawa et al. 1988, 1989).

No biomarkers specific for effects of radioactive cobalt isotopes have been reported. Biomarkers for response to ionizing radiation are discussed in Agency for Toxic Substances and Disease Registry (1999).

3.10 INTERACTIONS WITH OTHER CHEMICALS

A major medical use of cobalt is in combination with bleomycin, an antineoplastic antibiotic, as a tumor-localizing and therapeutic agent (Goodwin and Meares 1976; Hansen et al. 1976; Kapstad 1978, 1979). The anti-tumor effects of the two agents are amplified when given in combination with each other. The complex, wherein cobalt is coordinately bound to the bleomycin molecule, is intravenously injected and acts by binding to and cleaving the DNA in the tumor cells (Kakinuma and Orii 1982).

The interaction of cobalt with various chelators has been investigated in animals for mitigation of the toxicity of cobalt (Baker et al. 1987; Domingo et al. 1983; Llobet et al. 1988). Glutathione, N-acetyl-L-cysteine (NAC) and diethylenetriaminepentaacetic acid (DTPA), administered to rats previously exposed to cobalt, significantly increased urinary excretion of cobalt, while EDTA, NAC, and 2,3-di-mercaptosuccinic acid (DMSA) increased fecal excretion. NAC was the most effective chelator because it increased both urinary and fecal excretion of cobalt while decreasing its levels in liver and spleen (Llobet et al. 1988). Cysteine, also acting as a chelator, mitigated the toxicity of cobalt when both chemicals were given to chicks in the feed (Baker et al. 1987).

A number of studies have suggested an association between cobalt ions and calcium ions. Soluble cobalt has also been shown to alter calcium influx into cells, functioning as a blocker of inorganic calcium channels (Henquin et al. 1983; Moger 1983; Yamatani et al. 1998). This mechanism has been linked to a reduction of steroidogenesis in isolated mouse Leydig cells (Moger 1983). Additionally, soluble cobalt has been shown to alter the inorganic calcium influx in liver cells after exposure to glucagon (Yamatani et al. 1998), and calcium influx into pancreatic β cells (Henquin et al. 1983) and isolated rat islets (Henquin and Lambert 1975). Cobalt may also affect neuromuscular transmission through antagonism with calcium (Weakly 1973).

Hard metal, consisting of 5–10% cobalt with the balance being tungsten carbide, has been shown to be considerably more toxic than cobalt alone, resulting from interactions between particles of cobalt metal and tungsten carbide particles. The mechanisms responsible for this interaction are discussed in Section 3.6.2.

An interrelationship between cobalt and nickel sensitization has been reported in individuals exposed to the two metals (Rystedt and Fisher 1983; Veien et al. 1987), as well as in animal studies (Wahlberg and Lidén 2000). It was concluded that the combination of nickel sensitivity and irritant eczema resulted in a high risk for developing an allergy to cobalt. Studies of cultured alveolar type II cells showed a synergistic (greater than additive) response to co-exposure to cobalt and nickel chlorides (Cross et al. 2001).

3.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Individuals who are already sensitized to cobalt may be unusually susceptible because cobalt exposure may trigger asthmatic attacks (Shirakawa et al. 1988, 1989). Sensitization to cobalt results in cobalt-specific changes in serum antibodies (IgE and IgA) (Bencko et al. 1983; Shirakawa et al. 1988, 1989). Potolicchio et al. (1997, 1999) have suggested that individuals with a polymorphism in the HLA-DP gene (presence of glutamate 69 in the β chain) may be more susceptible to hard metal lung disease. Individuals with ongoing respiratory illness may also be more susceptible to the effects of inhaled cobalt. Following oral exposure, individuals with iron deficiency may at greater risk, as animal studies have shown an increased absorption of cobalt compounds in iron-deficient animals (Reuber et al. 1994; Schade et al. 1970). Studies of beer-cobalt cardiomyopathy have suggested that individuals with high alcohol consumption may be more susceptible to health effects of cobalt (Alexander 1969, 1972; Morin et al. 1971).

Ionizing radiation has greater effects on rapidly-dividing cells than on those that divide at a slower rate. The most sensitive population to exposure to cobalt radiation is likely to be the developing fetus, as even moderate exposures to cobalt radiation have been shown to cause dramatic effects on the developing fetus in animal studies (see Section 3.2.4.6), Likewise, growing children are likely to be more susceptible to cobalt radiation than adults, and people who are immunocompromised, have existing lung diseases, or who have defects in genetic repair enzymes would be expected to show an increased susceptibility to cobalt radiation. A detailed discussion on the effects of ionizing radiation in children can be found in Agency for Toxic Substances and Disease Registry (1999).

3.12 METHODS FOR REDUCING TOXIC EFFECTS

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

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd edition. Baltimore, MD: Williams & Wilkins, 1682–1723.

Goldfrank, LR, Flomenbaum, NE, Lewin, NA, et al., eds. 1998. Toxicological emergencies. 6th edition. Connecticut: Appleton & Lange, 481t, 489, 490t, 1338–1339.

REAC/TS. Radiation Emergency Assistance Center/Training Site. www.orau.gov/reacts/.

3.12.1 Reducing Peak Absorption Following Exposure

Methods for reducing peak absorption are similar for both the stable and radioactive forms of cobalt. General management and treatment of patients following acute exposure to cobalt includes removal of the victim from the contaminated area, and removal and isolation of contaminated clothing, jewelry, and shoes (Bronstein and Currance 1988; Stutz and Janusz 1988). The excess solid contaminant is gently brushed away, and excess liquids are blotted with absorbent material. If the victim is in respiratory distress, ventilation assistance is provided and oxygen is administered. Measures that are appropriate to the route of exposure are then taken to remove cobalt from the body. Following ocular exposure, the eyes are immediately flushed thoroughly with water. Skin is washed immediately with soap or mild detergent and water. Some evidence has been presented that the use of cheating creams on the skin can reduce the occurrence of symptoms in allergic persons (Wöhrl et al. 2001). Following ingestion of cobalt, two conflicting forms of treatment have been recommended. Stutz and Janusz (1988) recommend that victims over 1 year old be given ipecac, followed by activated charcoal (after vomiting). A cathartic, such as magnesium sulfate in water, is then administered to adults and children. Bronstein and Currance (1988) recommend that the victim be given water for dilution of the cobalt; however, they recommend that emetics not be administered. Following all routes of exposure, victims are monitored for pulmonary edema, circulatory collapse, and shock, and treated as necessary.

3.12.2 Reducing Body Burden

Chelation therapy with EDTA or dimercaprol can be effectively used if necessary (Goldfrank et al. 1990; Haddad and Winchester 1990; Stutz and Janusz 1988). Animal studies have investigated the effectiveness of various chelating agents for mitigating the toxicity of cobalt (Baker et al. 1987; Domingo et al. 1983; Llobet et al. 1988). NAC was found to be the most effective chelator because it increased both urinary and fecal excretion of cobalt as well as decreased the levels of cobalt in the liver and spleen (Llobet et al. 1988). These chelators react chemically with cobalt, so they are effective for both stable and radioactive cobalt isotopes. For more complete information on treatment of specific symptoms, refer to Bronstein and Currance (1988) and Stutz and Janusz (1988).

3.12.3 Interfering with the Mechanism of Action for Toxic Effects

No studies were located in humans or animals regarding interfering with the mechanism of action of stable or radioactive cobalt compounds.

3.13 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cobalt 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 cobalt.

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

3.13.1 Existing Information on Health Effects of Cobalt

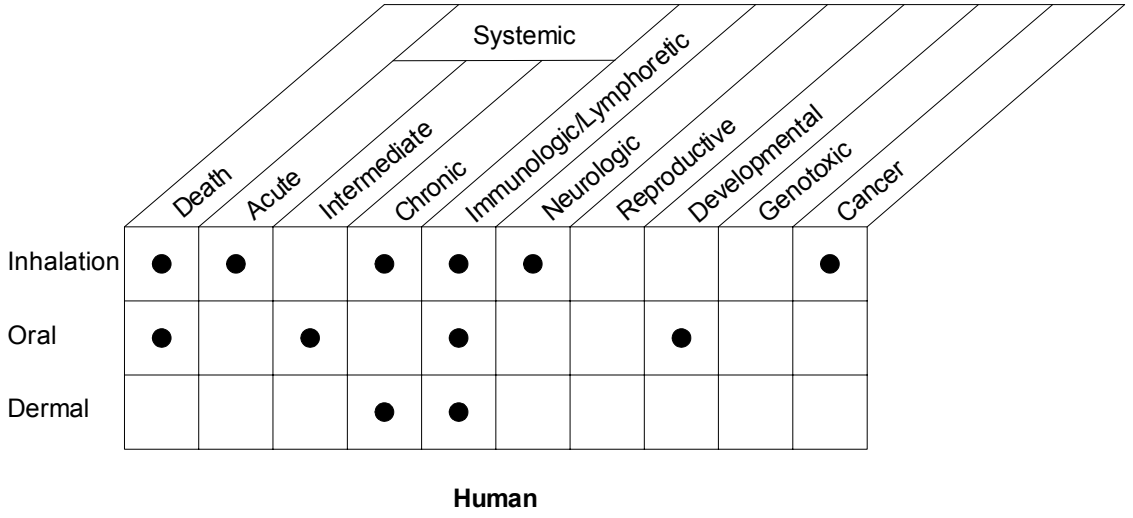
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals are summarized in Figure 3-11 for stable cobalt and in Figure 3-12 for radioactive cobalt. The purpose of these figures is to illustrate the existing information concerning the health effects of cobalt. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figures 3-11 and 3-12 represent studies conducted with all forms of cobalt. The effects of cobalt have been studied in humans following both inhalation and oral exposure. Human dermal studies designed to investigate nondermal systemic effects of cobalt have been reported. Similarly, the effects of cobalt in animals have been studied following inhalation and oral exposure. Few dermal studies are available.

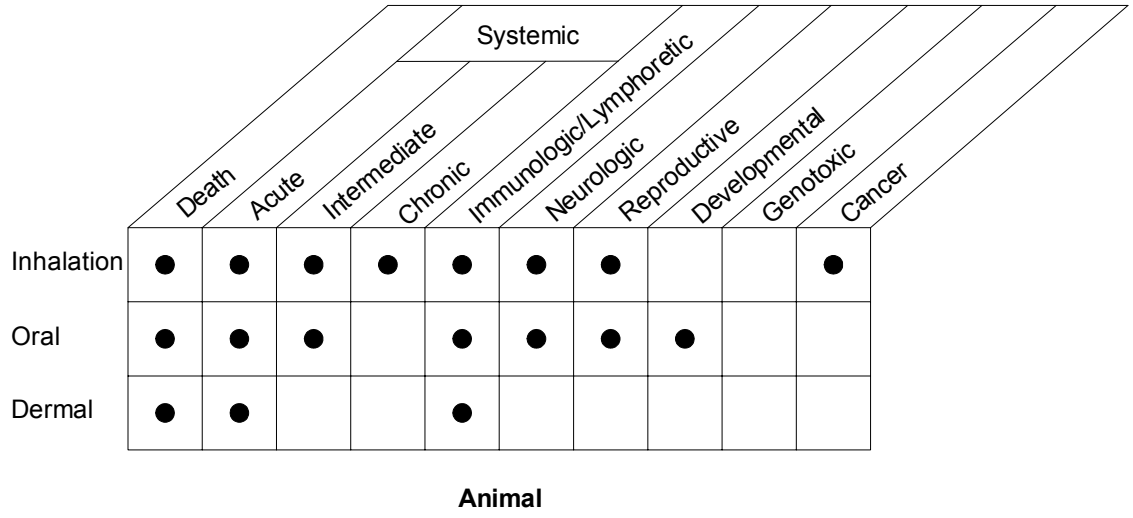
3.13.2 Identification of Data Needs

Stable Cobalt. Effects in humans following acute inhalation, oral, and dermal exposures to cobalt have been reported. In humans, the primary targets following acute exposure to cobalt include the respiratory system following inhalation exposure (Kusaka et al. 1986a), the thymus following oral exposure (Roche and Layrisse 1956), and the immunological system following dermal exposure (Alomar et al. 1985; Fischer and Rystedt 1983; Kanerva et al. 1988). Acute oral studies in animals have also identified the cardiovascular and hematopoietic systems as targets of cobalt toxicity (Domingo and Llobet 1984; Speijers et al. 1982). Although acute exposure levels associated with some of these effects in humans have been reported, the minimal acute exposure levels required to produce these effects are not known because few acute human studies exist. The results of animal studies of the acute toxicity of cobalt have been used to determine dose levels that produce death and respiratory effects following inhalation exposure, death and various systemic effects following oral exposure, and dermal and immunological effects following dermal exposure.

Figure 3-11. Existing Information on Health Effects of Stable Cobalt



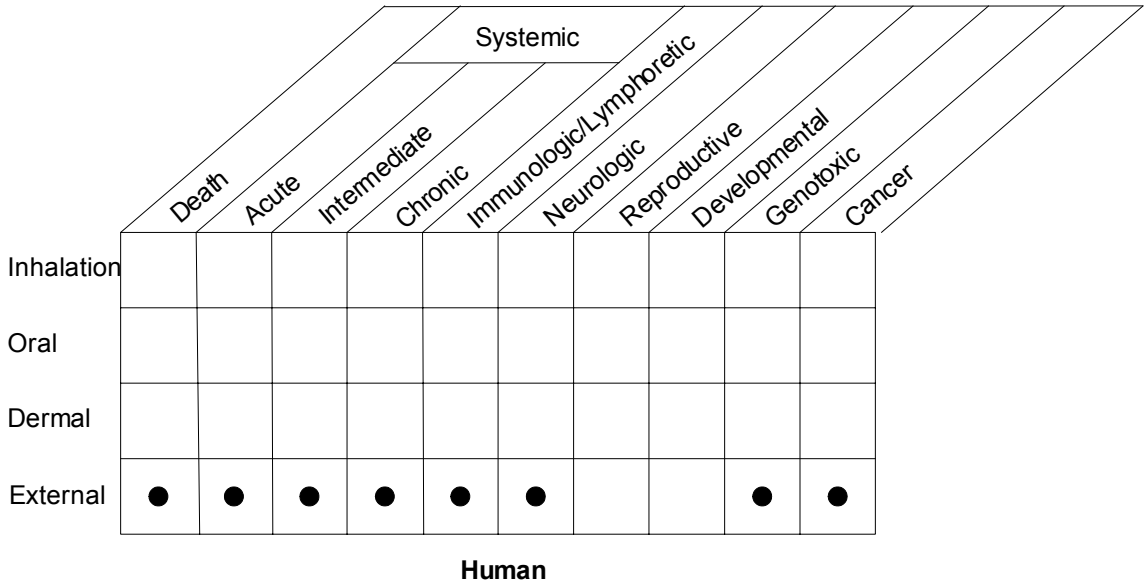
Human



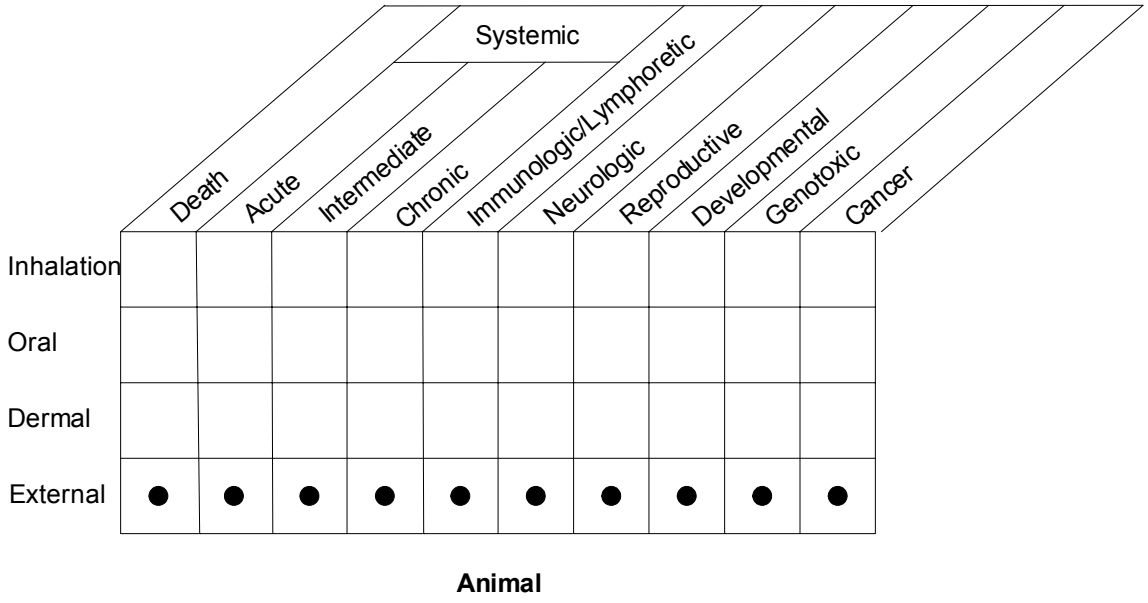
Animal

● Existing Studies

Figure 3-12. Existing Information on Health Effects of Radioactive Cobalt



Human



Animal

● Existing Studies

There were insufficient data for derivation of inhalation or oral acute MRLs because reported effects were severe and occurred at levels above those reported in the few human studies. Animal studies that identify minimally effective inhalation and oral exposure levels for the various cobalt compounds would be useful in estimating acute MRLs for each cobalt compound. Acute dermal studies would enable the determination of hazardous levels for this route of exposure. Because a small portion of the cobalt taken into the body is retained for a relatively long time, studies on the long-term consequences of acute exposure on the heart, respiratory tract, hematological system, and immune response could provide information about the potential for chronic effects of acute exposures in humans. Knowledge about the acute toxicity of cobalt is important because people living near hazardous waste sites might be exposed for brief periods.

Radioactive Cobalt. Data on health effects following acute exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because all cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. A number of health effects have been seen following cases of accidental acute exposure to high levels of external cobalt radiation in humans, including death, gastrointestinal disorders, hematological alterations, and dermal lesions (Klener et al. 1986; Stavem et al. 1985). Acute-exposure animal studies have shown pronounced effects, including death, cardiovascular changes, gastrointestinal effects, kidney effects, and neurobehavioral changes (Brady and Hayton 1977b; Bruner 1977; Cockerham et al. 1986; Darwezah et al. 1988; Down et al. 1986; Gomez-d-Segura et al. 1998; Hanks et al. 1966; King 1988a; Mele et al. 1988; Page et al. 1968; Robbins 1989a, 1989b, 1989c, 1991a). The most pronounced effects in animals following acute exposure to cobalt radiation have been reproductive and developmental effects (see Sections 3.2.4.5 and 3.2.4.6). Agency for Toxic Substances and Disease Registry (1999) has derived an acute MRL for external exposure to ionizing radiation, which is applicable to external exposures to cobalt radiation, so additional data for the derivation of an MRL are not needed.

Intermediate-Duration Exposure.

Stable Cobalt. Information on oral exposure of humans to cobalt, in the form of cobalt chloride added to beer as a foam stabilizer, provides the only human data available for exposure of intermediate duration (Alexander 1969, 1972; Morin et al. 1971). Inhalation and dermal data in humans were not located for this duration of exposure. The cardiac and hematopoietic systems are the primary targets in humans following oral exposure to cobalt. Some exposure levels associated with cardiomyopathy have been

reported following oral exposure, but the minimal exposure level required to produce this effect in humans is not known (Alexander 1969, 1972; Morin et al. 1971). Oral studies in animals reported dose levels associated with death, various systemic and neurological effects, and effects on reproduction and development (Domingo et al. 1984, 1985b; Krasovskii and Fridlyand 1971; Mohiuddin 1970; Mollenhauer et al. 1985; Pedigo et al. 1988). Intermediate-duration inhalation studies in animals reported that the respiratory tract is the target of the toxicity of inhaled cobalt (Bucher et al. 1990; Johansson et al. 1987; Kerfoot 1975; NTP 1991; Palmes et al. 1959). Animal studies were insufficient for derivation of an intermediate-duration MRL for oral exposure, since the reported effects were severe and the effects occurred at levels above those reported in the few human studies. Dermal data in animals were not located. Animal studies that investigate the possible toxic interaction between cobalt and alcohol may be helpful in understanding the role of cobalt in the cardiomyopathy reported in the heavy beer drinkers (Alexander 1969, 1972; Morin et al. 1971). One such study in guinea pigs already exists (Mohiuddin et al. 1970), but this study used a single, high dose of cobalt. Studies using a series of lower doses, both with and without alcohol preexposure, would be helpful in determining the threshold for the cardiac effects. Intermediate-duration dermal studies would enable determination of hazardous levels for this route of exposure. Intermediate-duration toxicity information is important because people living near hazardous waste sites might be exposed for corresponding time periods.

Radioactive Cobalt. Data on health effects following acute exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Substantial human data exist concerning intermediate-duration exposure to external radiation, as radiotherapy treatment regimens fall into this duration category. Animal data from intermediate-duration external exposure also exist, but are less numerous. Additional intermediate-duration studies are not likely to provide substantial additions to our knowledge of radiation-induced toxic effects.

Chronic-Duration Exposure and Cancer.

Stable Cobalt. Chronic inhalation exposure levels in humans associated with respiratory effects have been reported (Gennart and Lauwerys 1990; Nemery et al. 1992; Shirakawa et al. 1988; Sprince et al. 1988). In humans, the respiratory system is the primary target following chronic inhalation exposure. A chronic-duration inhalation MRL was derived from a NOAEL for decreased ventilatory function in exposed workers (Nemery et al. 1992). Wehner et al. (1977) reported no adverse effects in hamsters

exposed chronically to cobalt oxide. NTP (1998; Bucher et al. 1999) exposed rats and mice to cobalt sulfate for 2 years, reporting pronounced effects on the respiratory tract, including hyperplasia, inflammation, fibrosis, and metaplasia; an increased incidence of cancer was also reported. Chronic oral or dermal studies have not been reported in either humans or animals. Animal studies that identify minimally effective chronic oral exposure levels would be useful for estimating a chronic MRL. Chronic dermal studies would enable determination of hazardous levels for this route of exposure. Chronic toxicity information is important because people living near hazardous waste sites might be exposed to cobalt for many years.

Several studies of hard metal exposure in humans have reported increases in lung cancer mortality from occupational inhalation exposure to hard metal (Lasfargues et al. 1994; Moulin et al. 1998; Wild et al. 2000). In humans, cancer has not been reported following exposure to cobalt by the oral or dermal routes. An increased incidence of alveolar/bronchiolar neoplasms was noted following lifetime exposure of male rats to 1.14 mg cobalt/m^3 and in female rats to 0.38 mg cobalt/m^3 as cobalt sulfate, with tumors occurring in both sexes with significantly positive trends (Bucher et al. 1999; NTP 1998). Similarly, mice of both sexes exposed to 1.14 mg cobalt/m^3 showed an increase in alveolar/bronchiolar neoplasms, again with lung tumors occurring with significantly positive trends. Parenteral exposure to cobalt has been found to induce tumors (Gilman 1962; Gilman and Ruckerbauer 1962; Heath 1956, 1969; Heath and Daniel 1962; Shabaan et al. 1977). Further chronic exposure studies by the oral and dermal routes may determine the actual carcinogenic potential of cobalt. Also, studies examining the effect of cobalt speciation (i.e., cobalt metal vs. cobalt sulfate) would add to our understanding of the carcinogenic potential of cobalt.

Radioactive Cobalt. Data on health effects following chronic exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Limited data exist on chronic exposure to cobalt radiation in humans, with genotoxicity, immunologic effects, and cancer being the primary end points examined. Animal data are similarly limited. Additional human or animal data following chronic exposure to external cobalt radiation would be useful in further identifying possible long-term health effects or susceptible populations. Agency for Toxic Substances and Disease Registry (1999) has derived a chronic-duration MRL for external radiation exposure, which is applicable to external exposures to cobalt radiation, so additional data for the derivation of an MRL are not needed.

Genotoxicity.

Stable Cobalt. Gennart et al. (1993) reported an increase in sister-chromatid exchanges in workers exposed to a mixture of cobalt, chromium, nickel, and iron. De Boeck et al. (2000) reported no significant change in the comet assay on lymphocytes from nonsmoking workers who were occupationally exposed to cobalt or hard metal dusts; a positive association was found between hard metal exposure and increased micronucleus formation in smokers only.

Data regarding the mutagenic action of cobalt in bacterial cell lines and mammalian cell lines have been reported in the literature (Hamilton-Koch et al. 1986; Kharab and Singh 1985; Ogawa et al. 1986). *In vivo* mutagenicity studies in animals following inhalation, oral, or dermal exposure to cobalt would be helpful in ascertaining its true mutagenic potential. Further studies examining the differences in genotoxicity between different valence states of cobalt would also be useful.

Radioactive Cobalt. Data on genotoxic effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Several studies have demonstrated genotoxic effects in humans exposed to external cobalt radiation (Chang et al.1999c; House et al. 1992; Rauscher and Bauchinger 1983). Numerous data from animal studies exist demonstrating the genotoxic effects of ionizing radiation, including cobalt radiation.

Reproductive Toxicity.

Stable Cobalt. No studies were located regarding the reproductive effects of cobalt in humans following exposure by any route. Inhalation and oral studies in male animals have demonstrated adverse effects on reproductive organs (Anderson et al. 1992, 1993; Bucher et al. 1990; Corrier et al. 1985; Domingo et al. 1985b; Mollenhauer et al. 1985; NTP 1991; Pedigo et al. 1988). One study also reported effects on the estrous cycle in mice following inhalation exposure (Bucher et al. 1990; NTP 1991). Multigenerational studies would be helpful in assessing the significance of these effects on reproductive performance.

Radioactive Cobalt. Data on reproductive effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Human data on reproductive effects following external exposure to cobalt radiation are lacking,

but are sufficiently understood for gamma radiation. Available animal studies are limited, but have demonstrated radiation-induced deficits on reproductive ability in both genders (Cunningham and Huckins 1978; Laporte et al. 1985; Searl et al. 1976, 1980). Additional data in humans and animals would be helpful in refining minimal effective doses for radiation effects on reproduction.

Developmental Toxicity.

Stable Cobalt. No developmental effects were observed in the children of 78 women given cobalt chloride orally during pregnancy for treatment of anemia (Holly 1955); however, only a limited examination of offspring was reported, and details of examined end points were not reported. No studies of developmental effects by other routes of exposure in humans were located. Developmental effects in animals following oral exposure during gestation, however, have been observed (Domingo et al. 1985b). Further developmental studies in animals by all relevant routes of exposure (inhalation, oral, dermal) may clarify the potential developmental effects of cobalt in humans.

Radioactive Cobalt. Data on developmental effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. No human studies describing developmental effects of exposure to external cobalt radiation were located. Extensive data from animal studies have shown that even acute exposures to small amounts of cobalt radiation may elicit profound effects on the developing organism (see Section 3.2.4.6). The effects of ionizing radiation on the developing organism are also described in the Agency for Toxic Substances and Disease Registry Toxicological Profile for Ionizing Radiation (1999).

Immunotoxicity.

Stable Cobalt. Humans have been shown to develop sensitivity to cobalt following occupational exposure (Bencko et al. 1983; Shirakawa et al. 1988, 1989). No immunological effects were observed following oral exposure of humans to cobalt. Similar evidence of sensitization has been reported in animals (Lammintausta et al. 1985). Studies examining the mechanism of sensitization might be helpful in fully understanding and treating this effect in humans. A battery of immune function tests would further assess the immunotoxicity of cobalt in humans and animals.

Radioactive Cobalt. Data on immunotoxic effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Following external exposure to cobalt radiation, above levels normally encountered except for medical procedures, decreases in white blood cell counts have been seen in both humans and animals. Further studies on the immunotoxic effects of external cobalt radiation would be useful in refining the minimum effective dose.

Neurotoxicity.

Stable Cobalt. No studies were located regarding neurotoxic effects of cobalt in humans following oral or dermal exposure. Two occupational inhalation exposure studies have reported memory deficits, optic atrophy, or nerve deafness in humans exposed to cobalt (Jordan et al. 1990; Meecham and Humphrey 1991). In animals, alterations in several neurologic parameters were found following oral exposure (Bourg et al. 1985; Krasovskii and Fridlyand 1971; Mutafova-Yambolieva et al. 1994; Nation et al. 1983; Singh and Junnarkar 1991; Vassilev et al. 1993; Wellman et al. 1984). Additional studies in animals would assist in determining whether these neurological effects have any relevance to potential effects in humans.

Radioactive Cobalt. Data on neurotoxic effects following exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Human data following cobalt radiotherapy have demonstrated effects believed to result from neurological damage, but data are limited, doses were extreme, and effects have not been well-characterized. Several animal studies have shown neurobehavioral or neurophysiological changes following exposure to cobalt radiation (Bassant and Court 1978; Maier and Landauer 1989; Mele et al. 1988).

Epidemiological and Human Dosimetry Studies.

Stable Cobalt. Epidemiological studies relating to cobalt exposure are available in the literature. Studies of persons exposed to cobalt occupationally are available (Kusaka et al. 1986a, 1986b; Shirakawa et al. 1988, 1989; Sprince et al. 1988), dietetically (beer drinkers) (Alexander 1969, 1972; Morin et al. 1971), and medically (cobalt given to alleviate anemia) (Davis and Fields 1958; Holly 1955; Taylor et al. 1977).

Further studies assessing the cause/effect relationship between cobalt exposure and human health effects would be helpful in monitoring individuals living near a hazardous waste site to verify that documented exposure levels are not associated with adverse health effects.

Radioactive Cobalt. Epidemiological data on exposure to radioactive cobalt by the inhalation, oral, or dermal routes are lacking. Because cobalt radioisotopes are man-made (see Chapter 5), only low-level exposure to radioactive cobalt in the environment by these routes is likely to occur. Human external exposures to cobalt radiation have been documented in the literature. Radiotherapy exposures, though to extremely high radiation doses, are generally well-controlled and documented, whereas environmental and accidental workplace exposures are less frequent and less well-documented.

Biomarkers of Exposure and Effect.

Exposure.

Stable Cobalt. Information is available on the monitoring of cobalt exposure by the quantification of cobalt in urine and blood (Alexandersson 1988; Ichikawa et al. 1985; Scansetti et al. 1985). A portion of inhaled cobalt is rapidly excreted in the feces, and the amount retained in the body tends to be steadily excreted over time. Levels in body fluids, therefore, can be monitored up to several days after exposure. Many different methods for the detection of cobalt in body fluids have been reported (Section 7.1).

Radioactive Cobalt. No information is available regarding biomarkers specific for exposure to cobalt radionuclides by the inhalation, oral, dermal, or external exposure routes. Biomarkers for exposure to ionizing radiation are discussed in Agency for Toxic Substances and Disease Registry (1999). Personal dosimeters (film or luminescent) are an artificial surrogate to measure the amount of exposure to external beta or gamma radiation, though these are not specific for radiation from cobalt radionuclides.

Effect.

Stable Cobalt. Alterations in serum proteins and changes in serum antibodies have been found that are specific for cobalt exposure (Stokinger and Wagner 1958). These changes may be the earliest indication of the effects of cobalt exposure. Further studies may reveal other cobalt-specific biomarkers that, in

combination with these changes, may alert health professionals to cobalt exposure before serious toxicological effects occur.

Radioactive Cobalt. While in many cases radioactive cobalt itself can be measured following exposure, no information is available regarding biomarkers specific for effects of cobalt radionuclides following exposure by the inhalation, oral, dermal, or external exposure routes. Biomarkers for effects of ionizing radiation are discussed in Agency for Toxic Substances and Disease Registry (1999), and include changes in levels of formed elements of the blood as some of the most sensitive indicators. These biomarkers are believed to be suitable for monitoring exposure to cobalt radiation.

Absorption, Distribution, Metabolism, and Excretion. Pharmacokinetic data in humans indicate that cobalt is absorbed through the lungs (Foster et al. 1989) and the gastrointestinal tract (Harp and Scoular 1952; Sorbie et al. 1971; Valberg et al. 1969), that cobalt is well distributed in the body with the highest concentration being found in the lungs following inhalation (Gerhardsson et al. 1984; Hewitt 1988; Hillerdal and Hartung 1983; Teraoka 1981), and that some of the inhaled or ingested cobalt is rapidly excreted in the feces, with the amount retained in the body being excreted slowly, primarily in the urine (Foster et al. 1989; Paley et al. 1958; Smith et al. 1972). Pharmacokinetic studies in animals following inhalation and oral exposure have demonstrated similar responses (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Foster et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). Few data exist regarding the pharmacokinetics of cobalt following dermal exposure, though what data are available demonstrate that cobalt can be absorbed in small quantities through human (Scansetti et al. 1994) and animal (Inaba and Suzuki-Yasumoto 1979; Lacy et al. 1996) skin, with greater absorption occurring through damaged than intact skin.

Comparative Toxicokinetics. Several inhalation and oral studies have compared the toxicokinetics of cobalt in several different species of animals, including humans (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Foster et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). No comparative pharmacokinetic studies following dermal exposure were located. These studies would be useful because humans are exposed via the skin in the workplace and may potentially be exposed via this route at waste sites.

Methods for Reducing Toxic Effects.

Stable and Radioactive Cobalt. Chelation therapy is expected to apply equally well to stable and radioactive cobalt isotopes. EDTA or British anti-lewisite (BAL) has been shown to effectively mitigate the toxicity of cobalt in humans (Goldfrank et al. 1990; Haddad and Winchester 1990; Stutz and Janusz 1988). In animal studies examining the effectiveness of various chelators, n-acetyl cysteine (NAC) was shown to be the most effective (Llobet et al. 1988). It would be useful to determine the effective dose of NAC in humans. Studies examining the effectiveness of other chelating agents may be helpful in determining the most effective chelation therapy for humans.

Children's Susceptibility.

Stable Cobalt. Data comparing the susceptibility of children to cobalt compounds are limited. Animal studies have suggested that absorption following inhalation or oral exposure may be greater in very young animals, resulting in increased systemic dose. Data are not available on the differences between children and adults following dermal exposure. Further studies on the susceptibility of young animals relative to adult animals may be useful in determining whether children are at greater risk from exposure to cobalt in the environment than adults.

Radioactive Cobalt. No data are available on whether children are more susceptible to the effects of radioactive cobalt compounds than adults. Animal studies have shown that exposure *in utero* to even moderate amounts of cobalt radiation can cause dramatic effects in the developing organism. It would be expected that children would be more susceptible to the effects of external cobalt radiation, due to the greater percentage of rapidly-dividing cells during growth.

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

3.13.3 Ongoing Studies

Relevant ongoing studies were not located for cobalt.

4. CHEMICAL, PHYSICAL, AND RADIOLOGICAL INFORMATION

4.1 CHEMICAL IDENTITY

Cobalt is a naturally-occurring element that appears in the first transition series of Group 9 (VIII) of the periodic table along with iron and nickel. There is only one stable isotope of cobalt, ^{59}Co. There are about 26 known radioactive isotopes of cobalt, of which only two are of commercial importance, ^{60}Co and ^{57}Co. ^{60}Co, a commonly-used source of gamma radiation, is the most important radionuclide. It may be a low-level contaminant of cooling water released by nuclear reactors. Table 4-1 summarizes information on the chemical identity of elemental cobalt and some common cobalt compounds.

4.2 PHYSICAL, CHEMICAL, AND RADIOLOGICAL PROPERTIES

Cobalt commonly occurs in the 0, +2, and +3 valence states. Compounds containing cobalt in the -1, +1, +4, and +5 oxidation state are few and uncommon (Cotton and Wilkinson 1980). Cobalt (II) is much more stable than Co(III), and Co^{3+} is a sufficiently powerful oxidizing agent to oxidize water, liberating oxygen. Table 4-2 summarizes important physical and chemical properties of elemental cobalt and some common cobalt compounds. These properties are similar to those of its neighbors in Group 9 of the periodic table, iron and nickel. Metallic cobalt, Co(0), occurs as two allotropic forms, hexagonal and cubic; the hexagonal form is stable at room temperature. A biochemically important cobalt compound is vitamin B_{12}, or cyanocobalamin, in which cobalt is complexed with four pyrrole nuclei joined in a ring called the corrinoid ligand system (similar to porphyrin).

The Chemical Abstract Service (CAS) registry numbers, decay modes, half-lives, and specific activity of the three principal radioactive cobalt isotopes, ^{57}Co, ^{58}Co, and ^{60}Co, are presented in Table 4-3. ^{60}Co (half-life of 5.27 years) decays by beta decay to nickel-60, a stable isotope (ICRP 1983; Lide 1998).

$$^{60}_{27}\mathrm{Co} \rightarrow ^{60}_{28}\mathrm{Ni} + ^{0}_{-1}e + \gamma$$

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

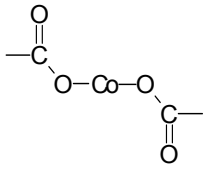
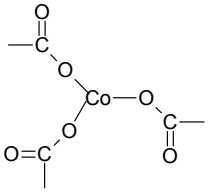
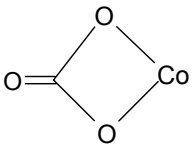
Characteristic	Cobalt	Cobalt(II) acetate	Cobalt(III) acetate	Cobalt(II) carbonate
Synonym(s)	Cobalt-59, cobalt metal	Cobaltous acetate, cobalt diacetate	Cobaltic acetate, cobalt triacetate	Cobaltous carbonate; carbonic acid; cobalt (+2) salt
Registered trade name(s)	No data	No data	No data	No data
Chemical formula	Co	$Co(C_2H_4O_2)_2$	$Co(C_2H_4O_2)_3$	$CoCO_3$
Chemical structure	Co			
Identification numbers:				
CAS registry	7440-48-4	71-48-7	917-69-1	513-79-10
NIOSH RTECS	GF8750000	AG3150000	No data	FF9450050
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping[a]	UN1318	No data	No data	No data
HSDB	519	997	No data	No data
NCI	C60311	No data	No data	No data

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

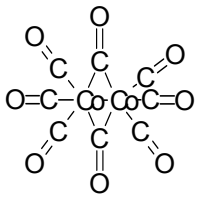
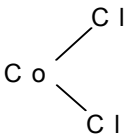
Characteristic	Cobalt carbonyl	Cobalt(II) chloride	Cobalt(II) hydroxide	Cobalt(II) meso-porphyrin
Synonym(s)	Dicobalt octa-carbonyl; cobalt tetracarbonyl	Cobalt dichloride; cobaltous chloride	Cobaltous hydr-oxide; cobalt dihydroxide	Cobalt meso-porphyrin IX Cobalt-iprotoporphyrin
Registered trade name(s)	No data	No data	No data	No data
Chemical formula	$Co_2(CO)_8$	$CoCl_2$	$Co(OH)_2$	$C_{34}H_{34}CoN_4O_4$
Chemical structure			HO—Co—OH	No data
Identification numbers:				
CAS registry	10210-68-1	7646-79-9	21041-93-0	21158-51-0
NIOSH RTECS	GG0300000	GF9800000	No data	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	7217328	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data
HSDB	6345	1000	No data	No data
NCI	No data	No data	No data	No data

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

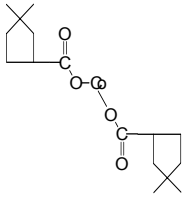
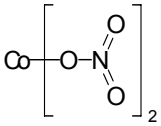
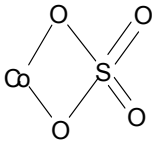
Characteristic	Cobalt(II) naphthenate	Cobalt(II) nitrate	Cobalt(II) oxide	Cobalt(III) oxide
Synonym(s)	Naftolite; naphthenic acid, cobalt salt	Cobaltous nitrate	Black 13; C.I. 77322; cobalt monoxide; cobaltous oxide	Cobalt black; cobaltic oxide; cobalt sesquioxide; cobalt trioxide; C.I. 77323
Registered trade name(s)	No data	No data	C.I. Pigment Black 13; Zaffre	No data
Chemical formula	$Co(C_{11}H_{10}O_2)_2$	$Co(No_3)_2•6H_20$	CoO	Co_2O_3
Chemical structure			Co═O	O═Co—O—Co═O
Identification numbers:				
CAS registry	10210-68-1	7646-79-9	21041-93-0	21158-51-0
NIOSH RTECS	GG0300000	GF9800000	No data	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	7217328	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data
HSDB	6345	1000	No data	No data
NCI	No data	No data	No data	No data

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

Characteristic	Cobalt(II, III) oxide	Cobalt(II) sulfate
Synonym(s)	Cobaltic-cobaltous oxide; cobalt tetra-oxide, tricobalt tetraoxide, cobaltosic oxide; cobalt black; C.I. Pigment Black 13	Cobalt sulfate; cobaltous sulfate
Registered trade name(s)	No data	No data
Chemical formula	Co_3O_4	$CoSO_4$
Chemical structure	Co=OO=Co–O–Co=O	
Identification numbers:		
CAS registry	1308-06-1	10124-43-3
NIOSH RTECS	No data	GG3100000
EPA hazardous waste	No data	No data
OHM/TADS	No data	7217330
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	No data	240
NCI	No data	No data

[a]The identification number for radioactive materials is UN2910

CAS = Chemical Abstract 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

Source: Budavari 1996; HSDB 2001; RTECS 1987

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

Property	Cobalt	Cobalt(II) acetate	Cobalt(III) acetate	Cobalt(II) carbonate
Molecular weight	58.93	177.03	236.07	118.94
Color	Silvery gray	Light pink	Dark green	Red
Physical state	Solid	Solid	Solid	Solid
Melting point, °C	1,495	No data	Decomposes at 100 °C	Decomposes
Boiling point, °C	2,870	No data	Not relevant	Not relevant
Density, g/cm^3	8.9 (20 °C)	No data	No data	4.13
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	Soluble	Soluble	0.18 g/100 g H_2O at 15 °C
Organic solvent(s)	Insoluble	2.1 g/100 g methanol at 15 °C	soluble in alcohol, acetic acid	Insoluble in ethanol
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1 mmHg at 1,910 °C	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	760 °C for dust cloud	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[a]	Not relevant[a]	Not relevant[a]	Not relevant[a]
Explosive limits	No data	No data	No data	No data

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

Property	Cobalt carbonyl	Cobalt(II) chloride	Cobalt(II) hydroxide	Cobalt(II) mesoporphyrin
Molecular weight	341.9	129.84	92.95	621.2[b]
Color	Orange (white when pure)	Blue	Rose red or blue green	No data
Physical state	Solid	Solid	Solid	No data
Melting point, °C	51	724	No data	No data
Boiling point, °C	Decomposes	1,049	No data	No data
Density, g/cm^3	1.73 at 18 °C	3.356 (36 °C)	3.597 at 15 °C	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	450 g/L at 7 °C	0.0032 g/L	No data
Organic solvent(s)	Soluble in ether; insoluble in naphtha	544 g/L in ethanol; 86 g/L in acetone	No data	No data
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	199.5 at 25 °C	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature, °C	No data	No data	No data	No data
Flashpoint, °C	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[a]	Not relevant[a]	Not relevant[a]	Not relevant[a]
Explosive limits	No data	No data	No data	No data

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

Property	Cobalt(II) naphthenate	Cobalt(II) nitrate	Cobalt(II) oxide	Cobalt(III) oxide
Molecular weight	407	182.94	74.93	165.86
Color	No data	Red	Pink	Black-gray
Physical state	Solid	Solid	Solid	Solid
Melting point, °C	140	Decomposes at 100–105[b]	1,795	895 (decomposes)
Boiling point, °C	No data	Not relevant	No data	Not relevant
Density g/cm^3	0.9	2.49[b]	6.45	5.18
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	133.8 at 0 °C[c]	Insoluble	Insoluble
Organic solvent(s)	No data	Soluble in ethanol, acetone	Insoluble in alcohol	Insoluble in ethanol
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{ow}	No data	No data	No data	No data
Vapor pressure	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[a]	Not relevant[a]	Not relevant[a]	Not relevant[a]
Explosive limits	No data	No data	No data	No data

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

Property	Cobalt(II, III) oxide	Cobalt(II) sulfate
Molecular weight	250.80	154.99
Color	Black	Dark blue
Physical state	Solid	Solid
Melting point, °C	-O_2 at 900–950	Decomposes at 735 °C
Boiling point, °C	Not relevant	Not relevant
Density g/cm^3	6.07	3.71
Odor	No data	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water	Insoluble	3.83 g/100 mL H_2O at 25 °C
Organic solvent(s)	No data	1.04 g/100 mL methanol at 18 °C
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{ow}	No data	No data
Vapor pressure	No data	No data
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	Not relevant[a]	Not relevant[a]
Explosive limits	No data	No data

[a]Substances exist in the atmosphere in the particulate state, and the concentration is expressed in weight per cubic meter
[b]CAS Online
[c]Hexahydrate

Source: Budavari 1996; HSDB 2001, 2004; Lide 1994; Stockinger 1981; Weast 1985

Table 4-3. Principal Radioactive Cobalt Isotopes

Isotope	CAS registry no.	Decay mode (product)	Decay mode energy (MeV)	Beta radiation Energy (MeV)	Beta radiation Intensity (percent)	Gamma radiation Energy (MeV)	Gamma radiation Intensity (percent)	Half-life
^{55}Co	13982-25-7	E.C. β^+ (^{55}Fe)	3.452	1.498	46	0.9312	75	17.53 hours
				1.021	25.6	0.4772	20	
				2.043	10.7	1.408	16.88	
^{57}Co	13981-50-5	E.C. (^{57}Fe)	0.836	0.700	99.8	0.1221	85.6	271.8 days
						0.1365	10.7	
						0.014	9.2	
^{58}Co	13981-38-9	E.C. β^+ (^{58}Fe)	2.30	1.4966	83.9	0.811	99	70.86 days
				0.4746	14.9			
^{60}Co	10198-40-0	β^- (^{60}Ni)	2.824	0.3181	99.9	1.173	100	5.271 years
						1.332	100	

B^- = negative beta emission; β^+ = positron emission; E.C. = orbital electron capture

Source: ICRP 1983; LBNL 2000; Lide 1998

The decay is accompanied by the emission of 1.173 and 1.332 MeV gamma rays. ^{57}Co (half-life of 271.8 days) and ^{58}Co (half-life of 70.9 days) decay by electron capture and electron capture/position (β+) emission to ^{57}Fe and ^{58}Fe, respectively. These decay processes are also accompanied by gamma emissions (Table 4-3).

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

5.1 PRODUCTION

Cobalt is the 33rd most abundant element, comprising approximately 0.0025% of the weight of the earth's crust. It is often found in association with nickel, silver, lead, copper, and iron ores and occurs in mineral form as arsenides, sulfides, and oxides. The most import cobalt minerals are: linnaeite, Co_3S_4; carrolite, $CuCo_2S_4$; safflorite, $CoAs_2$; skutterudite, $CoAs_3$; erythrite, $Co_3(AsO_4)_2 \cdot 8H_2O$; and glaucodot, CoAsS (Hodge 1993; IARC 1991; Merian 1985; Smith and Carson 1981). The largest cobalt reserves are in the Congo (Kinshasa), Cuba, Australia, New Caledonia, United States, and Zambia. Most of the U.S. cobalt deposits are in Minnesota, but other important deposits are in Alaska, California, Idaho, Missouri, Montana, and Oregon. Cobalt production from these deposits, with the exception of Idaho and Missouri, would be as a byproduct of another metal (USGS 2004). Cobalt is also found in meteorites and deep sea nodules.

The production of pure metal from these ores depends on the nature of the ore. Sulfide ores are first finely ground (i.e., milled) and the sulfides are separated by a floatation process with the aid of frothers (i.e., C_5–C_8 alcohols, glycols, or polyethylene or polypropylene glycol ethers). The concentrated product is subjected to heating in air (roasting) to form oxides or sulfates from the sulfide, which are more easily reduced. The resulting matte is leached with water and the cobalt sulfate leachate is precipitated as its hydroxide by the addition of lime. The hydroxide is dissolved in sulfuric acid, and the resulting cobalt sulfate is electrolyzed to yield metallic cobalt. For the cobalt-rich mineral cobaltite, a leaching process with either ammonia or acid under pressure and elevated temperatures has been used to extract cobalt. The solution is purified to remove iron and is subsequently reduced by hydrogen in the presence of a catalyst under elevated temperature and pressure to obtain fine cobalt powder (Duby 1995; Nagaraj 1995; Planinsek and Newkirk 1979).

Except for a negligible amount of byproduct cobalt produced from some mining operations, no cobalt is presently mined or refined in the United States. In addition to byproduct production, U.S. production is derived from scrap (secondary production). In 2003, an estimated 2,200 metric tons of cobalt were recycled from scrap (USGS 2004). Since 1993, production has been supplemented by sales of excess cobalt from the National Defense Stockpile (NDS), which the government maintains for military,

industrial, and essential civilian use during national emergencies. In fiscal year 2002, 2,720 metric tons of cobalt were released from the NDS. In 2001, the United States did not mine or refine cobalt, with the exception of small amounts of byproduct cobalt produced from mining operations in Missouri and Montana. The 2002 U.S. consumption of cobalt metal, organic and inorganic cobalt compounds, and purchased scrap (in terms of cobalt content) was 3,870, 1,270, and 2,800 metric tons, respectively (USGS 2002).

Current U.S. manufacturers of selected cobalt compounds are given in Table 5-1. Table 5-2 lists facilities in each state that manufacture, process, or use cobalt or cobalt compounds, the intended use, and the range of maximum amounts of these substances that are stored on site. In 2000, there were 618 reporting facilities that produced, processed, or used cobalt or cobalt compounds in the United States. The data listed in Table 5-2 are derived from the Toxics Chemicals Release Inventory (TRI) (TRI01 2004). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

^{60}Co is produced by irradiating stable cobalt, ^{59}Co, with thermal neutrons in a nuclear reactor: $^{59}Co(n,\gamma)^{60}Co$. The neutron flux employed is 10^{12}–10^{15} *n*/cm^2-sec and the conversion is 99%. The maximum specific activity obtained is $3.7x10^{13}$ Bq/g (1,000 Ci/g). Commercial ^{60}Co sources used for bacterial sterilization are made into rods with double metal shielding. The individual sources have an activity of about $2x10^{14}$–$6x10^{14}$ Bq (6–15 kCi). The annual output of ^{60}Co was about $2x10^{18}$–$3x10^{18}$ Bq (50–80 MCi) in the early 1990s. In 1991, there were 170 gamma irradiation systems operating in 45 countries having a total activity of about $6x10^{18}$ Bq (160 MCi) (Zyball 1993). Producers of ^{60}Co include MDS Nordion in Canada, AEA Technology (formerly Amersham QSA) in the United Kingdom, and Neutron Products in Dickerson, Maryland.

^{58}Co is not produced commercially. It can be produced by irradiating ^{58}Ni, a stable isotope, with neutrons, followed by positron decay: $^{58}Ni(n,\gamma)^{58}Co$. It can be produced in a nuclear reactor or a cyclotron. Both ^{60}Co and ^{58}Co may be produced unintentionally in reactors. These are the dominant sources of residual radiation in the primary circuit outside the reactor core of nuclear plants and are formed by neutron absorption of ^{59}Co and ^{58}Ni, both stable isotopes commonly used in plant construction materials (Taylor 1996). ^{60}Co is commonly found as one of the radionuclides present in the low-level radioactive waste discharges from many nuclear power plants; however, amounts rarely make a significant contribution to the radiation exposure of the public (Leonard et al. 1993a). The geometric

Table 5-1. Current U.S. Manufacturers of Cobalt Metal and Selected Cobalt Compounds[a]

Company	Location
Cobalt metal[b]:	
Kennametal, Inc.	Latrobe, Pennsylvania
OM Group, Inc.	Cleveland, Ohio
Cobalt (II) acetate:	
The IMC Group	Shelby, North Carolina
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OM Group, Inc.	Franklin, Pennsylvania
The Shepard Chemical Company	Cincinnati, Ohio
Cobalt (II) carbonate:	
The IMC Group	Shelby, North Carolina
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OMG Apex	St. George, Utah
OM Group, Inc.	Franklin, Pennsylvania
The Shepherd Chemical Co.	Cincinnati, Ohio
Cobalt (II) chloride:	
The IMC Group	Shelby, North Carolina
Johson Matthey, Inc., Alfa Aesar	Ward Hill, Massachusetts
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OM Group. Inc.	Franklin, Pennsylvania
The Shepard Chemical Company	Cincinnati, Ohio
Cobalt (II) hydroxide:	
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OM Group, Inc.	Franklin, Pennsylvania
The Shepard Chemical Company	Cincinnati, Ohio
Cobalt (II) nitrate:	
The IMC Group	Shelby, North Carolina
Johnson Matthey, Inc., Alfa Aesar	Ward Hill, Massachusetts
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OMG Apex	St. George, Utah
OM Group, Inc.	Franklin, Pennsylvania
The Shepard Chemical Company	Cincinnati, Ohio
Umicore USA, Inc., Cobalt Products	Laurinburg, North Carolina
Cobalt (II) oxide:	
OMG Apex	St. George, Utah
The Shepard Chemical Company	Cincinnati, Ohio

Table 5-1. Current U.S. Manufacturers of Cobalt Metal and Selected Cobalt Compounds[a]

Cobalt (III) oxide:	
Johnson Matthey, Inc., Alfa Aesar	Ward Hill, Massachusetts
Mallinckrodt Baker, Inc.	Phillipsburg, New Jersey
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OM Group, Inc.	Franklin, Pennsylvania
Osram Sylvania Inc.	Towanda, Pennsylvania
Cobalt (II) sulfate:	
The IMC Group	Shelby, North Carolina
McGean-Rohco, Inc., McGean Specialty Chemicals Division	Cleveland, Ohio
OMG Apex	St. George, Utah
OM Group, Inc.	Franklin, Pennsylvania
The Shepard Chemical Company	Cincinnati, Ohio

[a]Derived from Stanford Research Institute (SRI) 2003, except where otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or $10,000 in value annually) by the companies listed

[b]U.S. members of The Cobalt Development Institute that are listed as producers of cobalt powder or hard metal products

Table 5-2. Facilities that Produce, Process, or Use Cobalt and Cobalt Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	2	10,000	999,999	1, 5, 7, 12
AL	22	100	999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 12, 13
AR	9	100	99,999	1, 5, 7, 8,9
AZ	12	1,000	49,999,999	1, 2, 3, 5, 7, 8,9, 10, 12, 13, 14
CA	28	0	9,999,999	1, 2, 3, 5, 6, 7, 8,9, 10, 11, 12
CO	1	10,000	99,999	12
CT	9	0	999,999	2, 3, 7, 8
DE	2	1,000	9,999	1, 5,9, 13
FL	11	0	99,999	1, 2, 3, 4, 5, 6, 7, 8,9, 12, 13, 14
GA	17	100	999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 11, 12, 13
IA	6	100	99,999	3, 4, 7, 8, 12
ID	2	100,000	999,999	1, 3, 5, 12
IL	24	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 13, 14
IN	42	100	999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 13, 14
KS	5	10,000	99,999	1, 3, 5, 6, 7, 8,9, 10, 11, 12, 13
KY	22	100	999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 12, 13, 14
LA	15	1,000	999,999	1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14
MA	11	100	99,999	1, 5, 8,9, 12
MD	6	1,000	99,999	1, 2, 3, 4, 5, 6, 7,9, 13
ME	2	100	99,999	1, 5, 8
MI	24	0	999,999	1, 2, 3, 4, 5, 7, 8,9, 11, 12, 13, 14
MN	6	100	99,999	1, 2, 5, 7, 8,9, 10, 12, 13, 14
MO	5	1,000	999,999	1, 2, 3, 4, 5, 6, 8,9, 12, 13, 14
MS	7	100	99,999	1, 5, 6, 7, 8, 10
MT	1	10,000	99,999	1, 5, 12, 14
NC	24	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 12, 13, 14
ND	4	1,000	99,999	1, 5, 7, 12, 13, 14
NE	1	1,000	9,999	8, 11
NH	1	100	999	8
NJ	14	1,000	9,999,999	1, 3, 4, 5, 6, 7, 8, 10, 12, 14
NM	6	1,000	9,999,999	1, 3, 4, 5, 7, 8,9, 11, 12, 13
NV	8	1,000	10,000,000,000	1, 5, 6, 8, 12, 13, 14
NY	12	1,000	99,999	1, 2, 3, 4, 5, 7, 8,9, 11, 12
OH	44	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 11, 12, 13, 14
OK	14	100	999,999	1, 2, 3, 5, 6, 7, 8,9, 10, 11, 12
OR	6	1,000	99,999	1, 5, 7, 8, 12
PA	44	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Cobalt and Cobalt Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PR	2	1,000	99,999	8,9
RI	1	100,000	999,999	8
SC	26	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 13
SD	1	10,000	99,999	7
TN	18	0	999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 12, 13
TX	45	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 13, 14
UT	6	1,000	9,999,999	1, 3, 4, 5, 7, 8,9, 12, 13
VA	9	10,000	999,999	1, 2, 3, 4, 5, 6, 7, 8
VI	1	10,000	99,999	10
WA	2	10,000	99,999	1, 3, 4, 5,9, 10, 11, 12, 13
WI	20	100	999,999	1, 3, 4, 5, 7, 8,9, 11, 12, 13, 14
WV	13	100	999,999	1, 2, 3, 4, 5, 7, 8,9, 11, 12, 13, 14
WY	2	0	99,999	1, 5,9, 12, 13

Source: TRI01 2004

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

mean release of ^{60}Co in liquid effluents of light-water nuclear power stations was reported as in the early 1970s as 0.0805 Ci/year (3.0 GBq) (Morgan 1976).

The ^{60}Co activities for a representative pressurized-water reactor (PWR) and boiling water reactor (BWR) fuel assemblies are 1,100 and 170 Ci (41 and 6.3 TBq), respectively. There are 78 PWR and 40 BWR reactors in the United States, several of which have ceased operation. The postirradiation cobalt content of typical PWR and BWR reactor fuel assemblies are 38 g (0.01%) and 26 g (0.01%), respectively (DOE 2002).

^{55}Co may be produced by applying 12 MeV indirect deuteron energy to ^{54}Fe (^{54}Fe(d,n)^{55}Co), 40 MeV protons to natural iron (^{56}Fe(p,2n)^{55}Co), or 20 MeV protons to natural nickel foil (^{58}Ni(p,α)^{55}Co) followed by separation of the ^{55}Co on an ion exchange column (Wolf 1955). Due to the short half-life (17.5 hours), however, ^{55}Co would not be persistent in the environment or in waste sites. ^{57}Co (half-life of 270 days) is produced by AEA Technology (formerly Amersham QSA) in the United Kingdom (Web Research Co. 1999).

5.2 IMPORT/EXPORT

In 2002, 8,450 metric tons of cobalt were imported into the United States compared with 7,670, 8,150, 8,770, and 9,410 metric tons in 1998, 1999, 2000, and 2001 (USGS 2002). Between 1999 and 2002, Finland, Norway, Russia, and Canada supplied 24, 18, 13, and 10% of cobalt, respectively (USGS 2004). Imports for 2002 by form included (form, metric tons cobalt content): metal, 6,800; oxides and hydroxides, 936; acetates, 84; carbonates, 60; chlorides, 22; and sulfates 545. Cobalt exports for 1999, 2000, 2001, and 2002 were 1,550, 2,630, 3,210, and 2,080 metric tons, respectively; exports estimated in 2002 are 2,500 metric tons (USGS 2002; 2004).

^{60}Co and ^{57}Co are produced in Canada and in the United Kingdom and are imported from these countries. No import and export quantities for cobalt radioisotopes were available.

5.3 USE

The United States is the world's largest consumer of cobalt. Cobalt is used in a number of essential military and industrial applications. The largest use of metallic cobalt is in superalloys that are used in gas turbines aircraft engines. Superalloys are alloys developed for applications where elevated temperatures and high mechanical stress are encountered. It is also used in magnetic alloys and alloys that are required for purposes requiring hardness, wear resistance, and corrosion resistance. Cobalt is used as a binder for tungsten carbide (cemented carbides) cutting tools to increase impact strength. Cobalt compounds are used as pigments in glass, ceramics, and paints; as catalysts in the petroleum industry; as paint driers; and as trace element additives in agriculture and medicine.

Over 40% of nonmetallic cobalt is used in catalysis, and most cobalt catalysts are used in hydrotreating/desulfurization in the oil and gas industry, the production of terephthalic acid and dimethylterephthalate, and the production of aldehydes using the high pressure oxo process (hydroformylation). Cobalt chemicals primarily used as catalysts include cobalt(III) acetate, cobalt(II) bromide, carbonate, manganate, oxalate, and sulfide, cobalt carbonyl, and cobalt naphthenate. Cobalt carbonate and chromate are mainly used as pigments and cobalt(II) acetate, 2-ethylhexanoate, linoleate, naphthenate, nitrate, oleate, and stearate are mainly used as driers. Cobalt has been used for hundreds of years as a blue colorant in glass, ceramics, and paints (Richardson 1993).

A growing use for cobalt is as an addition to the Ni/Cd, Ni-metal hydride battery or as the main component of the lithium ion cell ($LiCoO_2$). In 2002, the reported U.S. cobalt consumption was 7,930 metric tons with a use pattern of (end use, metric tons cobalt content, percent): superalloys, 3,700, 46.7%; steel alloys, 555, 7.0%; other alloys, including magnetic alloys, 1,050, 13.2%; cemented carbides, 617, 7.8%; chemical and ceramic use, 1,950, 24.6%; and miscellany, 63, 0.8%. Cobalt is also used a target material in electrical x-ray generators (Cobalt Development Institute 2004; Donaldson 1986; Hodge 1993; IARC 1991; Richardson 1993; USGS 2002).

Gamma rays from ^{60}Co are used medically to treat cancer and industrially to sterilize medical and consumer products, to crosslink, graft and degrade plastics, and as an external source in radiography and radiotherapy. ^{60}Co, along with iridium 192 (^{192}Ir), are the most commonly used isotopes in industrial radiography. In this application, ^{60}Co is used for nondestructive testing of high-stress alloy parts, such as pipeline weld joints, steel structures, boilers, and aircraft and ship parts. Radiography may be conducted

at permanent, specially shielded facilities or temporary sites in the field (USNRC 1999). ^{60}Co is used in chemical and metallurgical analysis and as a tracer in biological studies. In 1990, about 95% of installed ^{60}Co activity was used for the sterilization of medical devices; about 45% of medical devices were sterilized using radiation. ^{60}Co is also a source of gamma rays used for food irradiation; depending on the dose levels, irradiation may be used to sterilize food, destroy pathogens, extend the shelf-life of food, disinfest fruits and grain, delay ripening, and retard sprouting (e.g., potatoes and onions). Sludge, waste water, and wood may also be treated with gamma rays to kill harmful organisms.

^{57}Co decays to an excited state of ^{57}Fe, the most widely used x-ray source in Mössbauer spectroscopy (Hodge 1993; Richardson 1993). It is also made into standards and sources for dose calibrators, gamma cameras, and gauges, and is used as markers and rulers to help estimate organ size/location. It is also used in *in vitro* diagnostic kits for the study of anemia related to vitamin B_{12} deficiency/malabsorption (MDS Nordion 2000). ^{55}Co-bleomycin has been used for scanning malignant tumors (e.g., lung and brain cancer) and is a practical isotope for positron emission tomography (PET) studies because it mainly (81%) decays by positron emission.

5.4 DISPOSAL

There is a paucity of data on the methods of disposal of cobalt and its compounds. Due to the lack of natural sources of economically extractable ores in the United States, cobalt is entirely imported in the United States, and it is considered a strategic mineral. It is economical to recycle certain cobalt wastes rather than to dispose of them. Recycling of superalloy scrap is an important method for the recovery of cobalt. About 2,200 metric tons of cobalt were recycled from purchased scrap in 2003. This was about 28% of reported consumption for the year (USGS 2004). According to TRI (TRI01 2004), 7.14 and 1.42 million pounds of cobalt and cobalt compounds combined were recycled onsite and offsite, respectively, in 2001. Waste containing cobalt dust and, presumably, waste containing cobalt in the solid state may be placed in sealed containers and disposed of in a secured sanitary landfill (HSDB 1989). Waste water containing cobalt can be treated before disposal, for instance, by precipitation of carbonate or hydroxide of cobalt or by passage through an ion-exchange resin (Clifford et al. 1986). According to TRI (TRI01 2004), 1,619,874 pounds of cobalt and cobalt compounds, were transferred offsite for disposal, in processes such as solidification/stabilization and waste water treatment, including publicly operated treatment plants (POTWs). The amount of cobalt so transferred by state is shown in Table 6-1.

In August 1998, EPA issued a final rule listing spent hydrotreated and hydrorefined catalysts as hazardous waste under the Resource Conservation and Recovery Act (USGS 1998). Listing under this act requires that releases of these substances will be subject to certain management and treatment standards and emergency notification requirements. Information regarding effluent guidelines and standards for cobalt may be found in Title 40 of the Code of Federal Regulations, Parts 421.230, 421.310, and 471.30.

^{60}Co sources used for irradiation purposes are valuable and are not to be discarded. However, some radioactive cobalt isotopes may occur in waste material from nuclear reactors. Radioactive waste is categorized according to origin, type of waste present, and level of activity. Radioactive cobalt isotopes may be commingled with other radioactive isotopes. The first distinction in radioactive waste is between defense waste and commercial waste, the former being generated during and after World War II principally at the Department of Energy (DOE) facilities at Hanford, Washington; Savannah River, South Carolina; and Idaho Falls, Idaho, where plutonium and other isotopes were separated from production reactor spent fuel or nuclear-powered naval vessels. Commercial wastes are produced predominantly by nuclear power plants as well as the long defunct commercial reprocessing facility at West Valley, New York and manufacturers of radioisotopes used in nuclear medicine for the treatment and diagnosis of disease. Nuclear waste is also classified as high-level waste (HLW), transuranic waste (TRU), and low-level waste (LLW). LLW is further differentiated into three classes, A, B, and C, according to increasing of the level of activity. A fourth category, commercial greater-than-class-C LLW (listed in 10 CFR 61.55 Tables 1 and 2 for long and short half-life radionuclides, respectively) is not generally suitable for near-surface disposal. This could include operating and decommissioning waste from nuclear power plant and sealed radioisotope sources. The final disposition for this waste has not been determined. If LLW also contains nonradioactive hazardous material (i.e., that which is toxic, corrosive, inflammable, or explosive), it is termed mixed waste. Mine tailings from uranium mining is yet another category of radioactive waste (DOE 1999; Murray 1994). While radioactive cobalt would not ordinarily be found in HLW or TRU, the definitions of these are included below for completion.

TRUs are those containing isotopes, like plutonium, that are above uranium in the periodic table and whose half-lives are >20 years. If their level of activity is <100 nanocuries (nCi) (<3,700 becquerels[Bq]) of alpha-emitters per gram of waste material (up from 10 nCi/g in 1982), the waste could be disposed of by shallow burial. Otherwise, the waste must be placed in retrievable storage for eventual transfer to a

permanent repository. The level of radioactivity in TRUs is generally low; they generate very little heat and can be handled by ordinary means without remote control (Eisenbud 1987, Murray 1994).

HLW includes spent fuels that are contained in fuel rods that have been used in a nuclear reactor. These may contain small amounts of transuranic elements. After removal from the reactor, these rods are placed into pools adjacent to the commercial nuclear power plants and DOE facilities where they were produced. It was originally intended that the fuel rods remain in these pools for only about 6 months to allow for a reduction in short-lived radioactivity and rate of heat production temperature and then be transferred to a reprocessing or storage facility. There is no commercial reprocessing facility or permanent disposal facility for HLW operating in the United States. The U.S. Nuclear Regulatory Commission (USNRC) has issued standards for the disposal of HLW (10 CFR 60), and the DOE is pursuing the establishment of an HLW facility in Yucca Mountain, Nevada. Efforts to establish an HLW facility, which began over 2 decades ago, have experienced many delays (Eisenbud 1987; Murray 1994). However, in July, 2002, the U.S. Congress and the President selected Yucca Mountain, Nevada as the nation's first long-term repository for HLW. The facility is projected to begin operation in 2010, and efforts are underway to consider establishing a nearby interim facility (DOE 2002b).

LLWs are officially defined as wastes other than those previously defined. These wastes come from certain reactor operations and from manufacturers of radioisotopes used in nuclear medicine and institutions such as hospitals, universities, and research centers. Most LLW contain very little radioactivity and contain practically no transuranic elements. It requires little or no shielding or special handling and may be disposed of by shallow burial. However, some LLW contains sufficient radioactivity as to require special treatment. Although USNRC regulations for LLW 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 (Eisenbud 1987; Murray 1994). The EPA has the authority to set generally acceptable environmental standards for LLW that would be implemented by the US NRC and DOE (EPA 2004). The Manifest Information Management System (MIMS), maintained by the Idaho National Engineering and Environmental Laboratory (INEEL), contains information on low-level radioactive waste shipments received at commercial low-level radioactive waste disposal facilities at Barnwell, South Carolina (1/1/86–present), Beaty, Nevada (4/1/86–12/31/92), Richland, Washington(1/1/86–present), and Envirocare, Utah (1/1/98–12/31/99). In 1999, 17 Ci (0.63 TBq) of ^{57}Co, 1,300 Ci (48 TBq) of ^{58}Co, and 1.08x10^{6} Ci (4.00x10^{4} TBq) of ^{60}Co contained in LLW was received at these facilities from academic, industrial, government, and utility generators throughout the United

States (INEL 2000). In addition, 4.26 Ci (0.158 TBq) of ^{57}Co of NARM ("naturally occurring and accelerator-related waste") was received.

At present, DOE stores most of its spent fuel at three primary locations: the Hanford site, Washington, the Idaho National Engineering and Environmental Laboratory (INEEL), Idaho, and the Savannah River site, South Carolina. Some spent fuel is also stored at the dry storage facility at Fort St. Vrain in Colorado. Much smaller amounts of spent nuclear fuel stored at other sites were to be shipped to the three prime sites for storage and preparation for ultimate disposal (DOE 1999). The DOE National Spent Fuel Program maintains a spent nuclear fuel database that lists the total volume, mass, and metric tons heavy metal (MTHM) of 16 DOE categories of spent nuclear fuel stored in each of the three locations. The categories having the highest ^{60}Co activities per spent nuclear fuel canister (decayed to 2030) are 'naval surface ship fuel' and 'naval submarine fuel'. The ^{58}Co and ^{60}Co solid wastes stored on the Hanford site in 1998 as LLW were 2,600 and 6,900 Ci (96 and 260 TBq), respectively (Hanford 1999). In addition, 40 Ci (1.5 TBq) of ^{60}Co was included in TRU.

In commercial irradiators, additional quantities of ^{60}Co are added, usually once a year to maintain preferred radiation levels of the source (MDS Nordion 2000). ^{60}Co sources are removed from the facility at the end of their useful life, which is typically 20 years. In general, manufacturers of ^{60}Co sources guarantee to accept the sources they originally supplied. These old sources may be reencapsulated, reprocessed, or recycled when technically, environmentally, and economically feasible.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Stable cobalt has been identified in at least 426 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). Radioactive cobalt as ^{60}Co has been identified in at least 13 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA NPL (HazDat 2004). However, the number of sites evaluated for stable cobalt and ^{60}Co is not known. The frequency of these sites can be seen in Figures 6-1 and 6-2, respectively. Of the cobalt sites, 421 are located within the United States, 1 is located in Guam (not shown), 3 are located in the Commonwealth of Puerto Rico (not shown), and 1 is located in the Virgin Islands (not shown). All of the sites at which ^{60}Co has been identified are located within the United States.

Cobalt occurs naturally in the earth's crust, and therefore, in soil. Low levels of cobalt also occur naturally in seawater and in some surface water and groundwater (Smith and Carson 1981). However, elevated levels of cobalt in soil and water may result from anthropogenic activities such as the mining and processing of cobalt-bearing ores, the application of cobalt-containing sludge or phosphate fertilizers to soil, the disposal of cobalt-containing wastes, and atmospheric deposition from activities such as the burning of fossil fuels and smelting and refining of metals (Smith and Carson 1981). Cobalt is released into the atmosphere from both anthropogenic and natural sources. However, emissions from natural sources are estimated to slightly exceed those from manufactured sources. Natural sources include windblown soil, seawater spray, volcanic eruptions, and forest fires. Primary anthropogenic sources include fossil fuel and waste combustion, vehicular and aircraft exhausts, processing of cobalt and cobalt-containing alloys, copper and nickel smelting and refining, and the manufacture and use of cobalt chemicals and fertilizers derived from phosphate rocks (Barceloux 1999; Lantzy and Mackenzie 1979; Nriagu 1989; Smith and Carson 1981). ^{60}Co and ^{58}Co, both radioactive forms of cobalt, may be released to the environment as a result of nuclear research and development, nuclear accidents, operation of nuclear power plants, and radioactive waste dumping in the sea or in radioactive waste landfills.

Cobalt compounds are nonvolatile and cobalt will be emitted to the atmosphere only in particulate form. Their transport in air depends on their form, particle size and density, and meteorological conditions. Cobalt so released will return to land or surface water as wet or dry deposition. Coarse particles, those

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

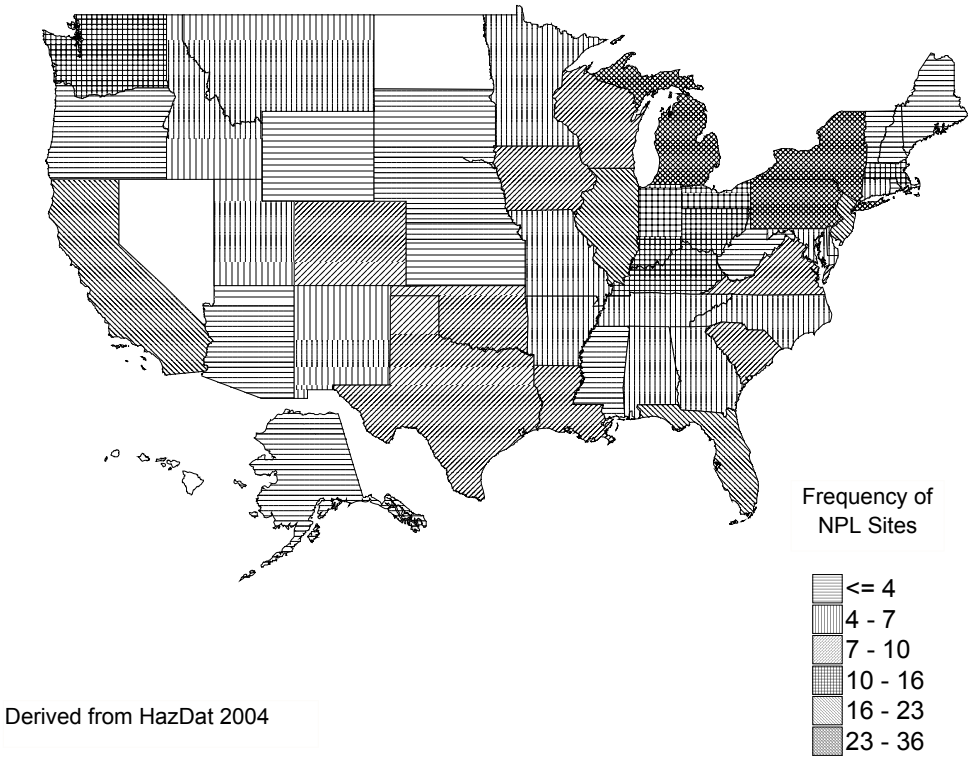
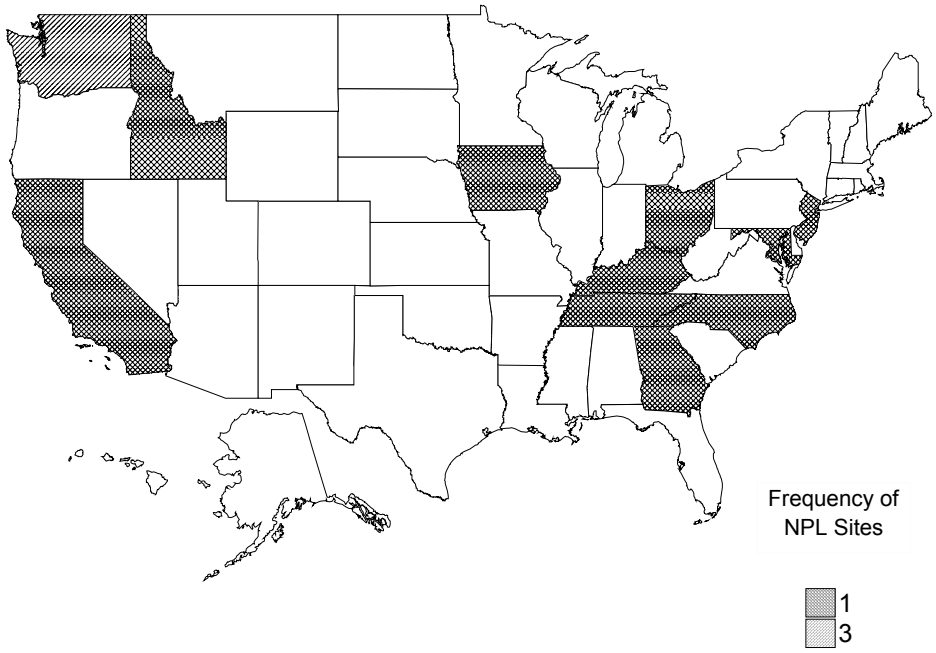


Figure 6-2. Frequency of NPL Sites with ^{60}Cobalt Contamination



Derived from HazDat 2004

with aerodynamic diameters >2 μm (such as those obtained during ore processing), may deposit within 10 km from the point of emission; finer particles (such as is obtained from thermal processes) may travel longer distances. It is generally assumed that anthropogenic cobalt originating from combustion sources exists primarily as the oxide; arsenides or sulfides may be released during mining and ore processing (Schroeder et al. 1987). Frequently, sediment and soil are the ultimate sinks for cobalt; however, this process is dynamic, and cobalt can be released into the water depending upon conditions. Soluble cobalt released into waterways will sorb to particles and may settle into the sediment or be sorbed directly by sediment. It may precipitate out as carbonates and hydroxides or with mineral oxides. It may also sorb to or complex with humic acid substances in the water. These processes are sensitive to environmental factors such as pH and the proportion of dissolved cobalt will be higher at low pH. In the case of ^{60}Co released into an experimental lake in northwestern Ontario, cobalt's half-life in the water column was 11 days; 5% of added ^{60}Co remained in the water after 100 days (Bird et al. 1998a). Cobalt can also be transported in dissolved form or as suspended sediment by rivers to lakes and the sea or by ocean currents. The proportion of cobalt transported in each form is highly variable (Smith and Carson 1981). In deep sediment where water is anoxic and hydrogen sulfide is present, some mobilization of cobalt from sediment may occur, probably due to the formation of bisulfides and polysulfides (Bargagli 2000; Brügmann 1988; Finney and Huh 1989; Glooschenko et al. 1981; Knauer et al. 1982; Nriagu and Coker 1980; Shine et al. 1995; Smith and Carson 1981; Szefer et al. 1996; Windom et al. 1989). Cobalt adsorbs rapidly and strongly to soil and sediment in which it is retained by metal oxides, crystalline minerals, and natural organic matter. The mobility of cobalt sediment depends on the nature of the soil or sediment; it increases with decreasing pH and redox potential (Eh) and in the presence of chelating/complexing agents (Brooks et al. 1998; Buchter et al. 1989; King 1988b; McLaren et al. 1986; Schnitzer 1969; Smith and Carson 1981; Swanson 1984; Yashuda et al. 1995).

While cobalt may be taken up from soil by plants, the translocation of cobalt from roots to above-ground parts of plants is not significant in most soils; the transfer coefficient (concentration in plant/concentration in soil) for cobalt is generally 0.01–0.3 (Mascanzoni 1989; Mermut et al. 1996, Smith and Carson 1981). However, in highly acidic soils (pH as low as 3.3) and in some higher plants (plants excluding algae), significantly higher transfer has been observed (Boikat et al. 1985; Francis et al. 1985; Jenkins 1980; Kloke et al. 1984; Mejstrik and Svacha 1988; Palko and Yli-Hala 1988; Tolle et al.1983; Watabe et al. 1984). The bioaccumulation factors (dry weight basis) for cobalt in marine fish and freshwater fish are ~100–4,000 and <10–1,000, respectively; accumulation is largely in the viscera and on the skin, as

opposed to the edible parts of the fish. Cobalt does not biomagnify up the food chain (Barceloux 1999; Evans et al. 1988; Freitas et al. 1988; Smith and Carson 1981).

Atmospheric cobalt is associated with particulate matter. Mean cobalt levels in air at unpolluted sites are generally <1–2 ng/m^3. In several open-ocean environments, geometric mean concentrations ranged from 0.0004 to 0.08 ng/m^3 (Chester et al. 1991). However, in source areas, cobalt levels may exceed 10 ng/m^3; the highest average cobalt concentration recorded was 48 ng/m^3 at the site of a nickel refinery in Wales (Hamilton 1994; Smith and Carson 1981). By comparison, the Occupational Safety and Health Administration (OSHA) limit for airborne stable cobalt is 100,000 ng/m^3. While ^{60}Co has been detected in some air samples at the Hanford, Washington site and Oak Ridge National Laboratories, Tennessee, levels were not reported (HazDat 2004; PNNL 1996).

The concentrations of stable cobalt in surface and groundwater in the United States are generally low; <1 µg/L in pristine areas and 1–10 µg/L in populated areas (Hamilton 1994; Smith and Carson 1981). However, cobalt levels may be considerably higher in mining or agricultural areas. Cobalt concentrations in surface water and groundwater samples collected in 1992 from area creeks near the Blackbird Mine in Idaho, one of the large deposits of cobalt in North America where mining occurred from the late 1800s to 1982, were reported to range from <1 to 625,000 µg/L, and from not detected to 315,000 µg/L, respectively (ATSDR 1995). Cobalt levels in most drinking water is <1–2 µg/L although levels as high as 107 µg/L have been recorded (Greathouse and Craun 1978; Meranger et al. 1981; NAS 1977; Smith and Carson 1981).

Little data are available on the levels of ^{60}Co in water. In 1989, subsequent to the largest effluent discharge from the Steam Generating Heavy Water Reactor at Winfrith on the south coast of England, ^{60}Co levels in offshore seawater from 18 sites contained 0.06–2.22 mBq/L (1.6–69 fCi) of particulate ^{60}Co, 0.30–10.3 mBq/L (8–280 fCi) of soluble ^{60}Co(II), and 0.12–1.55 mBq/L (3.2–42 fCi) of soluble ^{60}Co(III) (Leonard et al. 1993a). The U.S. NRC discharge limit is 111,000 mBq/L ($3x10^6$ fCi/L) (USNRC 1991).

The average concentrations of cobalt in the earth's crust are 20–25 mg/kg (Abbasi et al. 1989; Merian 1985; Smith and Carson 1981). Most soils contain 1–40 mg cobalt/kg; the average cobalt concentration in U.S. soils is 7.2 mg/kg (Smith and Carson 1981). Soils containing <0.5–3 mg cobalt/kg are considered cobalt-deficient because plants growing on them have insufficient cobalt (<0.08–0.1 mg/kg) to meet the

dietary requirements of cattle and sheep. Cobalt-deficient soils are found in some areas of the southeastern and northeastern United States. Soils near ore deposits, phosphate rocks, or ore smelting facilities, and soils contaminated by airport traffic, highway traffic, or other industrial pollution may contain high concentrations of cobalt; concentrations up to 800 mg/kg have been detected in such areas (Kloke et al. 1984; Smith and Carson 1981). Cobalt concentrations in 28 samples collected from surface deposits in the Big Deer and Blackbird Creek drainage basins near a site of former cobalt mining in Idaho ranged from 26.5 to 7,410 mg/kg (ATSDR 1995).

The level of cobalt in most foods is low. However, food is the largest source of exposure to cobalt in the general population. The estimated average daily dietary intake of cobalt in Canada was 11 μg/day. Food groups contributing most heavily to this intake were bakery goods and cereals (29.8%) and vegetables (21.9%) (Dabeka and McKenzie 1995). No estimates of the average dietary input of cobalt in the United States were located. People living near mining and smelting facilities or metal shops where cobalt is used in grinding tools may be exposed to higher levels of cobalt in air or soil. Similarly, people living near hazardous waste sites may be exposed to higher levels of cobalt in these media. Contaminated soils pose a hazardous exposure pathway to children because of both hand-to-mouth behavior and intentional ingestion of soil (pica) that contain metals and other contaminants (Hamel et al. 1998). However, much of the cobalt in soil may not be in a form that is available for uptake by the body. People who work in the hard metal industry, metal mining, smelting, and refining or other industries that produce or use cobalt and cobalt compounds may be exposed to substantially higher levels of cobalt, mainly from dusts or aerosols in air. Workers at nuclear facilities, irradiation facilities, or nuclear waste storage sites may be exposed to radioisotopes of cobalt. Exposure would generally be to radiation produced by these isotopes (e.g., gamma radiation from ^{60}Co).

6.2 RELEASES TO THE ENVIRONMENT

Stable cobalt has been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) collected at 426 of 1,636 current or former NPL hazardous waste sites (HazDat 2004). ^{60}Co has been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) collected at 13 of 1,636 current or former NPL hazardous waste sites (HazDat 2004).

According to the Toxic Chemical Release Inventory (TRI), in 2001, total releases of cobalt and cobalt compounds to the environment (including air, water, soil, and underground injection) from 605 reporting facilities that produced, processed, or used cobalt or cobalt compounds were 16,443,429 pounds (TRI01 2004). Table 6-1 lists amounts released from these facilities grouped by state. In addition, 1,619,874 pounds of cobalt and cobalt compounds were transferred offsite by these facilities (TRI01 2004). Starting in 1998, metal mining, coal mining, electric utilities, and Resource Conservation and Recovery Act (RCRA)/solvent recovery industries are required to report, to the TRI, industries with potentially large releases of cobalt and cobalt compounds. Industrial sectors producing, processing, or using cobalt that contributed the greatest environmental releases in 2001 were primary metals and RCRA/solvent recovery with 141,554 and 531,427 pounds, respectively. Industrial sectors producing, processing, or using cobalt compounds that contributed the greatest environmental releases in 2001 were metal mining and electrical utilities with 10,228,193 and 3,652,398, pounds, respectively. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

6.2.1 Air

The sources of cobalt in the atmosphere are both natural and anthropogenic (Barceloux 1999). Natural sources include wind-blown continental dust, seawater spray, volcanoes, forest fires, and continental and marine biogenic emissions. The worldwide emission of cobalt from natural sources has been estimated to range from 13 to 15 million pounds/year (Lantzy and Mackenzie 1979; Nriagu 1989). The global atmospheric emission of cobalt from anthropogenic sources is an estimated 9.7 million pounds/year. Therefore, natural sources contribute slightly more to cobalt emissions in the atmosphere than anthropogenic sources (Lantzy and Mackenzie 1979). The primary anthropogenic sources of cobalt in the atmosphere are the burning of fossil fuels and sewage sludge, phosphate fertilizers, mining and smelting of cobalt-containing ores, processing of cobalt-containing alloys, and industries that use or process cobalt compounds. Small amounts of cobalt are found in coal, crude oils, and oil shales. Therefore, burning of these fossil fuels for power generation will emit cobalt into the atmosphere. The cobalt contents of the fly ash and flue gases of a coal-burning power plant are approximately 25 mg/kg and 100–700 µg/L, respectively. Gasoline contains <0.1 mg cobalt/kg, but catalytic converters may contain cobalt; therefore, emissions from vehicular exhaust are also a source of atmospheric cobalt (Abbasi et al. 1989; Holcombe

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt and Cobalt Compounds[a]

State[c]	Number of facilities	Reported amounts released in pounds per year[b]						
		Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
AK	2	23	0	16,000	546,463	562,486	0	562,486
AL	21	5,893	8,612	0	315,853	330,358	30,040	360,398
AR	9	921	142	0	8,301	9,364	2,015	11,379
AZ	12	1,029	0	0	1,061,035	1,062,064	2,266	1,064,330
CA	26	646	20	0	307,654	308,320	7,463	315,783
CO	1	3	1	0	12,026	12,030	0	12,030
CT	9	632	65	0	0	697	4,133	4,830
DE	2	1,265	52	0	52	1,369	27,444	28,813
FL	11	2,397	345	0	93,049	95,791	15,464	111,255
GA	17	3,508	268	0	282,610	286,386	12,461	298,847
IA	6	566	0	0	0	566	2,123	2,689
ID	2	74	5	0	395,424	395,503	0	395,503
IL	23	1,630	1,278	0	16,999	19,907	102,088	121,995
IN	42	7,005	351	0	279,122	286,478	64,293	350,771
KS	5	4,269	0	0	10,200	14,469	3,859	18,328
KY	22	3,184	542	0	478,855	482,581	13,269	495,850
LA	15	385	8,477	2,700	66,858	78,420	91,274	169,694
MA	11	794	780	0	5	1,579	17,403	18,982
MD	6	2,472	15	0	6,629	9,116	45,382	54,498
ME	2	66	0	0	0	66	700	766
MI	24	4,699	559	0	125,405	130,663	33,737	164,400
MN	5	255	No data	0	0	255	7,666	7,921
MO	5	1,457	8	0	559,401	560,866	0	560,866
MS	7	386	120	12,000	44	12,550	3,044	15,594
MT	1	250	No data	0	31,000	31,250	505	31,755
NC	24	6,593	8,257	0	194,974	209,824	216,849	426,673
ND	4	1,165	21	0	108,300	109,486	39,842	149,328
NE	1	0	27	0	0	27	3,982	4,009
NH	1	0	No data	0	0	0	No data	0
NJ	12	1,191	26	0	413	1,630	26,894	28,524
NM	6	498	1	0	4,257,140	4,257,639	69	4,257,708
NV	8	678	0	0	4,099,136	4,099,814	9,950	4,109,764
NY	12	755	44	0	11,843	12,642	14,322	26,964
OH	44	4,977	771	1,100	310,653	317,501	96,116	413,617
OK	13	1,357	158	0	5,677	7,192	20,760	27,952

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt and Cobalt Compounds[a]

State[c]	Number of facilities	Reported amounts released in pounds per year[b]						
		Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
OR	6	1,262	20	0	16,487	17,769	2,862	20,631
PA	44	6,169	3,176	0	51,350	60,695	221,662	282,357
PR	2	2	No data	0	0	2	2,871	2,873
RI	1	1	1	0	0	2	50	52
SC	25	1,579	10,970	0	43,488	56,037	70,316	126,353
SD	1	0	No data	0	0	0	0	0
TN	18	5,560	4,013	0	330,615	340,188	36,520	376,708
TX	44	8,126	784	3,730	150,470	163,110	95,840	258,950
UT	6	278	No data	0	23,350	23,628	126,502	150,130
VA	9	1,451	518	0	89,388	91,357	9,683	101,040
VI	1	0	0	0	0	0	0	0
WA	2	72	91	0	106,618	106,781	5,112	111,893
WI	20	1,098	5	0	8	1,111	95,996	97,107
WV	13	1,341	566	0	212,254	214,161	37,047	251,208
WY	2	898	No data	0	38,927	39,825	0	39,825
Total	605	88,860	51,089	35,530	14,648,076	14,823,555	1,619,874	16,443,429

Source: TRI01 2004

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]The sum of fugitive and stack releases are included in releases to air by a given facility.
[e]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[f]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

et al. 1985; Ondov et al. 1982; Smith and Carson 1981). Cobalt has been detected in cigarette tobacco and therefore, smoking is a potential source of atmospheric cobalt that could impact on indoor air quality (Munita and Mazzilli 1986).

Stable cobalt has been identified in air samples collected at 5 of the 426 current or former NPL hazardous waste sites where it was detected in some environmental media (i.e., air, soil, sediment, or water) (HazDat 2004). ^{60}Co has been identified in air samples collected at 2 of the 13 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2004).

Air sampling data were used to estimate ^{60}Co release from the Savannah River Site (SRS) from the plant's start up in 1954 to 1989 (DOE 1991). From this monitoring, it was estimated that 0.092 Ci (3.4 GBq) of ^{60}Co was released to the atmosphere between 1968 and 1986. Total releases of ^{60}Co to the atmosphere from the SRS between 1968 and 1996 were 0.092 Ci (3.4 GBq) (DOE 1998). Data were not reported for all years in this interval. In 1999, atmospheric releases of ^{57}Co, ^{58}Co, and ^{60}Co as particulates were 4.71×10^{-8}, 1.27×10^{-4}, and 1.30×10^{-4} Ci (0.00174, 4.70, and 4.81 MBq), respectively (DOE 1999). The SRS was a major production facility to the U.S. defense program and included five nuclear reactors, a fuel fabrication plant, a naval fuel materials facility, two chemical separation plants, a heavy water production plant, and a laboratory. ^{60}Co has also been detected in air samples at the Hanford site and Oak Ridge National Laboratories (HazDat 2004; PNNL 1996).

According to the TRI, in 2001, releases of 88,860 pounds of cobalt and cobalt compounds to air from 605 reporting facilities accounted for 0.5% of the total onsite environmental releases of these substances (TRI01 2004). The industrial sectors contributing the largest release of cobalt and cobalt compounds to air were electrical utilities, chemicals, and primary metals. Table 6-1 lists the amounts of cobalt and cobalt compounds released to air from these facilities grouped by state. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

6.2.2 Water

Compounds of cobalt occur naturally in seawater and in some surface, spring, and groundwater (Smith and Carson 1981). Cobalt is also released into water from anthropogenic sources. While there has been

no mine production of cobalt in the United States in recent years, cobalt is a byproduct or coproduct of the refining of other mined metals such as copper and nickel. Historic mining operations that processed cobalt containing ores may continue to release cobalt into surface water and groundwater. Waste water from the recovery of cobalt from imported matte or scrap metal, refining of copper and nickel, or during the manufacture of cobalt chemicals are sources of cobalt in water (Smith and Carson 1981). Process water and effluent from coal gasification and residue from solvent-refined coal contain cobalt. The accidental discharge of activated sludge and sewage may be important sources of cobalamins in waterways, together with bioconcentration by benthic organisms (Smith and Carson 1981). The discharge of waste water by user industries, such as paint and pigment manufacture, also contributes to the release of cobalt into water. In one case, manufacturers of nickel-cadmium batteries operating between 1953 and 1979 discharged cobalt from a battery factory to the Hudson River in Foundry Cove, New York, of which 1.2 metric tons are estimated to be present in the eastern cove (Knutson et al. 1987). Atmospheric deposition is an additional source of cobalt in water. Lake Huron receives an estimated 76% of its cobalt input from natural sources and 24% from anthropogenic sources. The corresponding estimated values for Lake Superior are 85.4 and 14.6% (Smith and Carson 1981). In these Great Lakes, it therefore appears that natural inputs of cobalt far exceed anthropogenic ones.

Cobalt has been identified in groundwater and surface water at 255 and 106 sites, respectively, of the 426 NPL hazardous waste sites, where it was detected in some environmental media (i.e., air, soil, sediment, or water) (HazDat 2004). ^{60}Co has been identified in groundwater and surface water at 4 and 2 sites, respectively, of the 13 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2004).

According to the TRI, in 2001, the reported releases of 51,089 pounds of cobalt and cobalt compounds to water from 605 reporting facilities accounted for 0.3% of the total onsite environmental releases of these substances (TRI01 2004). Table 6-1 lists the amounts of cobalt and cobalt compounds released to water from these facilities grouped by state. As of 1998, TRI no longer separately collects data on substances released indirectly to Publicly-Owned Treatment Works (POTWs), part of which may ultimately be released to surface waters. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

^{60}Co is present in the low-level aqueous radioactive waste discharges from many nuclear power plants. Alloys that contain stable cobalt (^{59}Co), such as stellite, used in piping of nuclear reactors corrode and

may be activated, producing ^{60}Co, which accumulates in the reactor and must be periodically decontaminated. A common decontaminating agent includes a reducing metal ion (e.g., vanadium(II)) and a chelating agent (e.g., picolinate) resulting in low-level discharges of uncomplexed ^{60}Co(II) and complexed ^{60}Co(III). While soluble ionic and particulate forms predominate, at some sites stable, nonionic trivalent complexes of cobalt are present (Leonard et al. 1993a, 1993b; USNRC 2000d). For example, in 1987–1989 samples of treated effluent from the Steam Generating Heavy Water Reactor at Winfrith on the south coast of England, the percent of ^{60}Co as Co(III) picolinate ranged from 6.2 to 75.4%. Between 1978 and 1988, 12 TBq (320 Ci) of ^{60}Co was released into the Irish Sea by the British Nuclear Fuels reprocessing plant at Sellafield, United Kingdom (McCartney et al. 1994). These discharges are believed to be Co(II) (Leonard et al. 1993a). Both ^{58}Co and ^{60}Co are discharged into the Rhone River by the nuclear power plant at Bugey, France. This facility, which consists of a natural Uranium-Graphite-Gas unit and four pressurized water reactor (PWR) units, two of which are cooled by Rhone River water, discharged about 406 and 280 GBq (11.0 and 7.56 Ci) of ^{58}Co and ^{60}Co, respectively, in liquid waste during 1986–1990 (Beaugelin-Seiler et al. 1994).

Water sampling data were used to estimate effluent release from the SRS from the plant's start up in 1954 to 1989 (DOE 1991). From this monitoring, it was estimated that 17.8 Ci (659 GBq) of ^{60}Co were released into seepage basins and 66.4 Ci (2,460 GBq) were released into streams between 1955 and 1988. In addition, 2.7 Ci (100 GBq) of ^{58}Co were released into seepage basins between 1971 and 1988; no ^{58}Co was released into streams. Total releases of ^{60}Co to streams from the SRS for 1954–1995 were 66 Ci (2,400 GBq) (DOE 1998). No data were reported from 1985 to 1994. In 1999, 4.94×10^{-4} Ci (0.0183 GBq) of ^{60}Co was released to surface waters at the SRS (DOE 1999). ^{60}Co has also been reported in surface water at, Hanford, Washington, and Oak Ridge National Laboratories, and groundwater at Brook Industrial Park, New Jersey, the Hanford site and Oak Ridge National Laboratories, Tennessee (HazDat 2004). The Columbia River receives discharges from the unconfined aquifer underlying the Hanford Site via subsurface and surface (riverbank springs) discharges. This aquifer is contaminated by leachate from past waste-disposal practices at the site.

6.2.3 Soil

Cobalt occurs naturally in the earth's crust, and therefore, in soil. However, elevated levels of cobalt in soil may result from anthropogenic activities such as the mining and processing of cobalt-bearing ores,

the application of cobalt-containing sludge or phosphate fertilizers to soil, the disposal of cobalt-containing wastes, and atmospheric deposition from activities such as burning of fossil fuels, smelting, and metal refining (Smith and Carson 1981).

Cobalt has been identified in soil at 219 sites and sediment at 143 sites collected from 426 NPL hazardous waste sites, where it was detected in some environmental media (i.e., air, soil, sediment, or water) (HazDat 2004). ^{60}Co has been identified in soil at 8 sites and sediment at 2 sites collected from 13 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2004). ^{60}Co has been detected onsite in soils at the Hanford Site, Washington; INEEL, Idaho; Lawrence Livermore National Laboratory, Main Site, California; and Robins Air Force Base, Georgia at maximum concentrations of 87.7, 570, 0.21, and 0.07 pCi/g (3.24, 21, 0.0078, and 0.003 Bq/g) (HazDat 2004).

According to the TRI, in 2001, reported releases of 14,646,076 pounds of cobalt and cobalt compounds to land from 605 reporting facilities accounted for 98.8% of the total onsite environmental releases of these substances (TRI01 2004). An additional 35,530 pounds, accounting for 0.2% of the total onsite environmental releases were injected underground (TRI01 2004). Industrial sectors contributing the largest releases of cobalt and cobalt compounds to land were metal mining and electrical utilities with 10,210,508 and 3,197,209 pounds, respectively. Table 6-1 lists the amounts of cobalt and cobalt compounds released on land from these facilities grouped by state. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Cobalt compounds are nonvolatile, and thus, cobalt is emitted to the atmosphere in particulate form. The transport of cobalt in air depends on its particle size and density, and meteorological conditions; it can be returned to land or surface water by rain or it may settle to the ground by dry deposition. In nonarid areas, wet deposition may exceed dry deposition (Arimoto et al. 1985; Erlandsson et al. 1983). Coarse particles, with aerodynamic diameters >2 μm (such as those obtained during ore processing), may deposit within 10 km from the point of emission; finer particles may travel longer distances. It is the larger

particles that may be responsible for elevated local concentrations around emission sources. The mass median diameter for cobalt particles emitted from a power generator with a stack emission controlled by an electrostatic precipitator or scrubber ranged from <2 to 12 μm. The mass median diameter of cobalt in the ambient atmosphere is about 2.6 μm (Milford and Davidson 1985). Golomb et al. (1997) report average total (wet+dry) deposition rates of cobalt to Massachusetts Bay during the period September 15, 1992 to September 16, 1993. The total deposition rate was 58 $\mu g/m^2$-year, of which 47 $\mu g/m^2$-year was dry deposition and 12 $\mu g/m^2$-year was wet deposition. Total cobalt deposition flux at a site in the Rhone delta in southern France in 1988–1989 was 0.42±0.23 kg/km^2-year with 0.15 kg/km^2-year in the form of wet deposition (Guieu et al. 1991).

As with most metals, sediment and soil are frequently the final repository for cobalt released into the environment, although the process is dynamic, and cobalt can be released into the water depending upon conditions. Cobalt released into waterways may sorb to particles and settle into the sediment or be sorbed directly into the sediment. However, complexation cobalt to dissolved organic substances can significantly reduce sorption to sediment particles (Albrecht 2003). Studies by Jackman et al. (2001) suggest that interparticle migration of cobalt can influence the transport of metal ions, including cobalt, in sediments. For example, migration of a metal ion from a highly mobile sediment particle, such as clay, to less mobile gravels will slow the transport of that metal. Cobalt can also be transported in dissolved form or as suspended sediment by rivers to lakes and the sea or by ocean currents. Sediment in areas of active sedimentation would receive a large portion of the suspended sediment. In the case of the Peach Bottom Atomic Power Plant where ^{60}Co is released into the Conowingo Reservoir, an impoundment of the lower Susquehanna River, <20% of the radionuclide is trapped in the reservoir sediment, the rest being transported downstream and into the Chesapeake Bay (McLean and Summers 1990). It is often assumed that the primary mode of transport of heavy metals in aquatic systems is as suspended solids (Beijer and Jernelov 1986). However, in the case of cobalt, the percent that is transported by suspended solids is highly variable. Examples of the percentage of cobalt transported in suspended solids include (water body, percent): Main River (Germany), 33.4–42.2%; Susquehanna River (near its source in New York), 9%; New Hope River (North Carolina), 92%; Yukon River, >98%; Danube Rive (1961–1970), 27.4–85.9%; Columbia River (^{60}Co, downstream of the Hanford site), 95–98%; Strait of Juan de Fuca (Puget Sound, Washington), 11–15%; North Sea, 34%; and Lake Washington (Washington), 0% (Smith and Carson 1981).

In the oxic zones of many surface waters, dissolved cobalt levels decrease with increasing depth. This may be due to cobalt's continuous input into surface water from discharges or to increased adsorption and precipitation of the soluble forms with increasing depth. The fact that cobalt concentration profiles in deep water follow manganese and aluminum profiles strongly suggests that dissolved cobalt is precipitated in the adsorbed state with oxides of iron and manganese and with crystalline sediments such as aluminosilicate and goethite. A part of the cobalt may also precipitate out as carbonate and hydroxide in water. The higher concentration of organic pollutants in polluted water probably results in the formation of higher concentrations of soluble organic complexes. In a deep sediment where the water was anoxic and contained hydrogen sulfide, some mobilization of cobalt was observed, probably due to the formation of bisulfide and polysulfide complexes (Bargagli 2000; Brügmann 1988; Finney and Huh 1989; Glooschenko et al. 1981; Knauer et al. 1982; Nriagu and Coker 1980; Shine et al. 1995; Smith and Carson 1981; Szefer et al. 1996; Windom et al. 1989).

Cobalt strongly binds to humic substances naturally present in aquatic environments. Humic acids can be modified by UV light and bacterial decomposition, which may change their binding characteristics over time. The lability of the complexes is strongly influenced by pH, the nature of the humic material, and the metal-to-humic substance ratio. The lability of cobalt-humate complexes decreases in time ("aging effect") (Burba et al. 1994). The "aging effect" indicates that after a period of time (~12 hours), complexes that were initially formed are transformed into stronger ones from which the metal ion is less readily dislodged. In the Scheldt Estuary and the Irish Sea, between 45 and 100% of dissolved cobalt was found to occur in these very strong complexes (Zhang et al. 1990). Aquifer material from the contaminated aquifer at a low-level infiltration pit at the Chalk River Nuclear Laboratories in Canada was analyzed to assess the nature of the adsorbed ^{60}Co using sequential leaching techniques (Killey et al. 1984). Of the sediment-bound ^{60}Co, <10% was exchangeable, 5–35% was retained by iron oxide, and 55–>90% was fixed. Over 80% of the dissolved ^{60}Co was present as weakly anionic hydrophilic organic complexes. The average K_d for ^{60}Co between particulate matter and Po River (Italy) water was 451 m^3/kg over a 2-year monitoring period (Pettine et al. (1994). The mean K_d for ^{60}Co in Arctic surface sediment (Kara Sea) where large quantities of radioactive waste by the former Soviet Union was disposed was $1x10^5$ L/kg (range $1x10^3$–$7x10^5$), which is comparable to that in temperate coastal regions, $2x10^5$ L/kg (range, $2x10^4$–$1x10^6$) (Fisher et al. 1999).

The distribution coefficient of cobalt may vary considerably in the same sediment in response to conditions affecting the pH, redox conditions, ionic strength, and amount of dissolved organic matter

(Mahara and Kudo 1981b). Uptake of ^{60}Co from the water by sediment increased rapidly as the pH was increased from 5 to 7–7.5 and then slightly decrease (Benes et al. 1989a, 1989b). Therefore, pH would be an important factor affecting the migration of cobalt in surface water. Uptake was little affected by changes in liquid-to-solids ratio and ionic strength. ^{60}Co is more mobile in anaerobic marine aquatic environments than in freshwater aerobic ones (Mahara and Kudo 1981b). Therefore, ^{60}Co waste is most suitably stored underground in aerated zones away from possible seawater intrusions. In seawater-sediment systems under anaerobic conditions ^{60}Co was 250 times more mobile than ^{60}Co in freshwater-sediment systems under aerobic conditions. Under anaerobic conditions, 30% of the ^{60}Co added to a sediment-freshwater system was 'exchangeable' and therefore potentially mobile, while under aerobic conditions, 98% of the ^{60}Co was permanently fixed. Most of the mobile ^{60}Co produced under anaerobic conditions in seawater consisted of nonionic cobalt associated with low molecular weight organic substances that were stable to changes in pH; the exchangeable ^{60}Co appeared to be mostly ionic.

Bird et al. (1998b) added ^{60}Co to the anoxic hypolimnion of a Canadian Shield lake to simulate a nuclear waste scenario where radionuclides entered the bottom waters of a lake, and evaluated its behavior over 5 years. This situation was considered to be a likely pathway by which nuclear fuel waste stored deep underground in the plutonic (igneous) rock of this region would reach the surface environment via deep groundwater flow into the bottom waters of a lake. It was felt that adding a redox sensitive element such as cobalt to the anoxic hypolimnion might be different from adding it to the epilimnion. Monitoring vertical profiles in the lake established that the cobalt remained confined to the anoxic hypolimnion prior to the fall turnover (first 72 days) when mixing occurred throughout the water column. After 358 days, only about 4% of the ^{60}Co remained in the water. After the second year, approximately 2% of the ^{60}Co remained and after 5 years, only 0.4%. These results mirror previous experiments in which the ^{60}Co was added to the epilimnion, therefore establishing that there is little difference in the overall behavior of cobalt when added to the epilimnion or hypolimnion. The loss rate coefficient of ^{60}Co was 0.036/day (half-life=19 days) between days 90 and 131 (lake mixing) during which time, the cobalt sorbed to the suspended sediment and bottom sediment under anoxic conditions. Loss was to the sediment as there was no hydrological loss from the lake. In the previous experiment in which ^{60}Co was added to the epilimnion, the initial loss rate coefficient was somewhat higher, 0.056/day (half-life=12 days). Following the initial loss, ^{60}Co continued to be slowly removed from the water (loss rate coefficient 0.002/day; half-life=347 days); after 328 days, ^{60}Co was no longer detectable in the epilimnion. The half-life of ^{60}Co in the water column of an experimental lake in northwestern Ontario was 11 days; 5% of added ^{60}Co remained in the water after 100 days (Bird et al. 1998b). The redox potential also affects the

behavior of cobalt in sediment. Under moderately reducing conditions, cobalt is released from sediment as Co^{2+} and forms CoS in the presence of sulfide. The concentration of cobalt in the bottom water increases as the water becomes more anoxic (Brügmann 1988; Smith and Carson 1981).

The mobility of cobalt in soil is inversely related to how strongly it is adsorbed by soil constituents. Cobalt may be retained by mineral oxides such as iron and manganese oxide, crystalline materials such as aluminosilicate and goethite, and natural organic substances in soil. Sorption of cobalt to soil occurs rapidly (within 1–2 hours). Soil-derived oxide materials were found to adsorb greater amounts of cobalt than other materials examined, although substantial amounts were also adsorbed by organic materials. Clay minerals sorbed relatively smaller amounts of cobalt (McLaren et al. 1986). In addition, little cobalt was desorbed from soil oxides while substantial amounts desorbed from humic acids and montorillonite. In clay soil, adsorption may be due to ion exchange at the cationic sites on clay with either simple ionic cobalt or hydrolyzed ionic species such as $CoOH^+$. Adsorption of cobalt onto iron and manganese increases with pH (Brooks et al. 1998). In addition, as pH increases, insoluble hydroxides or carbonates may form, which would also reduce cobalt mobility. Conversely, sorption onto mobile colloids would enhance its mobility. In most soils, cobalt is more mobile than lead, chromium (II), zinc, and nickel, but less mobile than cadmium (Baes and Sharp 1983; King 1988b; Mahara and Kudo 1981b; Smith and Carson 1981). In several studies, the K_d of cobalt in a variety of soils ranged from 0.2 to 3,800. The geometric mean, minimum, median, and maximum K_ds of ^{60}Co in 36 Japanese agricultural soils were 1,840, 130, 1,735, and 104,000 L/kg, respectively (Yasuda et al. 1995). The soil properties showing the highest correlation with K_d were exchangeable calcium, pH, water content, and cation exchange capacity (CEC). In 11 U.S. soils, the mean Freundlich K_F and n values were 37 L/kg and 0.754, respectively; K_F values ranged from 2.6 to 363 L/kg and correlated with soil pH and CEC (Buchter et al. 1989). In 13 soils from the southeastern United States whose soil pH ranged from 3.9 to 6.5, cobalt sorption ranged from 15 to 93%; soil pH accounted for 84–95% of the variation in sorption (King 1988b).

Organic complexing agents such as ethylenediaminetetraacetic acid (EDTA), which are used for decontamination operations at nuclear facilities, greatly enhance the mobility of cobalt in soil. Other organic complexing agents, such as those obtained from plant decay, may also increase cobalt mobility in soil. However, both types of complexes decrease cobalt uptake by plants (Killey et al. 1984; McLaren et al. 1986; Toste et al. 1984). Addition of sewage sludge to soil also increases the mobility of cobalt, perhaps due to organic complexation of cobalt (Gerritse et al. 1982; Williams et al. 1985).

Leaching of cobalt has been observed from municipal and low-level radioactive waste sites (Cyr et al. 1987; Czyscinski et al. 1982; Friedman and Kelmers 1988). The mobility of cobalt was assessed in two soils from the Cabriolet and Little Feller event sites at the Nevada Test site as a function of various parameters such as pH, ionic strength, cobalt concentrations, soil solids concentrations, and particle size distribution (DOE 1996). Cobalt was quantitatively sorbed on these soils (at least 90% sorbed) when the pH was above 7 and the solid concentration was at least 20 g/L. The experiments suggest that binding is principally on amphoteric surface-hydroxyl surfaces. Since the pH of these soils is around 8, cobalt would bind strongly under normal environmental conditions. Migration would be severely retarded under all but the most extreme conditions, e.g., pH of 4 or below and high ionic strength soil solutions (approximately 0.1 M). In addition, unrealistically large quantities of water would be needed to displace cobalt from the upper layers of the soil profile.

Cobalt may be taken up from soil by plants. Surface deposition of cobalt on leaves of plants from airborne particles may also occur. Elevated levels of cobalt have been found in the roots of sugar beets and potato tubers in soils with high cobalt concentrations (e.g., fly ash-amended soil) due to absorption of cobalt from soil. However, the translocation of cobalt from roots to above-ground parts of plants is not significant in most soils, as indicated by the lack of cobalt in seeds of barley, oats, and wheat grown in high-cobalt soil (Mermut et al. 1996; Smith and Carson 1981). Mermut et al. (1996) found 0.01–0.02 mg/kg in 10 samples of durum wheat grain from different areas of Saskatchewan where surface soil cobalt levels ranged from 3.7 to 16.4 mg/kg. The enrichment ratio, defined as the concentration in a plant grown in amended soil (fly ash) over the concentration in unamended soil, was about 1. Other authors have determined the transfer coefficient (concentration in plant/concentration in soil) for cobalt to be 0.01–0.3. The mean ^{57}Co soil-plant transfer factors obtained for clover from eight soils over a 4-year period ranged from 0.02 to 0.35, in good agreement with results of other investigators (Mascanzoni 1989). However, in highly acidic soil (pH as low as 3.3), significantly higher than normal concentrations of cobalt were found in rye grass foliage, oats, and barley. For example, cobalt concentrations in rye grass grown in unlimed soil (pH<5.0) was 19.7 mg/kg compared with 1.1 mg/kg in rye grass grown in limed soil (pH>5.0) (Boikat et al. 1985; Francis et al. 1985; Kloke et al. 1984; Mejstrik and Svacha 1988; Palko and Yli-Hala 1988; Tolle et al. 1983; Watabe et al. 1984). Soil and plant samples taken in the 30-km zone around Chernobyl indicated that ^{60}Co was not accumulated by plants and mushrooms (Lux et al. 1995). Transfer factors obtained in 1992 ranged from 0.005 to 0.16 and those obtained in 1993 ranged from <0.001 to 0.008. Studies investigating the uptake of ^{60}Co by tomato plants watered with ^{60}Co-contaminated water showed that tomato plants absorbed <2% of the activity available from the soil. The

absorption was 6 times higher if the plants were watered aerially rather than ground watering. Using either watering method, >90% of the activity was absorbed by the stems and leaves (Sabbarese et al. 2002). Soil to plant transfer factors for ^{60}Co were determined for plants grown in containers with soil contaminated with ^{65}Zn and ^{60}Co over a 3-year period under outdoor tropical conditions. Average transfer factors for ^{60}Co over the 3-year period ranged from a high for spinach (1.030) to a low for rice (0.087) (Mollah and Begum 2001).

^{60}Co is taken up by phytoplankton and unicellular algae (*Senenastrum capricornutum*) with concentration factors (dry weight) ranging from 15,000 to 40,000 and 2,300 to 18,000, respectively (Corisco and Carreiro 1999). Elimination experiments with the algae indicate a two component biological half-life, 1 hour and 11 days, respectively, and suggest that the cobalt might be absorbed not only on the surface, but also intracellularly. Since these organisms are at the bottom of the food chain, they could play an important role in the trophic transfer of ^{60}Co released into waterways by nuclear facilities. However, cobalt levels generally diminish with increasing trophic levels in a food chain (Smith and Carson 1981).

The low levels of cobalt in fish may also reflect cobalt's strong binding to particles and sediment. The bioaccumulation factors (dry weight basis) for cobalt in marine and freshwater fish are ~100–4,000 and <10–1,000, respectively; accumulation in the muscle of marine fish is 5–500 (Smith and Carson 1981). Cobalt largely accumulates in the viscera and on the skin, as opposed to the edible parts of the fish. In carp, accumulation from water accounted for 75% of ^{60}Co accumulated from both water and food; accumulation from water and food was additive (Baudin and Fritsch 1989). Depuration half-lives were 53 and 87 days for fish contaminated from food and water, respectively. In the case of an accidental release of ^{60}Co into waterways, the implication is that effects would manifest themselves rapidly since the primary route of exposure is from water rather than food. Uptake of ^{60}Co by biota in lakes in northwestern Ontario was not affected by the tropic status of the lakes (Bird et al. 1998a). Uptake of ^{60}Co was very low in whitefish, with concentrations being highest in kidney and undetectable in muscle. Similarly, while accumulation of ^{60}Co by carp from food was dependent on food type, the transfer factor was very low, approximately 0.01, and no long-term bioaccumulation of the radionuclide occurred (Baudin and Fritsch 1987; Baudin et al. 1990). Accumulation of ^{60}Co from food for rainbow trout showed that after the 42-day exposure period, the highest concentrations of ^{60}Co were found in the kidneys, secondary gut, and viscera, and the trophic transfer factor was 0.0186. After 73 days of depuration, residual ^{60}Co concentrations were the highest in the kidneys, viscera, and fins (Baudin et al. 2000). In the experiment described above in which Bird et al. (1998a) added ^{60}Co to the anoxic

hypolimnion of a Canadian Shield lake to simulate a nuclear waste scenario where radionuclides entered the bottom waters of a lake, ^{60}Co levels in biota were low because of the rapid loss of cobalt to the sediment. Levels in forage fish, minnows, and sculpins were low, <0.3 Bq/g (8 pCi/g) dry weight; an occasional high level, ~4 Bq/g (110 pCi/g) dry weight, in slimy sculpin was thought to reflect the presence of detritus in the gut of the fish. Epilimnion additions of ^{60}Co in an earlier study resulted in lower maximum concentrations in fish, 0.07, 0.11, and 0.01 Bq/g (2, 3.0, and 0.3 pCi/g) dry weight in pearl dace, fathead minnows, and slimy sculpins, respectively, when similar quantities of radioactive cobalt were added to the lake.

Concentration factors have also been reported for various other aquatic organisms. Freshwater mollusks have concentration factors of 100–14,000 (~1–300 in soft tissue). Much of the cobalt taken up by mollusks and crustacae from water or sediment is adsorbed to the shell or exoskeleton; very little cobalt is generally accumulated in the edible parts (Amiard and Amiard-Triquet 1979; Smith and Carson 1981). A concentration factor for ^{60}Co of 265 mL/g (wet weight) was determined for *Daphnia magna* in laboratory studies. The rapid decrease in radioactivity during the depuration phase indicated that adsorption to the surface was the major contamination process (Adam et al. 2001). However, the digestive glands of crustaceans, which are sometimes eaten by humans, may accumulate high levels of ^{60}Co. Five different species of marine mollusks had whole-body ^{60}Co concentration factors between 6.3 and 84 after 1-month exposure to ^{60}Co in seawater (Carvalho 1987). The shell accounted for more than half of the body-burden. Among the soft tissue, the gills and viscera had the highest concentrations factors and the muscle had the lowest. Fisher et al. (1996) studied the release of ^{60}Co accumulated in mussels from water and ingested phytoplankton. In each case, there was a slow and fast component to the release; the rapid release was in the form of fecal pellets if uptake was from food and from desorption from the shell if uptake was from the dissolved phase. Biological half-lives obtained in laboratory studies were about 12–21 days from both the shell and soft parts. Higher absorption efficiencies and lower efflux rates were obtained for cobalamins than for inorganic cobalt, suggesting that it is a more bioavailable form of cobalt for mussels. Cobalt from fecal pellets is rapidly released into the overlying water and may play a role in its geochemical cycling (Fisher et al. 1996). The concentration of cobalt in clams in the Indian River Lagoon, Florida did not correlate with levels found in either water or sediment (Trocine and Trefry 1996). Kinetics of bioaccumulation of ^{57}Co from water and depuration by starfish (*Asterias rubens*) were carried out in laboratory studies. After 32 days of exposure to seawater containing ^{57}Co, whole body uptake from seawater reached a concentration factor of 23 (wet weight). ^{57}Co was released with a half-life of 27 days after removal to uncontaminated water. Comparison of the kinetics of loss of ^{57}Co following exposure to

^{57}Co-contaminated food versus exposure from ^{57}Co-contaminated water indicate that *A. rubens* accumulates ^{57}Co predominately from seawater rather than from food (Warnau et al. 1999).

6.3.2 Transformation and Degradation

6.3.2.1 Air

There is a paucity of data in the literature regarding the chemical forms of cobalt in air and their transformations in the atmosphere. It is generally assumed that anthropogenic cobalt originating from combustion sources exists primarily as the oxide (Schroeder et al. 1987). In addition, cobalt may be released into the atmosphere as its arsenide or sulfide during ore extraction processes. It is not clear if these species are transformed in the atmosphere. Should a relatively insoluble species such as the oxide be transformed into a more soluble form such as the sulfate, one would expect greater quantities to be washed out of the atmosphere in rain.

6.3.2.2 Water

Many factors control the speciation and fate of cobalt in natural waters and sediments. These include the presence of organic ligands (e.g., humic acids, EDTA), the presence and concentration of anions (Cl^-, OH^-, CO_3^{-2}, HCO_3^-, SO_4^{-2}), pH, and redox potential (Eh). Modeling the chemical speciation of a metal in water depends upon the environmental factors assumed and the stability constants of the various complexes. Mantoura et al. (1978) predicted the equilibrium levels of Co^{2+} species in fresh water to follow the order: free $Co^{+2} \geq CoCO_3 > CoHCO_3^+ >> CoSO_4 \geq$ Co•humic acid. However, the mole percent of various cobalt species in a Welsh lake was found to be: free Co^{+2}, 76%; $CoCO_3$, 9.8%; $CoHCO_3^+$, 9.6%; humate complexes, 4.0%; and $CoSO_4$, 0.4%. The rank order of species concentration in seawater was estimated to be: $CoCO_3$>free Co^{+2}>$CoSO_4 \geq CoHCO_3^+$. In another model, the speciation of cobalt was completely different with $CoCl^+$>free Co^{+2}>$CoCO_3$>$CoSO_4$ (Smith and Carson 1981). More recently, Tipping et al. (1998) estimated the equilibrium speciation of cobalt in riverine, estuarine, and marine surface water of the Humber system (England). In all but seawater, cobalt complexes with carbonate (HCO_3^- and CO_3^{2-}) constituted about 70% of dissolved cobalt while the free Co^{2+} ion, was a major

species, ~25%, which is much lower than the 61% predicted by Mantoura et al. (1978). As the alkalinity of the water increases, the proportion of cobalt complexed with carbonate increases at the expense of free Co^{2+}. The proportion, but not the concentration, of cobalt that exists as the free ion and the carbonate complexes in river water is independent of the level of fulvic acid in the water. In seawater, the carbonate species and the free aqua species assume roughly equal importance. The proportion of dissolved cobalt complexed with fulvic acid decreased with increasing salinity. About 20% of cobalt in seawater was estimated to be present as complexes with sulfate. In a bioconcentration study in which $CoCl_2$ was initially added to the seawater, at month's end, the cationic form of cobalt was progressively converted into anionic and neutral forms, possibly as a result of complexation with organic ligands (Carvalho 1987). Addition of humic acid to natural waters may merely increase the concentration of colloidal dispersed metal rather than form truly soluble humic complexes. In water that contains high organic wastes such as was the case in the Rhone River in France, cobalt was almost completely complexed. A recent study determined that the distribution of ^{60}Co in the Rhone River sampled at Arles, France was 45% in the particulate phase, 30% in the dissolved phase, and 25% in the colloidal phase (Eyrolle and Charmasson 2001). Cobalt forms complexes with EDTA that are very stable environmentally. EDTA is often used in agriculture, food and drug processing, photography, and textile and paper manufacturing, and therefore, it is a likely constituent of industrial discharges.

Acidity and redox potential have an effect on the behavior of cobalt in water. The adsorption of cobalt by particulate matter decreases with decreasing pH, since the increasing H^+ concentration competes with metal binding sites. This may lead to increased concentrations of dissolved cobalt at low pH. The effect of Eh (redox potential) on the speciation of cobalt has been shown by the increase in the concentration of dissolved cobalt by orders of magnitude with increasing depth in certain parts of Baltic waters. The increase in the concentration of dissolved cobalt may be due to the formation of soluble bisulfide and polysulfide complexes in the anoxic zones. The residence time of soluble cobalt in seawater has been estimated to range from <1 to 52 years (Brugmann 1988; Knauer et al. 1982; Smith and Carson 1981).

Vitamin B_{12}, which contains cobalt, is synthesized by 58 species of seven genuses of bacteria as well as blue-green algae and actinomycetes (mold-like bacteria). Consequently, vitamin B_{12} levels in marine water range from very low levels in some open ocean water to much higher levels in some coastal waters. Freshwater environments have comparable levels of vitamin B_{12}. The high level of cobalamins in coastal

water appears to be related to the occurrence of macrophytes in these areas with their high concentrations of vitamin B_{12}. Cobalamins are released into the water when the organisms die (Smith and Carson 1981).

Alkaline thermal groundwater in granitic areas have been studied as possible waste disposal sites for radioactive waste (Alaux-Negrel et al. 1993). Water in these areas is characterized by high pH, low CO_2 partial pressure, and generally low redox potential; sulfide concentrations are in the range of 10^{-4} to 10^{-3} mol/L. The solubility of cobalt is controlled by the solubility of CoS (log K_1 and log K_2 being 5.7 and 8.7 at 25°C) and therefore, levels of cobalt are very low, 10^{-8}–10^{-10} mol/L.

The ^{60}Co (III) picolinate complex that is released into water by some nuclear reactors does not break down immediately on release into seawater, but rather can coexist with the ^{60}Co (II) forms for lengthy periods in the environment (Leonard et al. 1993a, 1993b). Studies indicate that several processes occur to the Co(III) organic complexes, including reduction to the inorganic form, sorption of both species to particulate matter, and transformations of the uncomplexed species. It is possible that this more soluble and uncharged form of radioactive cobalt will increase the dispersion of ^{60}Co from its point of discharge.

6.3.2.3 Sediment and Soil

The speciation of cobalt in soil or sediment depends on the nature of the soil or sediment, concentration of chelating/complexing agents, pH, and redox potential (Eh) of the soil. Dissolved cobalt may be absorbed by ion exchange and other mechanisms, or may form complexes with fulvic acids, humic acid, or other organic ligands in soil. The humic and fulvic complexes of cobalt are not very stable compared with those of copper, lead, iron, and nickel. The speciation of cobalt in sediment from nine sites in the Red Sea, a sea that is unique in that it has no permanent streams flowing into it, was assessed using a sequential extraction technique (Hanna 1992). The mean percentages contained in the various fractions were: exchangeable, 5.5%; carbonate, 5%; Fe/Mn oxides, 24%; organic, 30.4%; sulfides, 13%; and lithogenous, 22%. While the mean concentration of cobalt in the sediment increased from 0.003 to 0.006 ppb between 1934 and 1984, its distribution among the different phases did not change appreciably.

The reduction of soil Eh, which may occur when soil is flooded or in deeper layers of soil that are oxygen-depleted, may change the speciation of cobalt. This may result in the reduction of soil iron and manganese and the subsequent release of adsorbed cobalt from the mineral oxides. Similarly, a decrease

in soil pH may result in the solubilization of precipitated cobalt and desorption of sorbed cobalt, resulting in increased cobalt mobility (Smith and Carson 1981). Co^{2+} may also be oxidized to Co^{3+} by manganese oxides, a common component of soils and aquifer material, with subsequent surface precipitation (Brusseau and Zachara 1993). This process may affect transport of cobalt in the subsurface environment.

EDTA complexes of cobalt are very stable and are likely to form in soils containing EDTA. EDTA is widely used as a decontaminating agent at nuclear facilities. Although cobalt-EDTA complexes are adsorbed by some soils, the mobility of cobalt in soil may increase as a result of complex formation (Schnitzer 1969; Smith and Carson 1981; Swanson 1984). ^{60}Co that is disposed of in shallow land trenches have sometimes been found to migrate more rapidly than expected from the disposal sites. Organic chelating agents are frequently present at these sites and would possibly increase the solubility and transport of the radionuclide.

Bacterial action can affect the mobility of a substance by mediating reactions or by participating in reactions that lower the pH. Another way of influencing radionuclide mobility is by degrading complexing agents used in cleaning reactors (e.g., citric acid), thereby releasing the radionuclide. However, experiments on the fate and transport of cobalt released upon the biodegradation of the complexing ligand indicate that results are not always predictable; the means of ligand removal and the geochemical environment are important factors that must be considered (Brooks et al. 1998).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Cobalt concentrations in environmental media, including food and human tissue, have been exhaustively tabulated by Smith and Carson (1981) and Young (1979). The International Agency for Research on Cancer (IARC 1991) contains reviews of more recent studies, but is primarily focused on occupational exposures and body burdens of cobalt.

6.4.1 Air

Atmospheric cobalt is associated with particulate matter. Mean cobalt levels in air at unpolluted sites are generally <1–2 ng/m^3 (Hamilton 1994; Smith and Carson 1981). At the South Pole, cobalt levels of 0.00049±0.00015 ng/m^3 were recorded in 1974–1975 (Maenhaut et al. 1979). Geometric mean cobalt

levels in several open-ocean environments ranged from 0.0004 to 0.08 ng/m^3 (Chester et al. 1991). The average annual PM-10 (particles with diameters ≤10 μm) cobalt concentration at Nahant, Massachusetts (near Boston) in 1992–1993 was 1.7 ng/m^3 (Golomb et al. 1997). Half of the cobalt was contained in fine particles (<2.5 μm) and half in coarse particles (2.5–10 μm). The mean cobalt level in southern Norway in 1985–1986 (n=346) was 0.10 ng/m^3 with 35% of the samples falling below the detection limit of 0.04 ng/m^3 (Amundsen et al. 1992). Atmospheric cobalt levels in industrial settings may exceed 10 ng/m^3. The highest recorded average cobalt concentration in air was 48 ng/m^3 in Clydach, Wales at the site, where nickel and cobalt were refined (Smith and Carson 1981). Some ambient atmospheric levels of cobalt are given in Table 6-2. These data show the contribution of anthropogenic sources in increasing the level of cobalt in the ambient air. Typical occupational cobalt levels are 1.0x10^4–1.7x10^6 ng/m^3 (Barceloux 1999; IARC 1991). While ^{60}Co has been detected in air samples at the Hanford site and Oak Ridge National Laboratories, levels were not reported (HazDat 2004; PNNL 1996). In 1995, the concentration of ^{60}Co in air at the Hanford site was below the detection limit in over 88% of the air samples.

6.4.2 Water

The concentrations of cobalt in surface water and groundwater in the United States are generally low, <1 μg/L in pristine areas and 1–10 μg/L in populated areas (Hamilton 1994; Smith and Carson 1981). However, cobalt levels may be considerably higher in mining or agricultural areas. Levels as high as

4,500 μg/L were reported in Mineral Creek, Arizona, near a copper mine and smelter; levels of 6,500 μg/L were reported in the Little St. Francis River, which receives effluent from cobalt mining and milling operations (Smith and Carson 1981). Mining at Blackbird Mine in Idaho, one of the large deposits of cobalt in North America, occurred from the late 1800s to 1982. Cobalt concentration in surface water and groundwater samples collected in 1992 from area creeks near this mine were reported to range from <1 to 625,000 μg/L, and from not detected to 315,000 μg/L respectively (ATSDR 1995), Eckel and Jacob (1988) analyzed U.S. Geological Survey (USGS) data for 6,805 ambient surface water stations and estimated the geometric mean and median dissolved cobalt concentration as 2.9 and 2.0 μg/L, respectively. Mean cobalt levels reported in seawater range from 0.078 μg/L in the Caribbean Sea to 0.39 μg/L in the Indian Ocean (Hamilton 1994). Vitamin B_{12} is synthesized by bacteria, macrophytes,

Table 6-2. Concentration of Cobalt in the Atmosphere

Location	Possible source/activity	Concentration[a]	Units	Type	Reference
Ambient levels—remote					
South Pole, 1974–1975	Crustal material	0.00049±0.00015	ng/m^3	Mean±SD	Maenhaut et al. 1979
Open-ocean		0.0004–0.08	ng/m^3	Geomean range	Chester et al. 1991
North Atlantic		0.006–0.09	ng/m^3	Range	Smith and Carson 1981
Baltic Sea, 1983		0.09, 0.01–0.43	ng/m^3	Mean, range	Hasanen etal. 1990
Remote sites		0.001–0.9	ng/m^3	Range	Schroeder et al. 1987
Ambient levels—rural/suburban/urban					
Rural sites		0.08–10.1	ng/m^3	Range	Schroeder et al. 1987
Massachusetts, Nahant, 1992–1993		1.7	ng/m^3	Annual mean	Golomb et al. 1997
Urban sites					Schroeder et al. 1987
United States		0.2–83	ng/m^3	Range	
Canada		1–7.9			
Europe		0.4–18.3			
Texas state average (1978–1982)		2.0	ng/m^3	Mean	Wiersema et al. 1984
Illinois, urban air (<2.5 µm; 2.5–10 µm)					Sweet et al. 1993
Bondville, Ill (rural)	Background	0.2; 0.1	ng/m^3	Mean (fine; coarse)	
Southeast Chicago	Steel mills	0.4; 0.4			
East St. Louis	Smelters	0.5; 0.4			
Washington, DC (1974)	Urban area	1.1	ng/m^3	Mean	Smith and Carson 1981
Ambient levels—industrial					
Maryland, Baltimore Harbor Tunnel (1973–1974)					Ondov et al. 1982
Air outside	Vehicular exhaust	0.8–1.9	ng/m^3	Range	
Air inside	Vehicular exhaust	2.2–5.3			
Ohio, Cleveland	Be-Cu alloy and other industrial activities	610	ng/m^3	Maximum	Smith and Carson 1981
Texas, El Paso (1978–1982)	Industrial	127	ng/m^3	Maximum	Wiersema et al. 1984

Table 6-2. Concentration of Cobalt in the Atmosphere

Location	Possible source/activity	Concentration[a]	Units	Type	Reference
Texas, Houston (1978–1982)	Urban area	81	ng/m^3	Maximum	Wiersema et al. 1984
Arizona, Tucson					Smith and Carson 1981
Urban	Copper smelting	1.9	ng/m^3	Mean	
Rural		0.7			
Maryland, Chalk Point Generator	Coal-burning power plant	3.86	ng/m^3	Mean	Smith and Carson 1981
Wales, Clydach	Nickel refining	48, 3–300	ng/m^3	Mean, range	Smith and Carson 1981
Wales, Llausamlet and Trebanos	Towns near Clydach	3.8		Mean	Smith and Carson 1981
Occupational air levels					
Northern Italy, exposure survey, 1991, area monitoring (n=259)	Diamond abrasive mfg.				Mosconi et al. 1994a
	Mould-filling	220, 47–960	ng/m^3	Median, range	
	Sintering	101.5, 32–240			
	Grinding	22, 15–45			
	Mechanical-working	20, 12–44			
	Grinding	5, 2.5–94			
	Tool production	6, 5–47			
	Hard metal alloy filing	2, 0.8–3			
	Other	2.7, 2.3–15			
Northern Italy, exposure survey, 1991, personal sampling (n=259)	Diamond abrasive mfg.				Mosconi et al. 1994a
	Mould-filling	382, 76–2,600	ng/m^3	Median, range	
	Sintering	309, 238–413			
	Grinding	230, 82–690			
	Mechanical-working	40, 7.1–65			
	Grinding	9.3, 1.5–178			
	Tool production	17, 4–28			
	Hard metal alloy filling	5, 1–107			
	Other	50, 10–290			

Table 6-2. Concentration of Cobalt in the Atmosphere

Location	Possible source/activity	Concentration[a]	Units	Type	Reference
Japan, personal sampling, hard metal tool manufacture, 8-hour TWA, 356 workers (n=935)	Powder preparation				Kumagai et al. 1996
	Rotation	459, 7–6,390	$\mu g/m^3$	Mean, range	
	Full-time	147, 26–378			
	Press				
	Rubber	339, 48–2,910			
	Steel	47, 6–248			
	Shaping	97, 4–1,160			
	Sintering	24, 1–145			
	Blasting	2, 1–4			
	Electron discharging	3, 1–23			
	Grinding	45, 1–482			

geomean = geometric mean; SD = standard deviation; TWA = time weighted average

blue-green algae, and actinomycetes, and cobalt levels in oceans often correlate with biological productivity. In the Baltic Sea, dissolved cobalt levels that are 1.0 ng/L near the surface, increase to 71.0 ng/L at a depth of 200 m (Brügmann 1988). The rise in dissolved cobalt is coincident with the onset of anoxic conditions and the presence of hydrogen sulfide, indicating that soluble bisulfide and polysulfide complexes may be present. Some cobalt levels reported in water are given in Table 6-3.

In a 1962–1967 survey, cobalt was detected in 2.8% of 1,577 U.S. raw surface waters from which drinking water is derived; the detection limit was 1 µg/L and the maximum concentration was 48 µg/L (NAS 1977). Of 380 U.S. finished drinking waters, only 0.5% contained cobalt levels exceeding 1 µg/L; the maximum concentration found was 29 µg/L (NAS 1977). These values are higher than the respective median and maximum levels of <2.0 and 6.0 µg/L found in Canadian finished drinking water (Meranger et al. 1981). Meranger et al. (1981) tested source water and drinking water in 71 municipalities across Canada and concluded that, in general, both surface water and groundwater used for drinking water supplies contain negligible amounts of cobalt. Greathouse and Craun (1978) analyzed 3,834 grab samples of household tap water from 35 geographical areas in the United States for 28 trace elements. Cobalt was found in 9.8% of the samples at concentrations ranging from 2.6 to 107 µg/L. It is not clear whether these higher levels could indicate that cobalt was picked up in the distribution system. In the earlier National Community Water Supply Study (2,500 samples), 62% of the samples contained <1 µg Co/L; the average and maximum cobalt concentrations were 2.2 and 19 µg/L, respectively (Smith and Carson 1981). Cobalt was not detected (detection limit 8 µg/L) in a 1982–1983 survey of drinking water in Norway that covered 384 waterworks serving 70.9% of the Norwegian population (Flaten 1991).

The mean concentrations of cobalt in rain is around 0.03–1.7 µg/L, with levels generally ranging from 0.002 µg/L at Enewetak Atoll to about 2.9 µg/L in the Swansea Valley, Wales (Arimoto et al. 1985; Dasch and Wolff 1989; Hansson et al. 1988; Heaton et al. 1990; Helmers and Schrems 1995; Nimmo and Chester 1993; Nimmo and Fones 1997; Smith and Carson 1981). The highest recorded level of cobalt in precipitation was 68.9 µg/L in the vicinity of a nickel smelter in Monchegorsk in the Russian Arctic (Reimann et al. 1997). An analysis of rain in the Mediterranean and urban and coastal sites in northwest England showed that about 33–44% of the cobalt occurred as very stable dissolved organic complexes (Nimmo and Chester 1993; Nimmo and Fones 1997).

As it was pointed out in Section 6.3.2.2, ^{60}Co discharged from the Steam Generating Heavy Water Reactor at Winfrith on the south coast of England was shown to be largely in the form of the nonionic

Table 6-3. Cobalt Levels in Water

Nature/location of water	Level	Units	Type	Reference
Sea water				
Florida (Indian River Lagoon) (43 sites)	0.031, 50	µg/L	Mean, range	Trocine and Trefry 1996
California (Baja) 2–45 km offshore (n=11)	0.022–0.17	nM	Range	Sañudo-Wilhelmy and Flegal 1996
<100 m off shore (n=11)	0.11–0.59			
Agean Sea, 1994; 8 sites (dissolved)	0.168–0.632, 1.917	nM	Range of means, maximum	Voutsinou-Taliadouri 1997
Baltic Sea (Gotland Deep site)				Brügmann 1988
10 m	1.0	ng/L	Mean (dissolved Co)	
50 m	1.0			
100 m	3.5			
150 m	4.2			
200 m (anoxic)	71.0			
235 m (anoxic)	49.2			
Seawater background	0.04	µg/L		Bargagli 2000
Seawater	0.27	µg/L	Mean	Abbasi et al. 1989
Fresh surface water				
Freshwater background	0.05	µg/L		Bargagli 2000
U.S. ambient surface water (6,805 stations)	<2.9, 2.0	µg/L	Mean, median	Eckel and Jacob 1988
Five Great Lakes waters	ND–0.09	µg/L	Range	Rossmann and Barres 1988
Japan, unpolluted lake	<0.004	µg/L		Nojiri et al. 1985
Norway, 11 rivers	0.94	µg/L	Maximum	Flaten 1991
Streams near populated areas	1–10	µg/L	Range	Smith and Carson 1981
Streams in agricultural and mining areas	11–50	µg/L	Range	Smith and Carson 1981
Suspended solids in rivers	7–94	mg/kg	Range	Smith and Carson 1981
Groundwater				
Canada (Chalk River nuclear waste site)	0.0001–0.002	µg/L		Cassidy et al. 1982
Colorado (Denver)–shallow groundwater, (n=30)	<1 (<1–9)	µg/L	Median, range	Bruce and McMahon 1996

Table 6-3. Cobalt Levels in Water

Nature/location of water	Level	Units	Type	Reference
Drinking water				
Canadian drinking water (71 municipalities)				Meranger et al. 1981
Raw:	<2.0	µg/L	Median	
Treated:	<2.0			
Distributed:	≤2.0			
Precipitation				
Massachusetts, 1984 (12 events)	0.045 (0.008), 0.02–0.12	µg/L	Mean (SD), range	Dasch and Wolff 1989
Rhode Island (rain/snow), 1985 (n=269)	0.038 (0.067)	ppb	Median (mean)	Heaton et al. 1990
	0.001–0.80		Range	
Western Mediterranean, 1988–1989				Nimmo and Chester 1993
Total cobalt	0.029–0.134, 0.043	µg/L	Range, mean	
Labile cobalt	0.009–0.104, 0.025			
Organic cobalt	ND–0.613, 0.019			
Arctic (7 sites in Finland, Norway, Russia)	<0.02–1.07, 3.32	µg/L	Median range, maximum	Reimann et al. 1997
Russia (Monchegorsk), nickel smelter	11.8, 68.9		Median, maximum	

ND = not detected; SD = standard deviation

trivalent complex, ^{60}Co(III) picolinate. The ^{60}Co(III) species is not immediately reduced to the more particle-reactive divalent form, and both oxidation states may coexist for long periods of time in the environment. The proportion of the more soluble and mobile ^{60}Co(III) would be expected to increase with time and distance from the point of discharge. Shoreline water samples (n=22) taken in 1987–1988 at two locations in the vicinity of the discharge from the Steam Generating Heavy Water Reactor at Winfrith contained 0.3–16.2 mBq/L (8–437 fCi/L) of particulate ^{60}Co, 2.8–44.4 mBq/L (76–1,200 fCi/L) of soluble ^{60}Co(II), and 0.2–4.8 mBq/L (5–130 fCi/L) of soluble ^{60}Co(III) (Leonard et al. 1993). The percent of the soluble ^{60}Co present as Co(III) ranged from 4.3 to 18.6%. In 1989, in conjunction with the largest discharge of effluent from the plant, offshore seawater samples from 18 sites contained 0.06–2.22 mBq/L (2–60 fCi/L) of particulate ^{60}Co, 0.30–10.3 mBq/L (8.1–278 fCi/L) of soluble ^{60}Co(II), and 0.12–1.55 mBq/L (3.2–41.9 fCi/L) of soluble ^{60}Co(III). The percent of the soluble ^{60}Co present as Co(III) ranged from 6.0 to 28.6%.

6.4.3 Sediment and Soil

Cobalt is the 33rd most abundant element in the earth's crust. Its average concentrations in the earth's crust and in igneous rocks are 20–25 and 18 mg/kg, respectively (Abbasi et al. 1989; Merian 1985; Smith and Carson 1981). Trace metals in soils may originate from parent rock or from anthropogenic sources, primarily fertilizers, pesticides, and herbicides. Most soils contain 1–40 mg cobalt/kg. The average cobalt concentration in U.S. soils is 7.2 mg/kg (Smith and Carson 1981). Soils containing <0.5–3 mg cobalt/kg are considered cobalt-deficient because plants growing on them have insufficient cobalt (<0.08–0.1 mg/kg) to meet the dietary requirements of cattle and sheep. Cobalt-deficient soils include the humus podzols of the southeastern United States, and the podzols, brown podzolic soils, and humus groundwater podzols in the northeastern parts of the United States. (Podzols are generally coarse-textured soils.) The cobalt content of surface soils from 13 sites in the brown and dark brown soil zones of southwestern Saskatchewan ranged from 3.7 to 16.0 mg/kg and only in one case was the soil appreciably elevated above the corresponding parent material (Mermut et al. 1996). Fertilizers used in this agricultural area contained 0.12–102 mg Co/kg, with a median of 5.7 mg/kg.

Mean cobalt concentrations in surface soil from nine sites on two active volcanic islands off of Sicily ranged from 5.1 to 59.0 mg/kg (Bargagli et al. 1991). Soils near ore deposits, phosphate rocks, or ore

smelting facilities, and soils contaminated by airport traffic, highway traffic, or other industrial pollution may contain much higher concentrations of cobalt; concentrations up to 800 mg/kg have been detected in such areas (Kloke et al. 1984; Smith and Carson 1981). Cobalt concentrations from 28 samples collected from surface deposits in the Big Deer and Blackbird Creek drainage basins in Idaho near the Blackbird Mine ranged from 26.5 to 7,410 mg/kg (Agency for Toxic Substances and Disease Registry 1995). Soils around the large copper-nickel smelters in Sudbury, Ontario have been shown to contain high levels of cobalt. Fifty kilometers from the smelters, cobalt levels in surface soil were 19 mg/kg. These levels increased to 48 mg/kg at 19 km, 33 mg/kg at 10 km, and 42–154 mg/kg between 0.8 and 1.3 km from the smelter (Smith and Carson 1981). Soils around a cemented tungsten carbide tool grinding factory contained cobalt levels as high as 12,700 mg/kg, almost 2,000 times the average in U.S. soils (Abraham and Hunt 1995). However, neighborhood soils between 30 and 160 meters from the factory only contained 12–18 mg Co/kg.

Unpolluted freshwater sediment contains about the same levels of cobalt as does cobalt-sufficient soil, generally <20 mg/kg (Smith and Carson 1981). In the Hudson River Estuary, cobalt levels in suspended sediment were an order of magnitude higher than in bottom sediment (Gibbs 1994). This can be attributed to the finer grain size of suspended sediment or local sources. Cobalt levels in core samples (surface to 42 cm deep) from the Upper St. Lawrence Estuary were independent of depth, indicating the lack of any recent significant anthropogenic releases (Coakley et al. 1993). Cobalt levels in sediment are shown in Table 6-4.

No broad-based monitoring studies of ^{60}Co or other radioactive cobalt isotopes in soil or sediment were found in the literature. Soil samples from the O-horizon taken from three sites in the 30-km zone around Chernobyl in 1992 and again in 1993 contained 14–290 and 4.5–245 Bq/kg (380–7,800 and 120–6,620 pCi/kg) dry weight of ^{60}Co, respectively (Lux et al. 1995). The Columbia River receives radiological contaminants along the Hanford Reach primarily through seepage of contaminated groundwater. The regional median concentration of ^{60}Co in sediment was highest along the Hanford reach, approximately 0.09 pCi/g (0.003 Bq/g) (PNNL 1996). ^{60}Co activity in a sediment cores in water off of Southampton in southern England contained up to 28 Bq/kg (760 pCi/kg) in the upper 3 cm; no activity was found below 12.5 cm (Croudace and Cundy 1995). Discharges of treated effluent occurred on closing a steam generating heavy water reactor west of where the sampling was done. The maximum discharge occurred in 1980–1981; however, no value was reported (Croudace and Cundy 1995).

Table 6-4. Cobalt Levels in Sediment

Nature/location of sediment	Level	Units	Type	Reference
Freshwater				
Polluted lakes and rivers	0.16–133	mg/kg	Range	Smith and Carson 1981
Lake Ontario near Miesissaqua, Canada	4.1–19.8	mg/kg	Range	Glooschenko et al. 1981
Hudson River, Foundry Cove, 1983, Ni-Cd battery plant, 1953–1979, surficial (0–5 cm) sediment, 16 sites	18–700	mg/kg	Range	Knutson et al. 1987
Estuaries and Marine				
Hudson River Estuary (0–80 km from ocean), 1991				Gibbs 1994
Bottom sediment	1–13	mg/kg	Range	
Suspended sediment (near surface)	30–140			
Upper St. Lawrence Estuary, 1989–1990				Coakley et al. 1993
Core C168	3.1 (0.6)	mg/kg	Mean (SD)	
Cores LE and LO	2.7 (0.5)			
Massachusetts, New Bedford Harbor- core (0–25 cm)				Shine et al. 1995
Outer Harbor	7.03, 3.64–9.79, range			
Inner Harbor	6.38, 2.62–10.52			
Buzzards Bay (control site)	4.76, 1.64–8.19			
Indian River Lagoon, Florida (43 sites)	2.3, 0.4–6.3	mg/kg	Mean, range	Trocine and Trefry 1996
Gulf of Mexico				Villanueva and Botello 1998
Coastal areas (11 sites)	12.30–36.26	mg/kg	Range of means	
Continental shelf (3 sites)	6.39–21.00			
Antarctica (Ross Sea) continental shelf (n=12)	19, 0.10–13	mg/kg	Mean, range	Bargagli 2000
Northern Arctic Alaska, continental shelf (n=136)	9, 3.3–18	mg/kg	Mean, range	Bargagli 2000
Chukchi Sea, northeast Alaska (31 stations, surficial sediment)	32.7, 19–74	mg/kg	Mean, range	Naidu et al. 1997
Baltic Sea, southern, off Poland (surficial sediment)	0.69–18.10	mg/kg	Range	Szefer et al. 1996
Baltic Sea (Gotland Deep site)	19, 11–33	mg/kg	Mean, range	Brügmann 1988

SD = standard deviation

Sediment samples were analyzed from the Peconic River system on Long Island, New York, downstream of Brookhaven National Laboratory (BNL). Near the sewage treatment plant, closest to the BNL, mean concentrations of ^{60}Co from three locations at the depth intervals 0.00–0.06, 0.06–0.15, 0.15–0.24, and 0.24–0.37 meters were 9.6, 6.7, 9.6, and 10.5 Bq/kg (0.25, 0.18, 0.25, and 0.28 nCi/kg) dry weight, respectively. At one location at the BNL property boundary, mean concentrations of ^{60}Co, using the same depth intervals, were 5.8 Bq/kg (0.16 nCi/kg) dry weight for the 0.00–0.06 m depth and <4 Bq/kg (<0.11 nCi/kg) dry weight for the remaining depth intervals. Sediment samples from a control river, Connetquot River, were <4 Bq/kg (<0.11 nCi/kg) in two locations at two depths (0.00–0.06 and 0.06–0.15 m) (Rapiejko et al. 2001).

Mururoa and Fangataufa Atolls were used for underground testing of nuclear weapons from 1975 to 1996. ^{60}Co was detected in the particle fraction of water in measurable levels at two of the nine Mururoa Atoll sites, Aristee and Ceto, at 0.58 and 1.06 mBq/L (0.016 and 0.029 pCi/L), respectively. ^{60}Co levels were found at levels below the detection limit, <0.1 mBq/L (<0.003 pCi/L), at the two Fangataufa Atoll sites and at the seven other Muruoa Atoll sites (Mulsow et al. 1999). Concentrations of ^{60}Co of soil samples used for growing onion, potatoes, tomatoes, cabbage, and maize in the Bulgarian village, Ostrov, in the vicinity (approximately 25–30 km) of the "Kozloduy" nuclear power plant were <8, 3, 320, 330, and 180 mBq/kg (2, 8.1, 8.6, 8.9, and 4.9 pCi/kg), respectively (Djingova and Kuleff 2002).

6.4.4 Other Environmental Media

The cobalt content of plants depends on the plant, the cobalt content of the soil, and numerous environmental factors. The mean cobalt concentration reported for terrestrial plants was 0.48 µg/g, while the mean and median levels for freshwater vascular plants were 0.48 and 0.32 µg/g, respectively (Outridge and Noller 1991). The median cobalt level in freshwater vascular plants from polluted waters was about the same as in unpolluted waters, 0.37 µg/g, although extremely high levels of cobalt, up to 860 µg/g, was reported in one species, *Myriophyllum verticillatum*, from central Ontario lakes. Grasses normally contain 0.2–0.35 µg/g of cobalt, but grasses from cobalt-deficient regions contain only 0.02–0.06 µg/g of cobalt (Hamilton 1994). Durum wheat grown in southeastern Saskatchewan contained 0.01–0.02 mg/kg dry weight (Mermut et al. 1996). In view of the cobalt content of the soil and the fact that almost half of the cobalt in fertilizers used in the area was in a readily available form, the uptake of cobalt by wheat was negligible.

^{60}Co levels in plants and mushrooms in the 30-km zone around Chernobyl were mostly below the detection limit in samples obtained in 1992 and 1993; the highest activity recorded was 3.9 Bq/kg (110 pCi/kg) dry weight in *Athyrium filix femina* (Lux et al. 1995).

Cobalt concentrations have been reported in various aquatic animals and seabirds. Eel and a freshwater fish from three Dutch polder lakes contained 2.5–25.0 and 2.50–5.63 mg cobalt/kg wet weight, respectively, (Badsha and Goldspink 1988). Muscle tissue of ocean fish and rock crabs caught near dump sites off New York City, New Haven, Connecticut, and Delaware Bay contained 10–40 and 16.0 µg/kg, respectively (Greig and Jones 1976). In a study of the levels and distribution of 14 elements in oceanic seabirds, the concentration of cobalt, an essential element, appeared to be highly regulated, with over 80% of the body burden residing in the skeleton. The mean cobalt concentration in the livers of 11 seabird species ranged from 0.048 to 0.078 µg/g dry weight, and cobalt had the lowest coefficient of variation in the different species of the elements studied (Kim et al. 1998a). In another study in Antarctica, mean cobalt levels in fish and amphipods were 0.11–0.14 and 1.01 µg/g dry weight, respectively, while those in the tissue of penguin and other sea birds ranged from 0.09 to 0.11 µg/g (Szefer et al. 1993). The concentration of cobalt in the tissue of 14 bluefin tuna caught by various commercial fishing vessels off Newfoundland was essentially the same, 0.01±0.004 µg/g (Hellou et al. 1992a). Similarly, in a broad survey of contaminant levels in nine species of fish and fiddler crabs from 11 sites in the lower Savannah River, Georgia and the Savannah National Wildlife Refuge, mean cobalt levels among different species and sites were statistically indistinguishable (Winger et al. 1990). These and other studies indicate that cobalt does not biomagnify up the food chain (Smith and Carson 1981). While high levels of cobalt were found in sediment from the Tigris River in Turkey and low levels in the water, cobalt was not detected in two species of fish, *Cyprinion macrostomus* and *Garra rufa* (Gümgüm et al. 1994). Cobalt was detected in two other species of fish collect between 1995 and 1996 in the upper Sakarya river basin, Turkey. Cobalt concentrations ranged from 0.038 to 0.154 µg/g dry weight for *Cyprinus caprio* and from 0.045 to 0.062 µg/g dry weight for *Barbus plebejus* (Barlas 1999).

^{60}Co was not detected in fish and mussel samples analyzed from the Peconic River system on Long Island, New York, downstream of the BNL. The lower detection limit for ^{60}Co was 0.4 Bq/kg (10 pCi/kg). ^{60}Co had been detected in sediment samples from this area (Section 6.4.3) (Rapiejko et al. 2001).

Some female birds sequester metals into their eggs under certain conditions, a phenomenon that may jeopardize the developing embryos. The geometric mean concentrations of cobalt in tern eggs collected from coastal New Jersey in 1971 and 1982 were 0.48 and 0.50 mg/kg, respectively. Unlike the levels of seven other common metals (e.g., mercury, cadmium, copper, lead, manganese, nickel, and zinc), the level of cobalt in tern eggs (and in the environment) showed no decline over the 11-year period (Burger and Gochfeld 1988).

Table 6-5 shows the levels of cobalt in food items and food categories from different countries. The level of cobalt in most Canadian foods was low; items with the highest concentrations in this study were waffles (0.076 μg/g), corn cereal (0.074 μg/g), and potato chips (0.070 μg/g) (Dabeka and McKenzie 1995). Green leafy vegetables and fresh cereals are the richest sources of cobalt (0.2–0.6 μg/g dry weight), while dairy products, refined cereals, and sugar contain the least cobalt (0.1–0.3 μg/g dry weight) (Barceloux 1999). The levels of cobalt were determined in 50 different food items, mainly meat, fish, fruit, vegetables, pulses, and cereals on the Swedish market during the years 1983–1990 (Jorhem and Sundström 1993). Beef liver and seeds were fairly high in cobalt and fish, fruit, and root and leafy vegetables were under 0.01 μg cobalt/g fresh weight. The cobalt levels in μg/g fresh weight were highest in alfalfa seeds, 0.86; linseed, 0.56; milk chocolate, 0.34; dark chocolate, 0.24; white poppy seeds, 0.30; blue poppy seeds, 0.15; soya beans, 0.084; green lentils, 0.054; and beef liver, 0.043. The cobalt content of 20 brands of alcoholic and nonalcoholic beer widely consumed in Spain ranged from 0.16 to 0.56 μg/L with a median of 0.39 μg/L (Cameán et al. 1998). Cobalt, which was at one time added to beer to increase the foam head, has been associated with cardiomyopathies (heart disease) in heavy beer drinkers.

A study of radionuclide levels in various foods and drinks in Hong Kong found that the ^{60}Co content in nearly all foods and drinks used in the study were below the minimal detection limit (Yu and Mao 1999). Analysis of wild plants in Bulgaria in villages near the “Kozloduy” nuclear power plant showed that the concentrations of ^{60}Co were below the detection limit. Mean activity concentrations of ^{60}Co in edible plants in this region were mostly <0.04 Bg/kg (<1 pCi/kg) (Djingova and Kuleff 2002).

Stable cobalt is present in various consumer products including cleaners, detergents, and soaps, which have resulted in dermatitis in sensitive individuals (Kokelj et al. 1994; Vilaplana et al. 1987). Tobacco contains about <0.3–2.3 μg Co/g dry weight and approximately 0.5% of the cobalt appears in mainstream smoke (Barceloux 1999; Munita and Mazzilli 1986; Ostapczuk et al. 1987; Stebbens et al. 1992).

Table 6-5. Cobalt Levels in Food

Food item	Level	Units[a]	Type	Reference
Infant formulas/milk				
Evaporated milk (n=21)	0.74, 0.52–2.6	µg/kg[b]	Median, range	Dabeka 1989
Ready-to-use formula (n=49)	0.53, 0.21–5.2	µg/kg[b]	Median, range	Dabeka 1989
Milk-based (n=33)	0.40, 0.21–0.99			
No added iron (n=6)	0.36, 0.21–0.61			
Added iron (n=27)	0.87, 0.41–0.99			
Soy-based (n=16)	2.27, 1.71–5.2			
Concentrated liquid formula (n=50)	2.27,0.25–11.8	µg/kg[b]	Median, range	Dabeka 1989
Milk-based (n=34)	1.57, 0.25–3.11			
No added iron (n=20)	1.06, 0.25–1.77			
Added iron (n=14)	2.59, 2.03–3.11			
Soy-based (n=16)	4.33, 2.7–11.8			
Powdered formula (n=64)	9.54, 2.6–53	µg/kg[b]	Median, range	Dabeka 1989
Milk-based (n=36)	4.96, 2.6–10.6			
No added iron (n=23)	4.24, 2.6–9.6			
Added iron (n=13)	8.26, 5.1–10.6			
Soy-based (n=28)	20.0, 10.6–53			
Agricultural crops				
Cabbage, United States	0.2	mg/kg[c]	Typical level	NAS 1977
Corn seed, United States	0.01	mg/kg[c]	Typical level	NAS 1977
Fruits, 12 types, Poland	0.01–0.02	mg/kg	Range	Bulinski et al. 1986
Lettuce, Sweden 1983–1990 (n=7)	0.002, 0.006	mg/kg	Mean, maximum	Jorhem and Sundström 1993
Lettuce, United States	0.2	mg/kg[c]	Typical level	NAS 1977
Onions, 11 Danish sites (n=110)	1.51, 0.119–5.1	µg/kg	Median, range	Bibak et al. 1998a
Peas, 10 Danish sites (n=93)	4.6, 0.57–17	µg/kg	Median, range	Bibak et al. 1998b
Potatoes, Sweden (n=8)	0.008, 0.017	mg/kg	Mean, maximum	Jorhem and Sundström 1993
Spinach, United States	0.4–0.6	mg/kg[c]	Typical range	NAS 1977
Strawberries, Sweden (n=10)	0.004, 0.010	mg/kg	Mean, maximum	Jorhem and Sundström 1993
Vegetables, 30 types, Poland	0.008–0.032	mg/kg	Range	Bulinski et al. 1986
White flour, United States	0.003	mg/kg[c]	Typical level	NAS 1977
Meat, fish, beverages				
Beef, Sweden (n=3)	0.001, 0.001	mg/kg	Range, maximum	Jorhem and Sundström 1993
Beef liver, Sweden (n=3)	0.043, 0.074	mg/kg	Range, maximum	Jorhem and Sundström 1993
Beef kidney, Sweden (n=3)	0.008, 0.010	mg/kg	Range, maximum	Jorhem and Sundström 1993

Table 6-5. Cobalt Levels in Food

Food item	Level	Units[a]	Type	Reference
Beer, Spain, 20 brands	0.39, 0.16–0.56	µg/L	Median, range	Cameán et al. 1998
Cocoa, Germany	1.31	mg/kg[c]		Ostapczuk et al. 1987
Coffee (whole), South Africa	0.93	mg/kg[c]		Horwitz and Van der Linden 1974
Coffee (whole), Germany (61% water extractable)	0.11–0.31	mg/kg[c]	Range	Ostapczuk et al. 1987
Fish, Sweden, 10 varieties (n=40)	<0.001–.008, 0.020	mg/kg	Range of mean, maximum	Jorhem and Sundström 1993
Pork, Sweden (n=36)	0.001, 0.012	mg/kg	Range, maximum	Jorhem and Sundström 1993
Pork liver, Sweden (n=36)	0.010, 0.023	mg/kg	Range, maximum	Jorhem and Sundström 1993
Pork kidney, Sweden (n=36)	0.004, 0.011	mg/kg	Range, maximum	Jorhem and Sundström 1993
Tea (whole), South Africa	0.2	mg/kg[c]		Horwitz and Van der Linden 1974
Tea (whole), Germany (40% water extractable)	0.18–6.7	mg/kg[c]	Range	Ostapczuk et al. 1987
Food categories				
Bakery good/ cereals, Canada (n=24)	10.9, 75.7	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Beverages, Canada (n=7)	5.9, 9.1	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Fats and oils, Canada (n=3)	<2.6, 37.6	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Fish, Canada (n=6)	18.6, 14.3–29.4	µg/kg	Median, range	Dakeba and McKenzie 1995
Fruits and fruit juices, Canada (n=25)	<6.6, 35.7	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Meat and poultry, Canada (n=18)	<5.5, 38.2	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Milk and milk products, Canada (n=13)	<1.4, 18.9	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Soups, Canada (n=4)	5.6, 8.5	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Sugar and candy, Canada (n=7)	<0.4, 3.5	µg/kg	Median, maximum	Dakeba and McKenzie 1995
Vegetables, Canada (n=38)	2.4, 18.1	µg/kg	Median, maximum	Dakeba and McKenzie 1995

[a]Produce on a fresh weight basis, unless otherwise specified
[b]As sold
[c]Dry weight basis

The cobalt content of sewage sludge, incinerator ash, fertilizers, soil amendments, and other substances appears in Table 6-6. The concentration of cobalt in U.S. coal averages about 5 mg/kg, levels in crude oil and fuel oil are 0.001–10 and 0.03–0.3 mg/kg, respectively, and those in gasoline are <0.1 mg/kg (Smith and Carson 1981). Cobalt levels were below the detection limit of 0.05 ppm dry weight in all but 1 of 26 samples of composted yard waste, sewage sludge, and municipal solid waste samples nationwide in 1991. The one positive sample of composted yard waste contained 1.53 ppm of cobalt (Lisk et al. 1992).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to cobalt occurs through inhalation of ambient air and ingestion of food and drinking water. In general, intake from food is much greater than from drinking water, which in turn, is much greater than from air. From the limited monitoring data available, the average concentration of cobalt in ambient air in the United States is approximately 0.4 ng/m^3. However, levels may be orders of magnitude higher in source areas. Therefore, intake to cobalt in air will vary substantially from nonsource areas to areas with cobalt-related industries. Similarly, the median cobalt concentration in U.S. drinking water is <2.0 µg/L; however, values as high as 107 µg/L have been reported in surveys of water supplies (Smith and Carson 1981). Therefore, exposure from drinking water may vary considerably from one location to another. In Canada, the daily cobalt intake of the average adult from drinking water is ≤2.6 µg; this could increase to 10 µg for those living in areas with the highest cobalt levels (Meranger et al. 1981).

General population exposure to cobalt from food is highly variable and normally higher than intake from drinking water. Most of the cobalt ingested is inorganic; vitamin B_{12}, which occurs almost entirely in food of animal origin, constitutes only a very small fraction of cobalt intake. The cobalt intake in food has been estimated to be 5.0–40.0 µg/day (Jenkins 1980). The daily cobalt intake, including food, water, and beverages of two men that were followed for 50 weeks was much higher, 310 and 470 µg (Smith and Carson 1981). The estimated average daily cobalt intake from diet in Canada was 11 µg/day; the intake varied from 4 to 15 µg/day between the various age/sex groups (Table 6-7) (Barceloux 1999; Dabeka and McKenzie 1995). The contributions of various food groups to cobalt intake in this study were (category, contribution of dietary intake): bakery goods and cereals, 29.8%; vegetables, 21.9%; beverages, 9.8%; milk and milk products, 9.4%; meat and poultry, 9.1%; soups, 6.4%; fruit and fruit juices, 5.0%; sugar

Table 6-6. Cobalt Content of Miscellaneous Substances

Substance/source	Level	Units	Type	Reference
Bituminous coal used for power generation	6.4	mg/kg	Median	Rubin 1999
Coal, United States	~5	mg/kg	Mean	Smith and Carson 1981
Fly ash	~25	mg/kg	Mean	Smith and Carson 1981
MSW Incinerator ash, Mississippi				Buchholz and Landsberger 1995
Fly ash (n=30)	11.3–13.5	µg/g	Range	
Bottom ash (n=30)	65.2–90.3			
Combined ash (n=30)	24.8–30.5			
MSW Incinerator ash, United States, 1987				Mumma et al. 1990
Fly ash (n=5)	18.2–54.0	µg/g	Range	
Bottom ash (n=7)	13.5–35.1			
Combined ash (n=8)	11.2–43.4			
Compost, Toronto				Evans and Tan 1998
Residential compost	8.1, 3.2–12	mg/kg	Median, range	
Greenhouse finished compost	6.1±1.03		Mean ± SD	
Sewage sludge				
16 large U.S. cities	11.3, 6.08–29.1	mg/kg	Median, range	Gutenmann et al 1994
32 U.S. cities	7.2, 2.4–30.1	mg/kg	Median, range	Mumma et al. 1984
Cow manure (comparison)	6.1	mg/kg		Mumma et al. 1984
Miscellaneous soil amendments[a]				Raven and Loeppert 1997
Compost	3.55, 3.57	mg/kg	Individual means	
Diammonium phosphate	3.24, 0.68			
Dolomite	0.33			
Manure	2.23			
Monoammonium phosphate	0.78, 3.38			
Rock phosphate, Tilemsi	19.6			
Rock phosphate, North Carolina	<0.08			
Sewage sludge, Austinite	4.10			
Sewage sludge, Milorganite	4.07			
Triple superphosphate	6.61, 2.24			
Street dust, New York City	8.7–12.9	µg/g	Range	Fergusson and Ryan 1984

[a]The rest of the 24 fertilizers and soil amendments tested were below the detection limit (typically <0.07 ppm)

MSW = municipal solid waste; SD = standard deviation

Table 6-7. Mean Daily Dietary Intake of Cobalt for Selected Population Groups in Canada

Group	Mean daily intake (µg/day)
1–4 years	7
5–11 years	10
12–19 years; male	14
12–19 years; female	10
20–39 years; male	15
20–39 years; female	9
40–65 years; male	12
40–65 years; female	9
65+; male	10
65+; male	8

Source: Dabeka and McKenzie 1995

and candies, 2.8%; fish, 2.7%; fats and oils, 2.2%; and miscellaneous, 1.1%. The average daily intake of cobalt in France was estimated to be 29 μg/day (Biego et al. 1998). In this study, foods were divided into nine categories. The foods accounting for the greatest contributions of cobalt intake were milk and dairy products, fish-crustaceans, and condiments-sugar oil, respectively contributing 32, 20, and 16% to the daily intake. The U.S. Department of Agriculture (USDA) conducted a special exploratory study in 1985–1986 to determine the concentration of trace metals in tissue of health livestock and poultry randomly selected from those slaughtered. Between 0.6 and 5.9% of samples in the 11 production classes had levels of cobalt that exceeded the lowest reliable quantitation level of 0.15 ppm (0.15 mg/kg) and the mean of positive samples ranged from 0.20 to 0.23 ppm in all classes but heifer/steer, which had a level of 1.92 ppm (Coleman et al. 1992). Cobalt, which has been added to beer to increase the foam head, has been associated with cardiomyopathies (heart disease) in heavy beer drinkers. However, according to a recent Spanish study, the low levels of cobalt presently found in beer do not make a significant contribution to the total cobalt intake in heavy beer drinkers (Cameán et al. 1998). Smokers may be exposed to cobalt in mainstream smoke, but the level of exposure has not been assessed (Barceloux 1999).

Since cobalt and other heavy metals have been used on hand-painted china, a study was conducted to see whether these metals are released into food under acidic conditions. Forty-six samples of porcelain dinnerware from Europe or Asia that were manufactured before the mid-1970s and had hand-painted designs over the glaze were filled with 4% acetic acid to within 7 mm of the rim and analyzed after 24 hours (Sheets 1998). Of these, 36 samples released <0.02 μg/mL of cobalt and 10 released 0.020–2.9 μg/mL. The Food and Drug Administration (FDA) has not established dinnerware extraction limits for cobalt.

Data are lacking on the levels of cobalt in tissues and fluids of the general populations in the United States; values from various countries are given in Table 6-8. This table shows that cobalt concentrations are greatest in nail, hair, and bone. The differences in cobalt levels in similar human tissues (e.g., hair, nail) in different countries may be due to differences in dietary and living habits and levels of cobalt in food (Takagi et al. 1988). The total amount of cobalt in the body of an adult as vitamin B_{12} is about 0.25 mg, of which 50–90% in contained in the liver (IARC 1991).

A recent study in the United States determined the concentrations of trace metals in seminal plasma in industrial workers in a petroleum refinery, smelter, and chemical plant as compared with those of hospital

Table 6-8. Cobalt Levels in Human Tissues and Fluids

Tissue or fluid	Level	Units[a]	Type	Reference
Urine, U.S., NHANES, representative population (n=1007)	0.36, 0.11–0.89	µg/L	Geomean, 10th–90th percentile	CDC 2001
Urine, U.S., NHANES 1999–2000, Total, age 6 and older (n=2,465)	0.372, 0.130–1.32	µg/L	Geomean, 10th–95th percentile	CDC 2003
6–11 years (n=340)	0.498, 0.130–1.32			
12–19 years (n=719)	0.517, 0.200–1.52			
20 years and older (n=1,406)	0.339, 0.120–1.28			
Males (n=1,227)	0.369, 0.150–1.01			
Females (n=1,238)	0.375, 0.120–1.49			
Mexican Americans (n=884)	0.415, 0.130–1.47			
Non-Hispanic blacks (n=568)	0.433, 0.160–1.45			
Non-Hispanic whites (n=822)	0.365, 0.120–1.29			
Urine, The Netherlands	<0.2–1.2	µg/L	Range	Bouman et al. 1986
Urine, Sweden	0.5, 0.1–2.2	µg/L	Mean, range	Alexandersson 1988
Urine, Denmark (3 reference groups)				Poulsen et al. 1994
Unexposed control females (n=46)	1.5, LOD–20.5	nmol[b]	Mean, range	
Unexposed males (n=12)	0.9, LOD–2.31			
Unexposed females (n=11)	5.9, LOD–25.02			
Urine, hip arthroplasty patients, observed 7–15 years (n=17)	0.9–1.05	µg/L	Range	IARC 1991
Urine, hip arthroplasty patients, observed 5–15.5 years (n=10)	3.8	µg/L	Mean	IARC 1991
Urine, 48 metal sharpening workers in 12 Italian factories	0–40.3, 86	µg/L	Range of means, maximum	Imbrogno et al. 1994
Urine, 12 female cobalt powder sintering workers, Italy				Ferdenzi et al. 1994
Monday, before shift	25, 1–51	µg/L	Mean, range	
Friday, before shift	29, 3–159			
Friday, end-of shift	85, 6–505			
After 3-week holiday	11, 4–34			
Urine, Italian workers wet grinding of hard metal tools (end of shift)				Sesana et al. 1994
Factory A no local exhausts (n=3)	138.3 (108), 123.7 (74)	µg/L	Mean (SD) Monday, Friday	
Factory B local exhausts (n=5)	15.3 (7.7), 24.4 (14.1)			
Factory C local exhausts (n=3)	48.2 (7.3), 74.7 (13)			

Table 6-8. Cobalt Levels in Human Tissues and Fluids

Tissue or fluid	Level	Units[a]	Type	Reference
Urine, Northern Italy, 1991, occupational exposure survey, 314 exposed people				Mosconi et al. 1994
Diamond abrasive production				
Mould-filling	320, 587, 39–2,100	µg/L	Median, mean, range	
Sintering	168, 193, 02–390			
Grinding	61, 151, 34–520			
Mechanical-working	50, 67, 143–165			
Grinding	15, 32, 0.8–730			
Tool production	12, 19, 0.8–100			
Hard metal alloy filling	5, 5, 0.8–18			
Other	1, 2.9, 0.8–72			
Blood, Denmark, porcelain factory				Raffn et al. 1988
Plate painters, off work for 6 weeks (n=46)	8.05, 1.70–22.1	nmol/L	Mean, range	
Plate painters, working 4 weeks (n=46)	36.7, 3.40–407			
Top glaze painters (unexposed) (n=51)	4.04, <1.70–10.2			
Urine, Denmark, porcelain factory				Raffn et al. 1988
Plate painters, off work for 6 weeks (n=46)	81.8, <1.70–445	nmol/L	Mean, range	
Plate painters, working 4 weeks (n=46)	1,308, 37.4–14,397			
Top glaze painters (unexposed) (n=51)	16.0, <1.70–234			
Plasma, Sweden	0.1–1.2	µg/L	Range	Alexandersson 1988
Whole Blood, Denmark (3 Reference groups)				Poulsen et al. 1994
Unexposed control females (n=46)	4.1, <1.7–10.2	nmol/L	Mean, range	
Unexposed males (n=12)	3.1, <1.7–6.8			
Unexposed females (n=11)	7.6, <1.7–30.5			
Lung, Sweden				Gerhardsson et al. 1988
Rural	0.007	mg/kg	Mean	
Urban	0.011			
Liver Tissue, United Kingdom, newborns and infants that died from SIDS (n=157)	17.4±11.3 (15.9)	ng/g wet mass	mean±SD (median)	Patriarca et al. 1999
Liver, New Zealand (n=96)	0.120	mg/kg	Mean	IARC 1991

Table 6-8. Cobalt Levels in Human Tissues and Fluids

Tissue or fluid	Level	Units[a]	Type	Reference
Tissue, Japan				Yamagata et al. 1962
Pectoral muscle	0.016	mg/kg	Mean	
Rib bone	0.036			
Stomach	0.021			
Liver	0.017			
Brain	0.0055			
Urinary bladder	0.0055			
Kidney	0.012			
Aorta	0.021			
Nails				Takagi et al. 1988
Canada (n=40)	0.09	mg/kg	Mean	
India (n=100)	0.06			
Japan (n=252)	0.17			
Poland (n=49)	0.04			
U.S. (n=71)	0.06			
Adipose tissue	0.035–0.078	mg/kg	Range	EPA 1986
Hair				Takagi et al. 1986
Canada (n=92)	0.043	mg/kg	Mean	
India (n=255)	0.051			
Japan (n=457)	0.18			
Poland (n=46)	0.022			
United States (n=55)	0.047			
Hair, Italy				Vienna et al. 1995
Male biology students (n=20)	0.007, 0.001–0.07	mg/kg	Geomean, range	
Female biology students (n=20)	0.017, 0.001–0.28			
Hair, Pakistan				Ashraf et al. 1995
Rural (n=28)	2.05, 0.10–4.80	mg/kg	Mean, range	
Urban (n=39)	3.86, 1.10–5.90			

[a]fresh weight, unless otherwise specified
[b]creatinine basis

geomean = geometric mean; LOD = limit of detection; NHANES = Nation Health and Nutrition Examination Survey; SD = standard deviation; SIDS = sudden infant death syndrome

workers (control group). There were four groups each with 50 adult men. The mean cobalt concentrations (μg/dL), including standard errors, were determined to be 31±2 (hospital workers), 25±0.8 (metal ore smelter workers), 19±0.6 (petroleum refinery workers), and 22±1 (chemical workers) (Dawson et al. 2000).

Surgical implants for knee and hip replacements often use cobalt-containing alloys, which may lead to elevated cobalt levels in body fluids. Indeed, cobalt levels in serum and urine have been used as an index of prosthesis wear. In some cases, significant increases in cobalt levels have been observed, while in other cases, elevations were much lower or only sporadic (IARC 1991). These differences have been ascribed to greater release rates from metal to metal than metal to polyethylene articular surfaces as well to differences in the cobalt-containing alloys.

There are several reports of cobalt exposure among occupational groups. The concentrations of cobalt in the air of hard metal manufacturing, welding, and grinding factories may range from 1 to 300 μg/m^3, compared to normal atmospheric levels of 0.4–2.0 ng/m^3 (Burr and Sinks 1989; Haddad and Zikovsky 1985; Koponen et al. 1982; Lichtenstein et al. 1975). The maximum OSHA permissible level is 100 μg/m^3. The concentration of cobalt in the dust of an electric welding factory was 4.2 μg/g compared to its normal dust level of 0.1–1.0 μg/g (Baumgardt et al. 1986). The higher rate of exposure to cobalt for occupational groups is also reflected in the higher cobalt content in tissues and body fluids of living and deceased workers in this group. The levels of cobalt in the urine of workers in the hard metal industry varied with the levels of cobalt concentration in the working atmosphere. At a concentration of 0.09 mg/m^3, the urinary excretion of cobalt exceeded normal values by orders of magnitude. When the cobalt concentration in the working atmosphere was 0.01 mg/m^3 or lower, urinary cobalt excretion was 4–10 times higher than normal level (Alexandersson 1988; Scansetti et al. 1985). At high exposure levels, the cobalt concentration in blood was 20 times higher than normal; in the low exposure group, it was only slightly higher than in the control group (Alexandersson 1988).

An extensive survey of workers potentially exposed to cobalt in the Bergamo Province in northern Italy in 1991 identified 403 exposed workers in different production areas (Mosconi et al. 1994a). Significant cobalt exposure occurred especially for operators working in diamond abrasive production, and in particular, in mold filling and sintering units where environmental limits are regularly exceeded. Exposure in tool production, tool sharpening, and hard metal alloy filling is much more restrained.

Occupational cobalt air levels and urinary excretion levels recorded in the survey appear in Tables 6-2 and 6-8.

Several studies of cobalt concentrations in air in the hard metal industry have been reported. In the hard metal industry in Japan, Kumagai et al. (1996) found that mean 8-hour time weighted averages (TWAs) of airborne cobalt were >50 μg/m^3 for workers involved in powder preparation (rotation), powder preparation (full-time), rubber press, and shaping operations; mean atmospheric concentrations were 459, 147, 339, and 97 μg/m^3, respectively. Workers involved in the manufacture and maintenance of hard metal and stellite blades in Finland were exposed to breathing zone cobalt concentrations ranging from 2 to 240 μg/m^3, with a geometric mean of 17 μg/m^3 (Linnainmaa et al. 1996). The average proportion of water soluble cobalt in airborne cobalt was 68% (range 14–100%). Wet grinding was not sufficient to adequately control cobalt levels and coolant cobalt levels were high. In a group of 12 factories in Italy in which 48 workers were tested who had been exposed to cobalt in operations such as sharpening with diamond grinding stones, the mean concentration of cobalt in air was 21.2 and 137.7 μg/m^3 (Permissible exposure limit [PEL]-TWA 100 μg/m^3) in work places with and without dust ventilation, respectively (Imbrogno et al. 1994).

Urine concentrations have been used to monitor workers' exposure to airborne cobalt. Ferdenzi et al. (1994) obtained a correlation between Friday TWA air cobalt levels and Friday end-of-shift urine levels among women in the powder sintering industry. Median urinary cobalt concentrations were 25 (range: 1–51) and 29 (3–159) μg/L, on Monday and Friday before the shift, respectively, and 85 (6–505) μg/L on Friday after the shift. Imbrogno and Alborghetti (1994) evaluated the levels of occupational exposure to cobalt during dry and/or wet hard metal sharpening. The mean urine cobalt level in the workers in 12 factories was found to range from 0 to 40.3 μg/L and the maximum was 86 μg/L. The average urinary cobalt level among workers using wet/mixed sharpening methods was 4 times higher than those using dry sharpening methods; 21.38 μg/L as compared to 5 μg/L, respectively. Gallorini et al. (1994) found that the ratio of inorganic to organic cobalt in the urine of hard metal workers was 2.3 compared to 1.01 in controls; the ratio was constant over the range of urinary cobalt levels analyzed (180–1,254 μg/L). Exposure to cobalt during the wet grinding of hard metal tools (Widia tools) used in the wood industry produced exposure to cobalt above the PEL-TWA of 100 μg/m^3 (Sesana et al. 1994). However, exhausts near the grinding wheels were shown to substantially reduce exposure levels (see Table 6-8). In the processing department of a small company producing carbide tip saw blades for the woodworking industry, area air sampling showed that exposure levels were low in all departments except tip grinding

where wet and dry tip grinding areas contained 55 and 21 μg/m^3 of cobalt, respectively, for the total collection method (Stebbins et al. 1992). For the method collecting respirable particles, cobalt levels ranged from 2 to 28 μg/m^3. Wet grinding is a traditional method for controlling dust during grinding. However, some coolants may contain significant concentrations of cobalt (in this case, 61–538 mg/mL) that can contribute to exposure during grinding (Stebbins et al. 1992). Among cobalt blue dye plate painters in a porcelain factory in Denmark, the blood and urine cobalt levels were, respectively, 2–4 and 5–15 times higher than in control groups (Raffn et al. 1988). Similarly, lungs taken from deceased, occupationally exposed workers also had higher levels of cobalt than lungs from control groups. Lungs of deceased hard metal industry workers in Sweden contained 2.5–4 times higher levels of cobalt than control lungs (Gerhardsson et al. 1988). Similarly, the lungs of coal miners from England contained 6 times higher cobalt levels than control lungs (Hewitt 1988).

Exposure to radioactive cobalt can occur through various means. Workers at nuclear facilities, irradiation facilities, or nuclear waste storage sites may be accidentally exposed to radioisotopes of cobalt. Also, workers using cobalt isotopes in tracer studies, in calibration or other devices, or ^{57}Co in Mössbauer spectroscopy, may be exposed to radioactive cobalt. Exposure would generally be to radiation produced by these isotopes (e.g., gamma radiation from ^{60}Co). Patients receiving ^{60}Co radiotherapy will obviously be exposed to its radiation. According to the USNRC (1999), the collective intake of ^{60}Co by ingestion and inhalation at power reactors in 1998 was 352 μCi (13 MBq) for 25 intake records and 27,000 μCi (1,000 MBq) for 281 intake records (USNRC 1999). The collective intake at fuel fabrication facilities was 0.486 μCi (0.180 MBq) for 502 intake records. The USNRC occupational inhalation annual limits of intake (ALIs) for ^{60}Co are 200 μCi (7.4 MBq) for all compounds, except oxides, hydroxides, halides, and nitrates, and 30 μCi (1.1 MBq) for compounds of oxides, hydroxides, halides, and nitrates (USNRC 2001k).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.8 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a

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

As with adults, most children are exposed to cobalt largely through their diet. Dabeka and McKenzie (1995) estimated that the dietary cobalt intake by Canadian children ages 1–19 ranged from 7 to 14 mg/day (see Table 6-7). Milk constitutes a larger part of children's diets than that of adults, and infants may consume infant formula. Cobalt concentrations ranging from 0.3 to 0.8 ng/g in cow's milk were reported by Iyengar (1982). The levels of cobalt in human milk from Nigeria, Zaire, Guatemala, Hungary, Philippines, and Sweden ranged from 150 (Hungary) to 1,400 ng/g (Philippines), median 320 ng/g (Nriagru 1992). Garg et al. (1993) reported much lower cobalt levels in three samples of human milk in India, 2.42 ng/g, and reported a cobalt concentration of 5.07 ng/g in cow's milk in India. Dakeba (1989) determined cobalt levels in various infant formulas (see Table 6-5). Milk-based infant formulas and evaporated milk contained <1 ng/g of cobalt on a "ready-to-use" basis. Milk-based formulas with added iron contained about twice the cobalt as those with no added iron and soy-based formulas contained about 5 times more cobalt. The influence of added iron suggests that the cobalt in formula is not primarily from vitamin B_{12}. Using literature values of cobalt in food, Dakeba also estimated that infants 0–12 months old ingest an average of 0.52 μg Co/kg-day (3.93 μg/day) from food and water and that for an infant, 0–12 months old, the total dietary cobalt intake would range from 0.42 μg/kg-day (3.39 μg/day) for a breast or milk-based formula fed infant to 1.0 μg/kg-day (7.33 μg/day) for an infant fed soy-based formula powder. The recommended dietary allowance for Canadian infants is 0.012 μg/day cobalt as vitamin B_{12}. In a 1967 study of the total dietary intake of some trace elements, excluding drinking water, of institutionalized children aged 9–12 in 28 U.S. cities, cobalt intake ranged from 0.297 to 1.767 mg/day with a mean value of 1.024 mg/day (Murthy et al. 1971).

Exposure to stable cobalt in communities near mining and smelting facilities or metal shops where cobalt is used in grinding tools is a public health concern, especially for infants and children. Since cobalt remains in the surface soil indefinitely and long past land uses may be forgotten, people may not realize that they are living in areas where high levels of cobalt may occur in soil. Contaminated soils pose a particular hazard to children because of both hand-to-mouth behavior and intentional ingestion of soil that

contain metals and other contaminants (Hamel et al. 1998). In these communities, cobalt may have been tracked in from outdoors and contaminate carpeting. Cobalt-containing dust may be brought home in the clothing of parents working in industries where they are exposed to cobalt. Children may be exposed to this cobalt while crawling around or playing on contaminated carpeting. Exposure may also result from dermal contact with soil, or by inhaling dust and then swallowing it after mucociliary transport up out of the lungs. Because there is little absorption of cobalt through the skin following dermal exposure, and because much of the cobalt in soil is embedded in or adsorbed to soil particles or insoluble, it may not be in a form accessible for uptake by the body, and therefore may not pose a serious health hazard.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to workers in the hard metal industry (tool production, grinding, etc.) and industries such as coal mining, metal mining, smelting and refining, cobalt dye painters, and the cobalt chemical production, the general population living near these industrial sites may be exposed to high levels of cobalt in air and in soil. Exposure to cobalt during the wet grinding of hard metal tools is especially high when local exhausts are not in use (Sesana et al. 1994). People living near hazardous waste sites may be exposed to cobalt by inhaling dust from contaminated sites or through dermal contact with cobalt-contaminated soil. In the case of children playing in and around unrestricted landfill sites, exposure via dermal and ingestion routes is possible. The general populations in agricultural areas that use sewage sludge or cobalt-containing fertilizers or other soil amendments may be exposed to higher levels of cobalt via inhalation of dust or dermal contact with the soil. However, no experimental evidence of higher than normal exposures for these population groups was found in the literature. People who live in areas that naturally contain higher levels of cobalt minerals may also be exposed to higher levels of cobalt from both the inhalation and dermal contact routes.

The higher exposure of cobalt in patients with cobalt-chromium knee implants has been demonstrated by the slightly higher levels of cobalt in whole blood, serum, and urine, and by very high levels of cobalt in bone of these patients (IARC 1991; Ostapczuk et al. 1985; Sunderman et al. 1989). Prosthetic devices that contain polyethylene components to avoid metal-to-metal contact do not appear to cause elevated levels of cobalt in tissues and body fluids (IARC 1991; Ostapczuk et al. 1985; Sunderman et al. 1989). People who use cobalt supplements as a treatment for anemia and those who take large amounts of vitamin B-12 as a dietary supplement would have higher intakes of cobalt than the general population.

Workers at nuclear facilities and nuclear waste storage sites may be exposed to potentially high levels of radiation exposure from ^{60}Co and ^{58}Co. Workers at irradiation facilities using ^{60}Co may be exposed to potentially high levels of gamma radiation exposure from this isotope. Patients receiving ^{60}Co radiotherapy will intentionally be exposed to high levels of gamma radiation.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cobalt 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 cobalt.

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

6.8.1 Identification of Data Needs

Physical, Chemical and Radiological Properties. As can be seen from Table 4-2 and Section 4.2, the relevant physical and chemical properties of cobalt and its compounds are sufficiently known to enable prediction of environmental fate and transport of cobalt compounds (Budavari 1996; Lide 1994; Stokinger 1981; Weast 1985). Information on the radiological properties of important cobalt isotopes are also well known (see Table 4-3) (ICRP 1983; Lide 1994). No data needs were identified.

Production, Import/Export, Use, Release, and Disposal. Information on the production, import/export, use, release, and disposal of a chemical is important because it is an indicator of possible environmental contamination and human exposure. Large releases and consumer use would indicate

higher general population exposure from environmental sources (e.g., air, drinking water, and food) and use of consumer products. Occupational exposure may also increase with increased production and use. U.S. production of cobalt is derived primarily from scrap (secondary production). Information is available on cobalt consumption derived from secondary production, import/export, and release of cobalt from the National Defense Stockpile (USGS 1998, 1999, 2002). However, production volumes of individual cobalt compounds are not available and information on the production of individual compounds would be useful in assessing exposure to specific cobalt compounds. Radioactive cobalt isotopes, primarily ^{60}Co and ^{57}Co, are not commercially produced in the United States, but rather are imported from Canada and the United Kingdom; consumption amounts are not available. Information on the uses of cobalt is available (Cobalt Development Institute 2004; Donaldson 1986; Hodge 1993; IARC 1991; Richardson 1993; USGS 1998, 2002). Cobalt-containing products are mostly used in the workplace, although some consumer products contain cobalt.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and offsite transfer information to the EPA. The TRI for 2001 is currently available (TRI01 2004). Starting in 1998, metal mining, coal mining, electric utilities, and RCRA/solvent recovery industries were required to report to the TRI. These sectors include those contributing greatest environmental releases of cobalt and cobalt compounds, giving us a much more complete picture of cobalt releases to the environment. The TRI also contains information on the onsite and offsite disposal and management of wastes (e.g., recycling, treatment, transfer to publicly owned treatment works [POTWs]). EPA guidelines address the disposal of hazardous cobalt wastes. The TRI database will be updated yearly and provides a list of industrial production facilities and emissions. The TRI data should be used with caution since the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list.

Environmental Fate. There are data that permit assessment of the environmental fate and transport of cobalt in water and soil (Section 6.3). Frequently, sediment and soil are the ultimate sinks for cobalt; however, this process is dynamic, and cobalt can be released into the water depending upon conditions. There is a paucity of data in the literature regarding the chemical forms of cobalt released to the atmosphere and their transformations in air and this information would facilitate the determination of the transport and persistence of cobalt in the atmosphere. Additional data elucidating the mode of speciation

of cobalt in water and soil would also be desirable. For example, under what circumstances Co(III) compounds might be formed in the environment and how long.

Bioavailability from Environmental Media. Absorption by the inhalation and oral routes in humans has been studied, but the results vary considerably (see Section 3.5.1) (Foster et al. 1989; Harp and Scoular 1952; Sedlet et al. 1958; Sorbie et al. 1971; Valberg et al. 1969). These variations were attributed to differences in the types and doses of cobalt compounds given, to the nutritional status of the subjects following oral exposure, and to particle size differences following inhalation exposure. Additional data assessing the absorption of cobalt following soil ingestion by children may be helpful. Data in animals are plentiful for both inhalation and oral routes and correlate well with the human data (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kreyling et al. 1986; Patrick et al. 1989; Talbot and Morgan 1989). Data in animals following dermal exposure suggested that cobalt is not absorbed well through intact skin, but is rapidly taken up through damaged skin. Data regarding the bioavailability of cobalt following dermal exposure are important because dermal exposure to cobalt in the workplace is probable.

Food Chain Bioaccumulation. Bioaccumulation in the food chain is important in assessing the human exposure to cobalt from the consumption of food. Data are available that indicate that cobalt is not taken up appreciably by plants and does not biomagnify up the food chain (Baudin and Fritsch 1987; Baudin et al. 1990; Boikat et al. 1985; Francis et al. 1985; Kloke et al. 1984; Lux et al. 1995; Mascanzoni 1989; Mejstrik and Svacha 1988; Mermut et al. 1996; Palko and Yli-Hala 1988; Smith and Carson 1981; Tolle et al. 1983; Watabe et al. 1984).

Exposure Levels in Environmental Media. Monitoring data on levels of cobalt in air, water, and food permits the estimation of exposure from these sources. Data are available on the cobalt levels in ambient air (Golomb et al. 1997; Hasanen et al. 1990; Schroeder et al. 1987; Smith and Carson 1981; Sweet et al. 1993; Wiersema et al. 1984). However, the data are not sufficiently recent or broad-based for estimating the current levels of exposure to cobalt in the general U.S. population and particularly those living near cobalt-containing hazardous waste sites. In addition, in only isolated studies was there an assessment of the concentration of cobalt associated with coarse and fine particles (Sweet et al. 1993) or an average annual level obtained at a site (Golomb et al. 1997). Similarly, levels of cobalt in ambient water, while generally low, are also not sufficiently broad-based or recent to be satisfactory (Bargagli 2000; Bruce and McMahon 1996; Cassidy et al. 1982; Eckel and Jacob 1988; Flaten 1991; Nojiri et al.

1985; Rossmann and Barres 1988; Smith and Carson 1981). This deficiency may be satisfied when the EPA's improved and updated STORET database becomes available. Cobalt levels in Canadian drinking water are ≤2.0 mg/L (Meranger et al. 1981). However, U.S. drinking water levels have not been reported and would be useful. The levels of cobalt in sediment are available (Bargagli 2000; Coakley et al. 1993; Gibbs 1994; Glooschenko et al. 1981; Knutson et al. 1987; Naidu et al. 1997; Shine et al. 1995; Smith and Carson 1981; Trocine and Trefry 1996; Villanueva and Botello 1998), but more data on levels in soil and in the vicinity of industrial and hazardous waste sites would be useful. Few data on the levels of cobalt in U.S. foods are available, although studies from Canada and Sweden are available that indicate that cobalt levels in food items are generally low (Barceloux 1999; Dabeka and McKenzie 1995; Jorhem and Sundström 1993). In particular, total diet studies of cobalt in U.S. food is lacking. A Canadian total diet study estimated average daily cobalt intake to range from 7 to 15 µg/day for different age-sex groups (Dabeka and McKenzie 1995).

Few data are available on levels of ^{60}Co and other cobalt isotopes in environmental media.

Exposure Levels in Humans. The levels of cobalt in hair, nail, and adipose tissues of the general U.S. population are known (EPA 1986; Takagi et al. 1986, 1988). No reliable data on the levels of this substance in blood (or plasma) and urine of the general U.S. population were found, although such data are available for certain European populations including occupationally-exposed groups (Table 6-8). These data may be important for establishing the background exposure level of cobalt. No data on the levels of cobalt in any body tissue or fluid for populations living near hazardous waste sites are available. Such data would be important in assessing the exposure levels of this group of people.

Exposures of Children. Dabeka (1989) reported the levels of cobalt in various formulas and milk products consumed by children in Canada, and Dabeka and McKenzie (1995) determined the mean dietary intake of Canadian children as young as 1–4 years of age. Nriagru (1992) reported levels of cobalt in human milk from several countries. No analogous U.S. studies were found. Cobalt levels is the tissue and body fluids of children have not been found.

Child health data needs relating to susceptibility are discussed in 3.13.2 Identification of Data Needs: Children's Susceptibility.

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

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2002, 2004) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-9.

Remedial investigations and feasibility studies conducted at the NPL sites known to be contaminated with cobalt, such as the Blackbird Mine in Idaho, will add to the available database on exposure levels in environmental media, exposure levels in humans, and exposure registries, and will increase the current knowledge regarding the transport and transformation of cobalt in the environment.

The Cobalt Development Institute (CDI) is implementing a research program to assess environmental risks posed by the manufacture and use of cobalt and cobalt compounds. Studies that are underway include the assessment of seasonal and background variability of cobalt compounds in aquatic environment and a literature survey for existing data on the effects of cobalt and cobalt compounds in soils and sediment. Environmental studies proposed for 2002 included the assessment of seasonal and background variability of cobalt compounds in soils and sediments and a literature survey for existing data on the effects of cobalt and cobalt compounds on marine environments.

Table 6-9. Ongoing Studies on Cobalt

Investigator	Affiliation	Research description	Sponsor
Hamilton, JW	Dartmouth College, Hanover, New Hampshire	The overall goal of the Dartmouth Superfund Basic Research Program (SBRP) Project, Toxic Metals in the Northeast: From Biological to Environmental Implications is to determine the impact of toxic metals found at waste sites, including Superfund sites on human health and the environment. The program-wide focus of this research program is on toxic metals, particularly on arsenic, and also chromium, nickel, cadmium, mercury, cobalt, and lead.	NIH
Jones, BT	Wake Forest University, Winston-Salem, North Carolina	The investigators developing a novel, low-cost, portable instrument for the simultaneous determination of trace radioactive elements in nuclear forensic samples. At issue is the routine, inexpensive sampling for radioactivity that could be released on transport or storage of potential "dirty bomb" material. The instrument to be developed is expected to provide analytical figures comparable to inductively coupled plasma mass spectrometry, but the instrument is much lower cost and more portable. The specific objectives of the project include determination of the analytical figures of merit for elements including cobalt, cesium, and strontium, and analysis of real samples such as soil, urban dust, water and agricultural materials.	NSF
Kpomblekou-Ademawou, K Ankumah, RO	Tuskegee University, Tuskegee, Alabama	This project will investigate if excessive accumulation of some trace elements, added to poultry diet and excreted through feces, affects nitrogen transformation in broiler (chicken) litter amended soils and if this compromises safe food and feed production. The goals of this work are (1) to study the effects of concentrations of key trace elements (e.g., As, Cd, Co, Cr, Cu, Mn, Ni, Pb, Se, and Zn) found in broiler litter on nitrogen transformation in litter amended soils, (2) to assess the effects of temperature on the nitrogen transformation in the presence of trace elements and (3) to assess the fate of trace elements in sudax (Sorghum bicolor) grown in trace element-enriched broiler litter amended soils.	USDA
Longnecker, M	NIEHS, NIH	Evaluate the use of toenail levels as a measure of exposure by analyzing toenail and whole-diet homogenates by neutron activation analysis. Toenails reflect exposure over a longer period of time than do blood or urine measures, and are less likely to be influenced by contamination than hair.	NIEHS

Table 6-9. Ongoing Studies on Cobalt

Investigator	Affiliation	Research description	Sponsor
Saito, MA	Woods Hole Oceanographic Institution, Woods Hole, MA	This research will examine the influence of cobalt and cadmium speciation on *Synechococcus* and *Crocosphaera* at two sites in the Pacific Ocean. In addition, the distribution of cobalt across transects in the Eastern Equatorial Pacific will be determined to improve understanding of the global biogeochemical cycle of cobalt.	NSF
Tavlarides, LL	Syracuse University, Syracuse, New York	This work will be towards the development of sol-gel synthesis methods for organo-ceramic adsorbants for the extraction of toxic and valuable metal ions, such as cobalt, chromium, and arsenic ions from aqueous streams.	NSF

NIEHS = National Institute of Environmental Health Sciences; NIH = National Institute of Health; NSF = National Science Foundation USDA = U.S. Department of Agriculture; USDOE = U.S. Department of Energy

7. ANALYTICAL METHODS

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

7.1 BIOLOGICAL MATERIALS

Entry of cobalt and its radioisotopes into the human body can be gained through ingestion, inhalation, or penetration through skin. The quantities of cobalt within the body can be assessed through the use of bioassays that are comprised of either *in vivo* and/or *in vitro* measurements. *In vivo* measurements can be obtained through techniques that directly quantitate internally deposited cobalt using, for example, whole body counters. These *in vivo* measurement techniques are commonly used to measure body burdens of cobalt radioisotopes (i.e., ^{60}Co), but cannot be used to assess the stable isotope of cobalt (^{59}Co). Instead, *in vitro* measurements provide an estimate of internally deposited cobalt (both the stable and radioactive isotopes), utilizing techniques that measure cobalt in body fluids, feces, or other human samples. Examples of these analytical techniques are given in NRCP Report No. 87 (1987) and are also listed in Tables 7-1 and 7-2.

7.1.1 Internal Cobalt Measurements

In vivo measurement techniques are the most direct and widely used approach for assessing the burden of cobalt radioisotopes within the body. The *in vivo* measurement of these radioisotopes within the body is

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Direct injection	GF-AAS with Zeeman background correction	0.3 µg/L	101% at 40µg/L	Bouman et al. 1986
	Addition of magnesium nitrate and nitric acid matrix modifiers and equal volume dilution of sample with water	GF-AAS with Zeeman background correction	2.4 µg/L	107.6% at 50 µg/L	Kimberly et al. 1987
	Sample chelated with dithiocarbamic acid derivative, solvent extracted	GF-AAS with Zeeman background correction	0.1 µg/L	No data	Alexandersson 1988; Ichikawa et al. 1985
	Sample wet digested with acid and chelated with 2,3-butanedion dioxide and complex preconcentrated at hanging mercury drop electrode	DPCSV	0.2 µg/L	No data	Heinrick and Angerer 1984
	Direct injection	GF-AAS with Zeeman background correction	0.1 µg/L	No data	Sunderman et al. 1989
Whole blood	Sample diluted with a homogenizer	GF-AAS with D_2 background correction	2 µg/L	No data	Heinrick and Angerer 1984
	Sample wet digested with acid and chelated with 2,3-butanedion dioxine and complex preconcentrated at hanging mercury drop electrode	DPCSV	0.8 µg/L	No data	Heinrich and Angerer 1984
	Sample acid digested, complexed with thiocyanate and N-phenylcinnamo-hydroxamic acid and extracted into ethyl acetate	Colorimetric	0.15 mg/L	No data	Afeworki and Chandravanshi 1987
Serum	Direct injection	GF-AA with Zeeman background correction	0.02 µg/L	No data	Sunderman et al. 1989

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood or tissue	Acid digestion	ICP-AES (NIOSH method 8005)	10 µg/g (blood); 0.2 µg/g (tissue)	81% at 110 µg/L (blood)	NIOSH 1984

D_2 = deuterium; DPCSV = differential pulse cathodic stripping voltammetry; GF-AAS = graphite furnace atomic absorption spectrometry; ICP-AES = inductively coupled plasma-atomic emission spectrometry; NIOSH = National Institute for Occupational Safety and Health

Table 7-2. Analytical Methods for Determining Radioactive Cobalt in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Urine	Direct count of sample	γ-spectrometry with NaI detector	No data (<MDL)	No data	Miltenberger et al. 1981
Soft tissue	Sample wet-ashed	γ-spectrometry (NaI)	No data	No data	Baratta et al. 1969
	Sample directly counted in detector	γ-spectrometry	5 pCi/g	No data	Rabon and Johnson 1973
	Sample digested in acid, oxidized with $HClO_4$, concentrated by precipitation with AMP, purified by resin column, precipitated with hexachloroplatinic acid	-counter	0.1 pCi/g	40–85%	Nevissi 1992
Feces	Direct count of sample	γ-spectrometry	No data	No data	Smith et al. 1972
Blood	Red cells separated from plasma and washed	γ-spectrometry with NaI detector	No data	No data	Smith et al. 1972

[a]1 Bq=2.7×10^{-11} Ci=27 pCi

AMP = ammonium molybdophosphate; MDL = minimum detectable level; NaI = sodium iodide

performed with various radiation detectors and associated electronic devices that are collectively known as whole body counters. These radiation detectors commonly utilize sodium iodide (NaI), hyperpure germanium, and organic liquid scintillation detectors to measure the 1,172 and 1,332 keV gamma rays from the decay of ^{60}Co. Because of the relatively low attenuation of the high energy gamma rays emitted from ^{60}Co by most tissues, cobalt radioisotopes can easily be detected and quantified using whole body counting techniques (Lessard et al. 1984; NCRP 1987; Raghavendran et al. 1978; Smith et al. 1972; Sun et al. 1997). Many configurations of the whole body counter and scanning methods have been utilized, ranging from unshielded single-crystal field detectors to shielded, multi-detector scanning detectors (IAEA 1962, 1970, 1972, 1976, 1985; NCRP 1987). Where appropriate, shielding of the room that houses the whole body counter and/or the detector is often used to increase the detection sensitivity of the equipment by minimizing background radiation. Additionally, care must be exercised to insure that external contamination with radioactive cobalt or other gamma-emitting radioisotopes on the clothing or skin of the individual to be scanned has been removed. Also, *in vitro* measurements of cobalt (see Section 7.1.2) are often used in conjunction with whole body counting when monitoring individuals working with cobalt, especially in conjunction with the assessment of individuals who have experienced accidental exposures to cobalt (Bhat et al. 1973).

Calibration of whole body counters is achieved through the use of tissue-equivalent phantoms. These phantoms are constructed to mimic the shape and density of the anatomical structure using tissue equivalent materials such as water-filled canisters or masonite (Barnaby and Smith 1971; Bhat et al. 1973; Sun et al. 1997). For example, the bottle mannequin absorber (BOMAB) consists of a series of water-filled polyethylene canisters constructed into seated or reclined human forms (Sun et al. 1997). ^{60}Co standards are measured either as point sources along the phantom or dissolved within the water-filled canisters. Comparisons of the actual counts obtained from the phantom to the known activity of the cobalt standards are used to determine the efficiency of the counting technique and, thus, provide the basis for calibrating the technique. Even so, differences in whole body measurement techniques, calibration methods, and background radiation count calculations between different laboratories can complicate the direct comparisons of body burden measurements and clearance rates for cobalt radioisotopes and should be taken into consideration when comparing data obtained from independent laboratories.

7.1.2 External Measurements

In vitro analyses of cobalt are routinely performed in situations where *in vivo* analyses can not be obtained or in support of an *in vivo* monitoring program. Urine and feces are the preferred samples for *in vitro* analyses of cobalt, although other sample types, such as tissue, bone, or blood, can also be used on a more limited basis. Urine provides for an analysis of soluble (inorganic) cobalt, fecal analysis can be used to assess the cobalt (organic) that is eliminated into the gut or the fraction of ingested cobalt not absorbed by the gut, and tissue/blood/bone are used to assess whole or regional body burdens of cobalt (NCRP 1987; Smith et al. 1972).

The analytical methods for determining the stable cobalt isotope, ^{59}Co, in biological matrices are given in Table 7-1. For accurate determination of cobalt, contamination of samples during sample collection, storage, and treatment must be avoided, particularly for biological samples containing low levels of cobalt. Cobalt contamination in blood samples has been reported from disposable syringes and technical-grade anticoagulants. Menghini needles, often used for liver biopsy, and mortar, pestles, and grinding devices used for homogeneous mixing may contaminate samples. Other sources of contamination may be collection and storage containers and chemical reagents used for preparing samples. In fact, sample contamination was responsible for erroneous reports in the earlier literature of grossly high levels of cobalt in biological specimens of unexposed persons. Therefore, blanks should always be run with the samples.

The commonly used classical methods for determining stable cobalt in biological samples are polarographic and colorimetric methods. Details about these methods are given by Saltzman and Keenan (1957). Since these older methods have interference problems and are unsuitable for determining low levels of cobalt in many biological samples, the samples are pretreated before quantification. Precipitation, chelation, chromatography, and ion-exchange are some of the methods used for this purpose. In recent years, the two single-element instrumental techniques most frequently used methods for determining cobalt are graphite furnace-atomic absorption spectrometry (GF-AAS) (also called electrothermal atomic absorption spectrometry) and differential pulse anodic stripping voltammetry (DPAVS). Multi-element techniques commonly used for cobalt determination are neutron activation analysis and inductively coupled plasma-atomic emission spectrometry (ICP-AES). Several other methods are available for determining stable cobalt in biological samples; these include x-ray fluorescence and Spark source mass spectrometry (Adeloju et al. 1985; Smith and Carson 1981).

For the *in vitro* analysis of cobalt radioisotopes in human samples, the majority of the analytical methods measure the cobalt radioisotopes directly in the samples, without the requirement for an extensive sample preparation procedure, using gamma spectrometry techniques. Of the cobalt radioisotopes that have been detected in the environment (e.g., ^{57}Co, ^{58}Co, and ^{60}Co), ^{60}Co is the most common. Consequently, most of the analytical methods that will be described in this chapter are those developed for the detection and quantitation of ^{60}Co in biological (see Table 7-2) and environmental samples (see Table 7-4).

The radiochemical analysis of ^{60}Co in urine has been used in conjunction with whole body scanning methods to assess acute and long-term body burdens of this isotope. The analysis of ^{60}Co in urine is the same as that described for a standardized method of analysis of cesium radioisotopes in urine (Gautier 1983). A urine sample of approximately 2 L is collected (either over 24 hours or before and after bedtime) and a 1-L aliquot is transferred to a Marinelli beaker for counting in a gamma-ray spectrometer (Gautier 1983). This simple procedure offers high recoveries of cobalt (98%) and the minimum detection sensitivity (100 pCi/L [3.7 Bq/L]) that is required to evaluate individuals for exposures to radioactive cobalt (Gautier 1983). Direct counting methods are also used for the analysis of cobalt radioisotopes in tissues, feces, and blood (Smith et al. 1972, Table 7-2). However, some of these methods may require sample preparation to reduce volume or increase concentration.

Accuracy of *in vivo* and *in vitro* measurements of cobalt is determined through the use of standard, certified solutions or radioactive sources with known concentrations or activities of cobalt. Certified standards for stable cobalt can be obtained through a number of commercial sources. The primary source of certified cobalt radioisotope standards is the National Institute of Standards and Technology (NIST). Gamma ray point sources for ^{60}Co (SRM 4200, 60,000 Bq [1.6 μCi] and SRM 4207, 300,000 Bq [56 μCi]) and standard solutions of ^{60}Co (SRM 4233, 600,000 Bq/g [16 μCi/g]) are available from NIST. Also, the determination of accuracy of a method often requires standard reference materials (SRMs). Unfortunately, very few biological SRMs are available. An SRM for cobalt in animal muscle is available from the International Atomic Energy Agency (IAEA), Vienna; an SRM for bovine liver (SRM-1577) is available from NIST (formerly the National Bureau of Standards) (Adeloju et al. 1985; Smith and Carson 1981).

7.2 ENVIRONMENTAL SAMPLES

There are two common approaches for measuring cobalt in the environment. Cobalt radioisotopes can either be measured directly in the field (*in situ*) using portable survey instruments or samples can be procured from the field and returned to the laboratory for quantitation. However, quantitation of the stable cobalt isotope ^{59}Co in environmental samples is generally conducted in the laboratory.

7.2.1 Field Measurements of Cobalt

In situ measurement techniques are extremely useful for the rapid characterization of radionuclide contamination in the environment, such as soils, sediments, and vegetation, or when monitoring personnel for exposure to radionuclides. The measurement of gamma-ray-emitting radionuclides, like cobalt, in the environment is conducted with portable survey instruments such as Gieger-Mueller detectors, sodium iodide scintillation detectors, and gamma-ray spectrometers. However, the use of gamma-ray spectrometers in field survey equipment is preferred for measuring cobalt in the field because of its selectivity and sensitivity. The relatively high energy and penetrability of the gamma ray that is emitted during the decay of ^{60}Co provides an advantage for assessing the level of cobalt both on and below the surface using portable field survey instruments such as the gamma-ray spectrometer. These gamma-ray spectrometers are equipped with a high purity germanium detector that is able to selectively and sensitively differentiate the 1,173 and 1,332 keV gamma rays emitted from ^{60}Co from the gamma-rays emitted from other radionuclides, for example ^{40}K or ^{137}Cs (USNRC 1997). Minimum detectable activities (MDAs) of 0.005 Bq/g (0.05 pCi/g) for ^{60}Co are routinely achieved using p-type germanium gamma-ray spectrometers with 10-minute counting times (USNRC 1997). However, counting errors can occur where the simultaneous detection of the 1,173 and 1,332 keV gamma rays produces a sum peak at 2,505 keV or a count in the continuum between the individual peaks and the sum peak (APHA 1998; USNRC 1997). These errors can be minimized by changing the geometry of the detector or the distance of the detector from the source of radioactivity. Computational methods have been derived to aid in determining the concentrations and distributions of ^{60}Co in different soil types and depths (USNRC 1997). The concentrations and distributions of ^{60}Co that have been derived from the computational analysis of the survey data are often verified by laboratory-based analyses of soil samples procured from the survey area.

7.2.2 Laboratory Analysis of Environmental Samples

Analytical methods for quantifying stable cobalt and cobalt radioisotopes in environmental samples (e.g. air, water, soil, and biota) are summarized in Tables 7-3 (^{59}Co) and 7-4 (^{60}Co). The methods that are commonly used in the analysis of stable cobalt are based on instrumental analytical techniques, such as atomic absorption spectrometry (AAS), instrumental neutron activation analysis (INAA), and mass spectrometry (MS). The analysis of ^{60}Co can be determined either as total mass or total activity, depending on the analytical technique that is used. Typically, radiochemical methods of analysis employing gamma-ray spectrometry techniques are used to quantitate ^{60}Co in environmental samples.

Analytical methods for determining stable cobalt in environmental samples are given in Table 7-3. Since cobalt exists in the particulate form in the atmosphere, it is sampled by drawing air through a metal-free filter (usually cellulose ester membrane), and the metal is quantified in the collected particles. Sample treatment prior to quantification is important for environmental samples. For example, the use of sodium carbonate for dry ashing plant materials results in poor cobalt recovery. Low-temperature ashing may be inadequate for some samples, and losses may occur during rigorous dry ashing. Wet ashing is the preferred method when sample treatment is necessary. Wet extraction with dilute nitric acid is most suitable for analyzing cobalt in dust samples. In some samples, the determination of soluble and insoluble cobalt is important, and analytical methods used to determine cobalt in filtered and unfiltered samples are available for this purpose.

As in the case of biological samples, contamination of environmental samples during sample collection, storage, and treatment should be avoided. Loss of cobalt from aqueous samples due to adsorption on storage containers should be avoided by using polyethylene or similar containers and acidifying the solution to the proper pH (Smith and Carson 1981). Because of its rapidity, accuracy, and low detection limit, GF-AAS with Zeeman background correction is the most commonly used method for quantifying cobalt in environmental samples. To meet the detection limits of the available analytical methods, preconcentration prior to quantification may be necessary for some samples (e.g., seawater). A few commonly used methods for determining cobalt in environmental samples are given in Table 7-3. Other less frequently used methods are inductively coupled plasma-mass spectrometry (ICP-MS) (Henshaw et al. 1989; McLaren et al. 1985), gas, liquid, and ion chromatography with colorimetric, electron capture, and electrochemical detection (Bond and Wallace 1984; Carvajal and Zienius 1986; Cheam and Li 1988; King and Fritz 1987; Schaller and Neeb 1987), photoacoustic spectroscopy with colorimetry (Kitamori

Table 7-3. Analytical Methods for Determining Stable Cobalt in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (workplace)	Weighed filter irradiated in a reactor	INAA	0.17 µg/m^3	No data	Haddad and Zikovsky 1985
	Sample filter digested by wet acid ashing	Flame-AAS with background correction (NIOSH method 7027)	0.4 µg/m^3	98% with 12–96 µg spiked filter	NIOSH 1984
	Sample filter digested by wet acid ashing	ICP-AES (NIOSH method 7300)	0.5 µg/m^3	95–100% with 2.5–1,000 spiked filter	NIOSH 1984
Water (low ionic strength)	Direct injection	GF-AAS with Zeeman or deuterium back-ground correction	<0.5 µg/L	93–115% at 8.5–30 µg/L	Fishman et al. 1986
Lake water	Sample complexed with 8-hydroxyquinoline absorbed on a column, desorbed and digested with acid	ICP-AES	<0.004 µg/L	No data	Nojiri et al. 1985
Rainwater	Sample preconcentrated onto polystyrene films by spray-drying	PIXE	0.08 µg/L	No data	Hansson et al. 1988
Seawater	Sample complexed with 8-hydroxyquinoline absorbed on a column, desorbed and digested with acid	GF-AAS with Zeeman back-ground correction	0.0002 µg/L	90%	Nakashima et al. 1988
Water and waste water	Direct aspiration of sample	Flame-AAS (EPA method 219.1)	0.05 mg/L	97–98% at 0.2–5.0 mg/L	EPA 1983
	Direct injection	GF-AAS with background correction (EPA method 219.2)	1 µg/L	No data	EPA 1983
Groundwater or leachate	Direct aspiration	Flame-AAS with background correction (EPA method 7200)	0.05 mg/L	97–98% at 0.2–5.0 mg/L	EPA 1986b
Groundwater or leachate	Direct injection	GF-AAS with background correction (EPA method 7201)	1 µg/L	No data	EPA 1986b

Table 7-3. Analytical Methods for Determining Stable Cobalt in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Sample digested with acid	GF-AAS with background correction	1.88 µg/L in dissolved extract	100–107% at 0.2–0.6 mg/kg (leaves, liver)	Barbera and Farre 1988
Milled Wheat	Wet ashing (HNO_3), preconcentration and chelation	ET-AAS	20 ng/L	approximately 100%	González et al. 2000

AAS = atomic absorption spectrometry; EPA = Environmental Protection Agency; ET-AAS = electrothermal atomic absorption spectrometry; GF-AAS= graphite furnace atomic absorption spectrometry; ICP-AES = inductively coupled plasma-atomic emission spectrometry; INAA = instrumental neutron activation analysis; NIOSH = National Institute for Occupational Safety and Health; PIXE = photon induced x-ray emission

Table 7-4. Analytical Methods for Determining Radioactive Cobalt in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Air	Direct count of sample collected on paper filter	γ-spectrometry with Ge/Li detector	0.001 pCi/m^3	No data	USAEC 1974a
Air	Sample filter ashed	Scintillation counter with NaI detector	No data	No data	De Franceschi et al. 1974
Drinking water	Direct count of sample	γ-spectrometry with Ge detector	<2 pCi/L	99%	APHA 1998
Drinking water	Direct count of sample	γ-spectrometry	2 pCi/L	No data	USAEC 1974b
Water	Direct count of sample	γ-spectrometry with Ge/Li detector	2 pCi/L	No data	ASTM 1999
Water	Direct count of sample	γ-spectrometry	10 pCi/L	No data	Cahill et al. 1972
Seawater	Sample concentrated using continuous-flow coprecipitation-flotation separation technique	Scintillation detector	50 fCi/L	92–95%	Hiraide et al. 1984
Sediments	Sample dried and ground	γ-spectrometry	0.04 pCi/g	No data	Cahill et al. 1972
Fish	Samples dried and ashed	γ-spectrometry	0.001 pCi/g (DW)	No data	Cushing et al. 1981
Mollusc	Samples dried and ashed	γ-spectrometry	<0.01 pCi/g	No data	De Franceschi et al. 1976

[a]1 Bq=2.7×10^{-11} Ci=27 pCi

DW = dry weight; Ge/Li = lithium drifted geranium; NaI = sodium iodide

et al. 1986), electrothermal vaporization with ICP-AES (Malinski et al. 1988) and chemiluminescence with spectrofluorimetry (Jones et al. 1989).

Analytical methods for determining cobalt radioisotopes in the environment are shown in Table 7-4. The analysis of cobalt in air is based on quantifying cobalt within aerosols or particles that become trapped on cellulose (paper) or glass fiber filters after a calibrated amount of air is passed through the filters. Since the cobalt radioisotopes do not occur naturally, but may be released as a result of nuclear weapons testing (which has been discontinued for several years), neutron-activation of specific materials (e.g., cobalt containing alloys used in piping of nuclear reactors), or a severe core damage accident in a nuclear plant, the amounts of these isotopes within the ambient environment are near or below the minimum detectable levels for these isotopes (DOE 1995). However, trace amounts of ^{60}Co can be detected in air, water, and sediments within or near nuclear weapons or fuel production facilities, nuclear reactors, and nuclear waste storage sites (DOE 1995; Boccolini et al. 1976; USAEC 1973). Analysis of cobalt radioisotopes in air filters, water, sediments, vegetation, and biota can be performed directly using gamma-ray spectrometry, or following some sample preparation (e.g., drying, ashing, or extraction) (Boccolini et al. 1976; Cahill et al. 1972; Cushing 1981; Hiraid et al. 1984; Windham and Phillips 1973).

The detection limits, accuracy, and precision of any analytical methodology are important parameters in determining the appropriateness of a method for quantifying a specific analyte at the desired level of sensitivity within a particular matrix. The Lower Limit of Detection (LLD) has been adopted to refer to the intrinsic detection capability of a measurement procedure (sampling through data reduction and reporting) to aid in determining which method is best suited for the required sample quantitation (USNRC 1984). Several factors influence the LLD, including background, size or concentration of sample, detector sensitivity and recovery of desired analyte during sample isolation and purification, level of interfering contaminants, and, particularly, counting time. Because of these variables, the LLDs between laboratories, utilizing the same or similar measurement procedures, will vary.

The accuracy of a measurement technique in determining the quantity of a particular analyte in environmental samples is greatly dependent on the availability of standard reference materials. Several SRMs for cobalt in environmental samples are also available. Some of these are coal, fly ash, diet, and orchard leaf SRMs available from NIST. The Community Bureau of Reference, European Communities offers SRMs for cobalt in sludges, and an SRM for cobalt in thin polymer films is available from NIST for x-ray fluorescence analysis in aerosol particle samples (Dzubay et al. 1988; Miller-Ihli and Wolf

1986; Schramel 1989; Smith and Carson 1981; Tinsley et al. 1983). Gamma ray point sources for ^{60}Co (SRM 4200, 60,000 Bq [1.6 μCi] and SRM 4207, 300,000 Bq [56 μCi]) and standard solutions of ^{60}Co (SRM 4233, 600,000 Bq/g [16 μCi/g]) are available from NIST.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cobalt 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 cobalt.

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

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Cobalt concentrations in blood or urine can serve as exposure indicator (Alexandersson 1988; Ichikawa et al. 1985; Scansetti et al. 1985). The available analytical methods are capable of determining the levels of cobalt in both the blood and urine of normal and occupationally exposed persons (Table 7-1). For the quantitation of cobalt radioisotopes, whole body counters can be used to assess radioactive cobalt body burdens that have occurred both from acute and chronic exposures to cobalt radioisotopes (Bhat et al. 1973; NCRP 1987). *In vitro* analytical methods are available for analyzing cobalt radioisotopes in urine, feces, and tissues obtained from normal and occupationally exposed persons (Table 7-2).

Sensitive serum protein responses were found in animals exposed to cobalt at levels below those that produce hematopoietic effects. This unique serum protein response to cobalt exposure includes an increase in alpha globulin fractions of serum proteins and associated serum neuraminic acid. Details of this effect are given in Chapters 2 and 3. If similar changes occur in humans, this measurement may provide the earliest indications of effects of cobalt exposure. The available analytical methods are capable of determining these effects of cobalt exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods with good sensitivity and specificity are available for determining cobalt in air, water, soil, and other environmental media (Table 7-3). Analytical methods for cobalt, like those for most metals, measure total metal content rather than the particular compound. Therefore, analytical methods do not generally differentiate between the parent compound and a transformation product as would be the case, for example, were cobalt oxide to be converted to cobalt sulfate. (An exception to this would be the case of radioactive decay in which the parent could be readily distinguished from the decay product.) Analytical methods with the capability of distinguishing between different cobalt species would be important an important tool for assessing the fate of cobalt compounds in the environment. However, methods for quantifying specific cobalt compounds were not found in the literature.

The levels of the parent compound or its reaction products in different environmental media can be used to assess the exposure to cobalt by humans through the inhalation of air and ingestion of food and drinking water. In the case of cobalt, a correlation between its levels in environmental media (e.g., occupational air) and in biological tissues and body fluids has been found (Alexandersson 1988; Ichikawa et al. 1985; Scansetti et al. 1985). Therefore, it is possible to estimate the total body burden of cobalt in workers exposed to airborne cobalt vapor and fumes from its concentration in workplace air.

For cobalt radioisotopes, analytical methods also exist that have good sensitivity and specificity for determining radioactive cobalt in air, water, soil, and other environmental media are available (Table 7-4). Because ^{60}Co decays to the stable element ^{60}Ni, there is no need to develop methods to detect and quantify the decay products.

7.3.2 Ongoing Studies

Two studies involving analytical techniques for cobalt was listed in the Federal Research in Progress database (FEDRIP 2002, 2004). N.J. Miller-Ihli and co-workers of the Agricultural Research Service in Beltsville, Maryland are developing single and multielement methods for the determination of trace elements of nutritional and health concern. This work will develop new/improved methods permitting direct analysis of solids by GF-AAS and ICP-MS, as well as methods for the determination of different chemical forms of these elements by coupling capillary zone electrophoresis with inductively coupled plasma mass spectrometry (ICP-MS). This research is supported by the U.S. Department of Agriculture (USDA) Agricultural Research Service. B.T. Jones of Wake Forest University in Winston-Salem, North Carolina along with C. Calloway of Winthrop College, South Carolina, are working to develop a novel, low-cost, portable instrument for the simultaneous determination of trace radioactive elements in nuclear forensic samples. The instrument to be developed is expected to provide analytical figures comparable to ICP-MS, but the instrument is much lower cost and more portable. The specific objectives of the project include determination of the analytical figures of merit for elements including cobalt, cesium, and strontium, and analysis of real samples such as soil, urban dust, water, and agricultural materials.

8. REGULATIONS AND ADVISORIES

International and national guidelines and state regulations regarding exposure to stable cobalt and its compounds are summarized in Table 8-1. The regulations regarding radioactive cobalt are summarized in Table 8-2.

Stable Cobalt. An MRL of $1x10^{-4}$ mg cobalt/m^3 has been derived for chronic-duration inhalation exposure. The MRL is based on a NOAEL of 0.0053 mg cobalt/m^3 for decreased respiratory function in exposed workers (Nemery et al. 1992). An MRL of $1x10^{-2}$ mg/kg-day has been derived for intermediate-duration oral exposure, based on a LOAEL of 1 mg/kg-day for polycythemia in human volunteers (Davis and Fields 1958). No other inhalation or oral MRLs were derived.

The EPA has not derived an RfC or RfD for cobalt and compounds. Similarly, no cancer classification has been performed by the EPA (IRIS 2000). The American Conference of Governmental Industrial Hygienists (ACGIH) has given cobalt a classification of A3, *confirmed animal carcinogen with unknown relevance to humans*, and established an 8-hour time-weighted average (TWA) of 0.02 mg/m^3 for occupational exposure (ACGIH 2000). The Occupational Safety and Health Administration (OSHA) has promulgated an 8-hour permissible exposure limit (PEL) of 0.1 mg/m^3 (OSHA 2001e), and the National Institute for Occupational Safety and Health (NIOSH) recommends an 8-hour TWA of 0.05 mg/m^3 (NIOSH 2001). IARC (2001b) reports that cobalt and cobalt compounds are *possibly carcinogenic to humans* (Group 2B), based on sufficient evidence for cobalt metal and cobalt oxides and limited evidence for cobalt chloride and cobalt sulfate.

Cobalt and its compounds are regulated by the Clean Water Effluent Guidelines for the following industrial point sources: nonferrous metal manufacturing, asbestos, timber products processing, paving and roofing, paint formulating, ink formulating, gum and wood, carbon black, and battery manufacturing (EPA 1988).

Radioactive Cobalt. No MRLs were derived for inhalation or oral exposure to radioactive cobalt. MRLs for acute and chronic exposure to ionizing radiation exist (Agency for Toxic Substances and Disease Registry 1999) and are applicable to cobalt. The EPA has not derived an RfC or RfD for radioactive

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2001b
	Cobalt and cobalt compounds[a]	Group 2B[b]	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA		ACGIH 2000
	Cobalt, elemental, and inorganic compounds (as Co)	0.02 mg/m^3	
NIOSH	REL (TWA)		NIOSH 2001
	Cobalt metal, dust, and fumes (as Co)	0.05 mg/m^3	
	IDLH		
	Cobalt metal, dust, and fumes (as Co)	20 mg/m^3	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2001e 29CFR1910.1000 Table Z
	Cobalt metal, dust, and fumes (as Co)	0.1 mg/m^3	
	PEL (8-hour TWA) for construction industry		OSHA 2001d 29CFR1926.55
	Cobalt metal, dust, and fumes (as Co)	0.1 mg/m^3	
	PEL (8-hour TWA) for shipyard industry		OSHA 2001c 29CFR1915.1000
	Cobalt metal, dust, and fumes (as Co)	0.1 mg/m^3	
USC	HAP (cobalt compounds)		USC 2001a 42USC7412
b. Water			
EPA	NPDES permit application testing requirements; conventional and nonconventional pollutants required to be tested by existing dischargers if expected to be present		EPA 2001g 40CFR122 Appendix D Table IV
	BPT effluent limitations		EPA 2001b 40CFR415.652
	Maximum for 1 day	3x10^{-4} kg/kkg	
	Average of daily values for 30 consecutive days	1.2x10^{-4} kg/kkg	
	Groundwater monitoring		EPA 2001d 40CFR264 Appendix IX
	Suggested method	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
NATIONAL (cont.)			
c. Food			
FDA	Drug products withdrawn or removed from the market for reasons of safety or effectiveness	All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives)	FDA 2000a 21CFR216.24
	New drug status accorded through rulemaking procedures	Cobalt preparations intended for use by man	FDA 2000b 21CFR310.502 (a)(7)
	Over-the-counter drugs; recommended warning and caution statement for cobalt as a cobalt salt	Required on articles containing ≥0.5 µg per dose and ≥2 µg per 24-hour period	FDA 2000e 21CFR369.20
	Substances generally recognized as safe; trace minerals added to animal feeds	Cobalt acetate Cobalt carbonate Cobalt chloride Cobalt oxide Cobalt sulfate	FDA 2000f 21CFR582.20
	Substances prohibited from use in human food	Cobaltous salts and its derivatives	FDA 2000g 21CFR189.120
d. Other			
ACGIH	Carcinogenicity classification Cobalt, elemental, and inorganic compounds (as Co)	 A3[c]	ACGIH 2000
	BEI Cobalt in urine—end of shift at end of workweek Cobalt in blood—end of shift at end of workweek	 15 µg/L 1 µg/L	
EPA	Carcinogenicity classification RfC RfD	No data	IRIS 2000
	Toxic chemical release reporting; Community Right-to-Know; effective date	01/01/87	EPA 2001c 40CFR372.65(a)
	Hazardous waste; identification and listing	Contain ≤1 ppmv in synthesis gas fuel generated from hazardous waste	EPA 2001e 40CFR261.38 (b)(5)
	TSCA; health and safety data reporting		EPA 2001j 40CFR716.120
EPA	Municipal solid waste landfills; hazardous constituent for detection monitoring Suggested method 6010 7200 7201	 PQL 70 µg/L 500 µg/L 10 µg/L	EPA 2001f 40CFR258 Appendix I and II
	Reportable quantity (cobalt compounds)	1 pound	EPA 2001h 40CFR302.4

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
NATIONAL (cont.)			
USC	Superfund imposition of tax on cobalt	$4.45 per ton	USC 2001c 26USC4661
	Exemption of tax imposed on recycled cobalt		USC 2001b 26USC4662
STATE Regulations and Guidelines			
a. Air			
Alabama	HAP (cobalt compounds)		BNA 2001
Alaska	Air contaminant standard (TWA)		BNA 2001
	Cobalt metal, dust, and fumes	0.05 mg/m^3	
California	Airborne contaminant (cobalt metal, dust, and fumes)		BNA 2001
	HAP (cobalt compounds)		BNA 2001
	Toxic air contaminant (cobalt compounds)		CA Air Resources Board 2000
Colorado	HAP (cobalt metal, dust, and fumes)		BNA 2001
	"High-concern" pollutant (cobalt and compounds)		BNA 2001
	Reportable pollutants (cobalt metal, dust, and fumes)		CO Dept. of Public Health and Environment 2000
Connecticut	HAP—hazard limiting value (cobalt metal, dust, and fumes)		BNA 2001
	8 hours	2 µg/m^3	
	30 minutes	10 µg/m^3	
Delaware	Reportable quantities		DE Air Quality Management 2000
	Cobalt carbonyl	1 pound	
	Cobaltous sulfamate	1,000 pounds	
	Cobalt, ((2,2'-(ethane-diylbis(nitrilomethylidyne)	1 pound	
Hawaii	Air contaminant limit (PEL-TWA)		BNA 2001
	Cobalt metal, dust, and fumes	0.05 mg/m^3	
	HAP (cobalt compounds)		BNA 2001
Idaho	TAP non-carcinogenic increments		ID Dept. of Environmental Quality 2000
	Cobalt carbonyl and cobalt hydrocarbonyl (as Co)		
	OEL	1x10^{-1} mg/m^3	
	EL	7x10^{-3} pounds/hour	
	AAC (24-hour average)	5x10^{-3} mg/m^3	
	Cobalt metal, dust, and fumes		
	OEL	5x10^{-2} mg/m^3	
	EL	3.3x10^{-3} pounds/hour	
	AAC (24-hour average)	2.5x10^{-3} mg/m^3	
Illinois	Toxic air contaminant (cobalt)		IL EPA 2000a
Kansas	HAP (cobalt compounds)		KS Dept. of Health and Environment 2000

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
STATE (cont.)			
Kentucky	HAP (cobalt compounds)		BNA 2001
Louisiana	Toxic air pollutant (cobalt compounds		BNA 2001
Maine	Emissions standards	2,000 pounds	BNA 2001
Maryland	Toxic air pollutant (cobalt compounds)		BNA 2001
Michigan	High concern toxic air pollutants (cobalt compounds)		BNA 2001
Minnesota	HAP threshold (cobalt metal and cobalt carbonyl)	0.1 tons/year	BNA 2001
Missouri	HAP (cobalt compounds)		BNA 2001
Montana	Occupational air contaminant (cobalt metal, dust, and fumes)	0.1 mg/m^3	BNA 2001
Nebraska	HAP (cobalt compounds and cobalt)		BNA 2001
New Mexico	Toxic air pollutant (cobalt metal, dust, and fumes [as Co])		BNA 2001
	OEL	$1x10^{-1}$ mg/m^3	
	Emissions	$6.67x10^{-3}$ pounds/hour	
New York	Annual guideline concentrations	$5x10^{-3}$ $\mu g/m^3$	NYS Dept. of Environmental Conservation 2000
	Dangerous air contaminants (TLV) for cobalt metal, dust, and fumes	0.1 mg/m^3	BNA 2001
	HAP (cobalt compounds)		BNA 2001
	Transition limits (PEL)		BNA 2001
	Cobalt metal, dust, and fumes	0.1 mg/m^3	
	Final rule limits (TWA)		
	Cobalt metal, dust, and fumes	0.05 mg/m^3	
North Carolina	PEL-TWA (cobalt metal, dust, and fumes)	0.05 mg/m^3	BNA 2001
Ohio	TRI		Ohio EPA 2000
Oregon	Air contaminant (cobalt metal, dust, and fumes)	0.1 mg/m^3	BNA 2001
Rhode Island	HAP (cobalt compounds)		BNA 2001
South Carolina	Toxic air emissions (MAC) for cobalt compounds	0.25 $\mu g/m^3$	BNA 2001
Texas	HAP (cobalt metal, dust, and fumes)	0.1 mg/m^3	BNA 2001
Vermont	HAP (cobalt compounds)		BNA 2001
	Hazardous ambient air standards		BNA 2001
	Cobalt compounds		
	Annual average	0.12 $\mu g/m^3$	
	Averaging time	24 hours	
	Action level	$6.2x10^{-3}$ pounds/8 hours	
Washington	Class B TAP and ASIL (24-hour average)		WA Dept. of Ecology 2000
	Cobalt metal, dust and fumes	0.17 $\mu g/m^3$	
	Cobalt carbonyl and cobalt hydrocarbonyl	0.33 $\mu g/m^3$	

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
STATE (cont.)			
	Thresholds for HAPs		BNA 2001
	Cobalt carbonyl	0.1 tons/year	
	Cobalt metal, dust, and fumes	0.1 tons/year	
Wisconsin	HAP—existing sources		WI Dept. of Natural Resources 1999
	AAC <25 feet	4.08×10^{-3} pounds/hour	
	AAC ≥25 feet	1.704×10^{-2} pounds/hour	
b. Water			
Alabama	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
Arizona	Drinking water guideline	0.70 µg/L	FSTRAC 1999
Arkansas	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
California	Chemicals known to cause cancer or reproductive toxicity; date of initial appearance on the list		Cal/EPA 2000
	Cobalt metal powder		
	Cobalt[II] oxide	07/01/92	
	Cobalt sulfate heptahydrate	07/01/92 06/02/00	
Colorado	Groundwater standard (cobalt)	0.05 mg/L	BNA 2001
Delaware	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
Illinois	Groundwater quality standards for Class II	1 mg/L	IL EPA 2000b
Kentucky	Hazardous waste constituent for groundwater monitoring (cobalt)		BNA 2001
Louisiana	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
Massachusetts	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
Minnesota	Drinking water guideline	2 µg/L	FSTRAC 1995
	Groundwater protection hazardous constituent for cobalt (total)		BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
STATE (cont.)			
Missouri	Water quality standards		BNA 2001
	Livestock, wildlife watering	$1x10^3$ µg/L	
	Groundwater	$1x10^3$ µg/L	
New Mexico	Standards for groundwater of 10,000 mg/L TDS concentration or less (cobalt)	0.05 mg/L	BNA 2001
New York	Groundwater monitoring (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
Tennessee	Effluent limitations—daily maximum concentration (cobalt)	10 mg/L	BNA 2001
Wisconsin	Drinking water guideline	40 µg/L	FSTRAC 1999
	Groundwater standards (cobalt)		BNA 2001
	Enforcement standard	40 µg/L	
	Preventive action limit	8 µg/L	
c. Food		No data	
d. Other			
Alabama	Detection limit values for comparable fuel specification for cobalt; concentration limit	4.6 mg/kg at 10,000 BTU/pound	BNA 2001
Arizona	Soil remediation levels (cobalt)		BNA 2001
	Residential	$4.6x10^3$ mg/kg	
	Non-residential	$9.7x10^4$ mg/kg	
Arkansas	Detection limit values for comparable fuel specification for cobalt; concentration limit	4.6 mg/kg at 10,000 BTU/pound	BNA 2001
	Solid waste management (cobalt)		BNA 2001
	Suggested methods	PQL	
	6010	70 µg/L	
	7200	500 µg/L	
	7201	10 µg/L	
California	Characteristics of toxicity for cobalt and cobalt compounds		BNA 2001
	STLC	80 mg/L	
	TTLC	8,000 mg/kg (wet-weight)	
	Chemicals known to cause cancer or reproductive toxicity (cobalt metal powder); initial appearance on the list	07/01/92	BNA 2001
	Hazardous substance (cobalt, cobalt carbonyl, and cobalt hydrocarbonyl)		BNA 2001
Delaware	Detection limit values for comparable fuel specification for cobalt; concentration limit	4.6 mg/kg at 10,000 BTU/pound	BNA 2001
Florida	Toxic substance in the workplace (cobalt metal, dust, and fumes)		BNA 2001
Georgia	Soil concentration (cobalt)	20 mg/kg	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
STATE (cont.)			
Illinois	Analytical parameters and required quantitation limits for cobalt Water Soil Method	 50 µg/L 10 mg/kg 6010A	BNA 2001
Indiana	Constituent subject to assessment monitoring (cobalt [total and dissolved])		BNA 2001
Maine	Screening standards for beneficial use (cobalt)	5,875 mg/kg (dry weight)	BNA 2001
Michigan	Identification and listing of hazardous waste (cobalt)	When in the form of 100 microns or less	BNA 2001
Minnesota	Hazardous substance Cobalt metal, dust, and fumes (as Co) Cobalt carbonyl (as Co) Cobalt, elemental and inorganic compounds (as Co) Cobalt hydrocarbonyl (as Co)		BNA 2001
Missouri	Hazardous constituent (cobalt [total])		BNA 2001
New Jersey	Hazardous substance Cobalt Cobalt carbonyl Cobalt compounds		BNA 2001
New York	Occupational lung disease; hard metal disease	Cobalt	BNA 2001
Ohio	Toxic release inventory		BNA 2001
Oklahoma	Fertilizer labels and labeling; minimum percentage accepted for registration (cobalt)	$5x10^{-4}$ percent	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Stable Cobalt

Agency	Description	Information	Reference
Oregon	Toxic substance (cobalt)		BNA 2001
Pennsylvania	Hazardous substance (cobalt and cobalt fumes)		BNA 2001

[a]Cobalt compounds: includes cobalt(II) carbonate, cobalt(II) chloride, cobalt(II) nitrate, cobalt(II) oxide, cobalt(II,III) oxide, cobalt(III) oxide, and cobalt(II) sulfate
[b]Group 2B: possibly carcinogenic to humans
[c]A3: confirmed animal carcinogen with unknown relevance to humans

AAC = acceptable ambient concentrations; ACGIH = American Conference of Governmental Industrial Hygienists; ASIL = acceptable source impact level; BEI = biological exposure indices; BNA = Bureau of National Affairs; BPT = best practicable control technology; BTU = British thermal unit; CFR = Code of Federal Regulations; EL = emissions levels; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FSTRAC = Federal-State Toxicology and Risk Analysis Committee; HAP = hazardous air pollutant; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IRIS = Integrated Risk Information System; MAC = maximum allowable concentration; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation limit; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; STLC = soluble threshold limit concentrations; TAP = toxic air pollutant; TDS = total dissolved solids; TLV = threshold limit value; TRI = Toxic Release Inventory; TSCA = Toxic Substances Control Act; TTLC = total threshold limit concentrations; TWA = time-weighted averages; USC = United States Code

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information	Reference
INTERNATIONAL Guidelines:			
IARC	Carcinogenicity classification	Group 1 (carcinogenic to humans)	IARC 2001b
ICRP	Occupational dose limits; effective dose	20 mSv per year, averaged over defined periods of 5 years	ICRP 1991
	Annual equivalent dose		
	Lens of the eye	150 mSv	
	Skin	500 mSv	
	Hands and feet	500 mSv	
	General population dose limits; effective dose	1 mSv in a year	ICRP 1991
	Annual equivalent dose		
	Lens of eye	15 mSv	
	Skin	50 mSv	
WHO	Drinking water quality	No data	
NATIONAL Regulations and Guidelines:			
a. Air			
ACGIH	All radiation exposures must be kept as low as reasonably achievable		ACGIH 2000
	Effective dose		ACGIH 2000
	Any single year	50 mSv	
	Averaged over 5 years	20 mSv per year	
	Annual equivalent dose		
	Lens of the eye	150 mSv	
	Skin	500 mSv	
	Hands and feet	500 mSv	
	Embryo-fetus exposures once the pregnancy is known		
	Monthly equivalent dose	0.5 mSv	
	Dose to the surface of women's abdomen (lower trunk)	2 mSv for the remainder of the pregnancy	
	Intake of radionuclide	1/20 of the ALI	

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
DOE	Radiation standards			DOE 2000
	Inhalation DAC (µCi/mL)	Class Wa	Class Yb	10CFR835
	^{55}Co	$1x10^{-6}$	$1x10^{-6}$	Appendix A
	^{56}Co	$1x10^{-7}$	$8x10^{-8}$	
	^{57}Co	$1x10^{-6}$	$3x10^{-7}$	
	^{58}mCo	$4x10^{-5}$	$3x10^{-5}$	
	^{58}Co	$5x10^{-7}$	$3x10^{-7}$	
	^{60}mCo	$2x10^{-3}$	$1x10^{-3}$	
	^{60}Co	$7x10^{-8}$	$1x10^{-8}$	
	^{61}Co	$3x10^{-5}$	$2x10^{-5}$	
	^{62}mCo	$7x10^{-5}$	$7x10^{-5}$	
	Radiation standards for air immersion DACc (µCi/mL) for ^{60}mCo	1x10-3		DOE 2000 10CFR835 Appendix C
NIOSH	REL	No data		
USNRC	Effluent concentrations—air			USNRC 2001k
	^{55}Co	ALI (µCi/mL)		10CFR20
	Class Wd	$4x10^{-9}$		Appendix B
	Class Ye	$4x10^{-9}$		Table 2
	^{56}Co			
	Class Wd	$4x10^{-10}$		
	Class Ye	$3x10^{-10}$		
	^{57}Co			
	Class Wd	$4x10^{-9}$		
	Class Ye	$9x10^{-10}$		
	^{58}Co			
	Class Wd	$2x10^{-9}$		
	Class Ye	$1x10^{-9}$		
	^{58}mCo			
	Class Wd	$1x10^{-7}$		
	Class Ye	$9x10^{-8}$		
	^{60}Co			
	Class Wd	$2x10^{-10}$		
	Class Ye	$5x10^{-11}$		
	^{60}mCo			
	Class Wd	$6x10^{-6}$		
	Class Ye	$4x10^{-6}$		
	^{61}Co			
	Class Wd	$9x10^{-8}$		
	Class Ye	$8x10^{-8}$		
	^{62}mCo			
	Class Wd	$2x10^{-7}$		
	Class Ye	$2x10^{-7}$		

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
USNRC	Occupational values			USNRC 2001k
	Inhalation			10CFR20
	^{55}Co	ALI (µCi)	DAC (µCi/mL)	Appendix B
	Class Wd	$3x10^{3}$	$1x10^{-6}$	Table 1
	Class Ye	$3x10^{3}$	$1x10^{-6}$	
	^{56}Co			
	Class Wd	$3x10^{2}$	$1x10^{-7}$	
	Class Ye	$2x10^{2}$	$8x10^{-8}$	
	^{57}Co			
	Class Wd	$3x10^{3}$	$1x10^{-6}$	
	Class Ye	$7x10^{2}$	$3x10^{-7}$	
	^{58}Co			
	Class Wd	$1x10^{3}$	$5x10^{-7}$	
	Class Ye	$7x10^{2}$	$3x10^{-7}$	
	^{58}mCo			
	Class Wd	$9x10^{4}$	$4x10^{-5}$	
	Class Ye	$6x10^{4}$	$3x10^{-5}$	
	^{60}Co			
	Class Wd	$2x10^{2}$	$7x10^{-8}$	
	Class Ye	$3x10^{1}$	$1x10^{-8}$	
	^{60}mCo			
	Class Wd	$4x10^{6}$	$2x10^{-3}$	
	Class Ye	$3x10^{6}$	$1x10^{-3}$	
	^{6}1Co			
	Class Wd	$6x10^{4}$	$3x10^{-5}$	
	Class Ye	$6x10^{4}$	$2x10^{-5}$	
	^{62}mCo			
	Class Wd	$2x10^{5}$	$7x10^{-5}$	
	Class Ye	$2x10^{5}$	$6x10^{-5}$	
OSHA	Safety and health regulations for construction—ionizing radiation			OSHA 2001e 29CFR1926.53
	Toxic and hazardous substances—ionizing radiation			OSHA 2001d 29CFR1910.1096
b. Water				
EPA	Drinking water standards			EPA 2000
	Beta particle and photon activity (formerly man-made radionuclides)			
	MCL	4 mrem		
	Caner risk at 10^{-4}	4 mrem/year		
	Gross alpha particle activity			
	MCL	15 pCi/L		
	Caner risk at 10^{-4}	15 pCi/L		
	Carcinogenic classification	Group A (human carcinogen)		

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
USNRC	Effluent concentrations		USNRC 2001k
	Water		10CFR20
	^{55}Co	ALI (µCi/mL)	Appendix B
	Class Wd	$2x10^{-5}$	Table 2
	^{56}Co		
	Class Wd	$6x10^{-6}$	
	^{57}Co		
	Class Wd	$6x10^{-5}$	
	^{58}Co		
	Class Wd	$2x10^{-5}$	
	^{58}mCo		
	Class Wd	$8x10^{-4}$	
	^{60}Co		
	Class Wd	$3x10^{-6}$	
	^{60}mCo		
	Class Wd	$2x10^{-2}$	
	^{61}Co		
	Class Wd	$3x10^{-4}$	
	^{62}mCo		
	Class Wd	$7x10^{-4}$	
	Releases to sewers—monthly average concentration		USNRC 2001k 10CFR20
	^{55}Co	ALI (µCi/mL)	Appendix B
	Class Wd	$2x10^{-4}$	Table 3
	^{56}Co		
	Class Wd	$6x10^{-5}$	
	^{57}Co		
	Class Wd	$6x10^{-4}$	
	^{58}Co		
	Class Wd	$2x10^{-4}$	
	^{58}mCo		
	Class Wd	$8x10^{-3}$	
	^{60}Co		
	Class Wd	$3x10^{-5}$	
	^{60}mCo		
	Class Wd	$2x10^{-1}$	
	^{61}Co		
	Class Wd	$3x10^{-3}$	
	^{62}mCo		
	Class Wd	$7x10^{-3}$	
c. Food and Drug			
FDA	Ionizing radiation for the treatment of poultry feed and poultry feed ingredients (energy sources)	Ioninzing radiation is limited to gamma rays from sealed units of ^{60}CO	FDA 1999 21CFR579.40
	Requirements regarding certain radioactive drugs for ^{58}Co or ^{60}Co	Labeled cyanocobalamin for use in intestinal absorption studies	FDA 2000d 21CFR310.503(c)

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information			Reference
NATIONAL *(cont.)*					
FDA	Sources of radiation used for inspection of food, packaged food, and controlling food processing				FDA 2000c 21CFR179.21 (a)(2)
d. Other					
DOE	Values for establishing sealed radioactive source accountability and radioactive material posting and labeling requirements				DOE 2000 10CFR835 Appendix E
		Activity (µCi)			
	^{56}Co	4.0×10^{1}			
	^{57}Co	2.3×10^{2}			
	^{58}Co	1.4×10^{2}			
	^{60}Co	1.8×10^{1}			
DOT	Activity values (Ci)	A1	A2		DOT 2001a 49CFR173.435 Table
	^{55}Co	13.5	13.5		
	^{56}Co	8.11	8.11		
	^{57}Co	216	216		
	^{58}mCo	1080	1080		
	^{58}Co	27.0	27.0		
	^{60}Co	10.8	10.8		
	Superfund, reportable quantity (Ci) (pounds)				DOT 2001b 49CFR172.101 Appendix A Table 2
	^{55}Co	10			
	^{56}Co	10			
	^{57}Co	100			
	^{58}Co	10			
	^{58}mCo	1,000			
	^{60}Co	10			
	^{60}mCo	1,000			
	^{61}Co	1,000			
	^{62}mCo	1,000			
EPA	Carcinogenicity classification	No data			IRIS 2000
	RfC				
	RfD				
	Annual possession quantities for environmental compliance (Ci/year)	Gas	Liquid/ Powder	Solid	EPA 2001a 40CFR61 Appendix E Table 1
	^{56}Co	2.3×10^{-6}	2.3×10^{-3}	2.3	
	^{57}Co	1.8×10^{-2}	1.8×10^{1}	1.8×10^{4}	
	^{58}Co	2.5×10^{-6}	2.5×10^{-3}	2.5	
	^{58m}Co	2.3×10^{-6}	2.3×10^{-3}	2.3	
	^{60}Co	4.6×10^{-2}	4.6×10^{1}	4.6×10^{4}	
	^{60m}Co	7.0	7.0×10^{3}	7.0×10^{6}	
	^{61}Co	9.8×10^{-1}	9.8×10^{2}	9.8×10^{5}	

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Concentration levels for environmental compliance (Ci/m^3)		EPA 2001a 40CFR61 Appendix E Table 2
	^{56}Co	$1.8x10^{-13}$	
	^{57}Co	$1.3x10^{-12}$	
	^{58}Co	$6.7x10^{-13}$	
	^{58m}Co	$1.2x10^{-10}$	
	^{60}Co	$1.7x10^{-14}$	
	^{60m}Co	$4.3x10^{-9}$	
	^{61}Co	$4.5x10^{-9}$	
	Carcinogenicity—slope factors		EPA 2002
	Lifetime risk per pCi—ingestion		EPA 2002
	Water		
	^{57}Co	$1.04x10^{-12}$	
	^{58m}Co	$2.95x10^{-12}$	
	^{58}Co	$1.26x10^{-13}$	
	^{60}Co	$1.57x10^{-11}$	
	Lifetime risk per pCi—ingestion		EPA 2002
	Food		
	^{57}Co	$1.49x10^{-12}$	
	^{58m}Co	$4.18x10^{-12}$	
	^{58}Co	$1.83x10^{-13}$	
	60Co	$2.23x10^{-11}$	
	Lifetime risk per pCi—ingestion		EPA 2002
	Soil		
	^{57}Co	$2.78x10^{-12}$	
	^{58}mCo	$7.44x10^{-12}$	
	^{58}Co	$3.47x10^{-13}$	
	^{60}Co	$4.03x10^{-11}$	
	Lifetime risk per pCi—inhalation		EPA 2002
	^{57}Co	$2.09x10^{-12}$	
	^{58}mCo	$5.99x10^{-12}$	
	^{58}Co	$6.88x10^{-14}$	
	^{60}Co	$3.58x10^{-11}$	
	External exposure—risk/year per pCi/g soil		EPA 2002
	^{57}Co	$3.55x10^{-7}$	
	^{58}mCo	$4.48x10^{-6}$	
	^{58}Co	$1.00x10^{-12}$	
	^{60}Co	$1.24x10^{-5}$	

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
EPA	Superfund, reportable quantities (Ci) (pounds)			EPA 2001i 40CFR302.4
	^{55}Co	10		Appendix B
	^{56}Co	10		
	^{57}Co	100		
	^{58}mCo	1,000		
	^{58}Co	10		
	^{60}mCo	1,000		
	^{60}Co	10		
	^{61}Co	1,000		
	^{62}mCo	1,000		
NCRP	Occupational exposures			NCRP1993
	Effective dose limits			
	Annual	50 mSv		
	Cummulative	10 mSv x age		
	Equivalent dose annual limits			
	Lens of eye	150 mSv		
	Skin, hands, and feet	500 mSv		
	Public exposures (annual)			
	Effective dose limits, continuous or frequent exposure	1 mSv		
	Effective dose limits, infrequent exposures	5 mSv		
	Equivalent dose limits			
	Lens of eye	15 mSv		
	Skin, hands, and feet	50 mSv		
	Embryo and fetus exposures (monthly)			
	Effective dose limit	0.5 mSv		
USNRC	Activity values for radionuclides (Ci)	A1	A2	USNRC 2001a 10CFR71
	^{55}Co	13.5	13.5	
	^{56}Co	8.11	8.11	
	^{57}Co	216	216	
	^{58}mCo	1080	1080	
	^{58}Co	27.0	27.0	
	^{60}Co	10.8	10.8	
	Byproduct material listing; exempt concentrations			USNRC 2001e 10CFR30.70
	Liquid and solid concentration (μCi/mL^2)			Schedule A
	^{57}C	$5x10^{-3}$		
	^{58}C	$1x10^{-3}$		
	^{60}C	$5x10^{-4}$		

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
USNRC	Byproduct material listing (μCi)			USNRC 2001b
	^{58}mCo			10CFR30.71
	^{58}Co	10		Schedule B
	^{60}Co	10		
		1		
	Byproduct material listing (Ci)	Column If	Column IIg	USNRC 2001c
	^{58}mCo	100	1.0	10CFR33.100
	^{58}Co	1.0	0.01	Schedule A
	^{60}Co	0.1	$1x10^{-4}$	
	Items containing byproduct material listing—^{60}Co (μCi)			USNRC 2001d 10CFR30.15(a)(8)
	Electron tubes	1.0		
	Spark gap irradiators	1.0		
	Medical use—^{60}Co as a source for brachytherapy	As a sealed source in needles and applicator cells for topical, interstitial, and intracavitary treatment of cancer		USNRC 2001h 10CFR35.400
	Occupational values—oral ingestion			USNRC 2001k 10CFR20
	^{55}Co	ALI (μCi)		Appendix B
	Class Wd	$1x10^{3}$		Table 1
	^{56}Co			
	Class Wd	$5x10^{2}$		
	Class Ye	$4x10^{2}$		
	^{57}Co			
	Class Wd	$8x10^{3}$		
	Class Ye	$4x10^{3}$		
	^{58}Co			
	Class Wd	$2x10^{3}$		
	Class Ye	$1x10^{3}$		
	^{58}mCo			
	Class Wd	$6x10^{4}$		
	^{60}Co			
	Class Wd	$5x10^{2}$		
	Class Ye	$2x10^{2}$		
	^{60}mCo			
	Class Wd	$1x10^{6}$		
	St. wall	$1x10^{6}$		
	^{61}Co			
	Class Wd	$2x10^{4}$		
	Class Ye	$2x10^{4}$		
	^{62}mCo			
	Class Wd	$5x10^{4}$		
	St. wall	$4x10^{4}$		

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
USNRC	Quantities of radioactive material requiring labeling (µCi)		USNRC 2001g 10CFR30 Appendix B
	^{58}mCo	10	
	^{58}Co	10	
	^{60}Co	1	
	Quantities of licensed material requiring labeling (µCi)		USNRC 2001i 10CFR20 Appendix C
	^{55}Co	100	
	^{56}Co	10	
	^{57}Co	100	
	^{58}mCo	1,000	
	^{58}Co	100	
	^{60}mCo	1,000	
	^{60}Co	1	
	^{61}Co	1,000	
	^{62}mCo	1,000	
	Quantities of radioactive materials requiring need for an emergency plan		USNRC 2001j 10CFR30.72 Schedule C
	Release fraction	0.001%	
	Quantity (Ci)	5,000	
	Radioactive waste classification		USNRC 2001l 10CFR61.55
	Class A (Ci/m3)		
	60Co	≤700	
	Reports of individual monitoring—processing or manufacturing for distribution, byproduct material in quantities exceeding		USNRC 2001f 10CFR20.2206 (a)(7)
	^{60}Co (Ci)	1.0	
STATE Regulations and Guidelines:			
a. Air			
Alabama	HAP—radionuclides		BNA 2001
California	HAP—radionuclides		BNA 2001
Hawaii	HAP—radionuclides		BNA 2001
Illinois	Toxic air contaminant—radionuclides		BNA 2001
Kansas	HAP—radionuclides		BNA 2001
Kentucky	HAP—radionuclides		BNA 2001
Minnesota	HAP—radionuclides		BNA 2001
Missouri	HAP—radionuclides		BNA 2001

Table 8-2. Regulations and Guidelines Applicable to Radioactive Cobalt

Agency	Description	Information	Reference
STATE *(cont.)*			
Nebraska	HAP—radionuclides		BNA 2001
New York	HAP—radionuclides		BNA 2001
Rhode Island	HAP—radionuclides		BNA 2001
Wyoming	HAP—radionuclides		BNA 2001

[a]Class W: refers to the approximate length of retention in the pulmonary region which is 10–100 days for this class
[b]Class Y: refers to the approximate length of retention in the pulmonary region which is greater than 100 days for this class
[c]Air immersion DAC values: based on a stochastic dose limit of 5 rems (0.05 Sv) per year or a nonstochastic (organ) dose limit of 50 rems (0.5 Sv) per year
[d]Class W: all compounds except those given for Y
[e]Class Y: oxides, hydroxides, halides, and nitrates
[f]Column I: gas concentration
[g]Column II: liquid and solid concentration

ACGIH = American Conference of Governmental Industrial Hygienists; ALI = annual limits on intake; BNA = Bureau of National Affairs; CFR = Code of Federal Regulations; DAC = derived air concentrations; DOE = Department of Energy; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; ICRP = International Commission on Radiological Protection; IRIS = Integrated Risk Information System; mSv = millisievert; NCRP = National Council on Radiation Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted averages; USNRC = U.S. Nuclear Regulatory Commission; WHO = World Health Organization

cobalt (IRIS 2000). Slope factors have been derived for exposure to cobalt radioisotopes (EPA 2002). The slope factors for ^{60}Co are 1.57×10^{-11}, 2.23×10^{-11}, and 4.03×10^{-11}/pCi for ingestion of water, food, and soil, respectively. The slope factor for inhalation exposure is 3.58×10^{-11}/pCi, and 1.24×10^{-5}/year/pCi/g soil for external exposure. The slope factors for ^{58}Co are $1.26 \times 10^{-13,}$, $1.83 \times 10^{-13,}$, and 3.47×10^{-13}/pCi for ingestion of water, food, and soil, respectively. The slope factor for inhalation exposure is 6.88×10^{-14}/pCi for inhalation exposure, and 1.00×10^{-12}/year/pCi/g soil for external exposure. The slope factors for ^{58m}Co are $2.95 \times 10^{-12,}$, $4.18 \times 10^{-12,}$, and 7.44×10^{-12}/pCi for ingestion of water, food, and soil, respectively. The slope factor for inhalation exposure is 5.99×10^{-14}/pCi for inhalation exposure, and 4.48×10^{-6}/year/pCi/g soil for external exposure. The slope factors for ^{57}Co are 1.04×10^{-12}, 1.49×10^{-12}, and 2.78×10^{-12}/pCi for ingestion of water, food, and soil, respectively. The slope factor for inhalation exposure is 2.09×10^{-12}/pCi for ingestion, and 3.55×10^{-7}/year/pCi/g soil for external exposure.

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10. GLOSSARY

Some terms in this glossary are generic and may not be used in this profile.

Absorbed Dose, Chemical—The amount of a substance that is either absorbed into the body or placed in contact with the skin. For oral or inhalation routes, this is normally the product of the intake quantity and the uptake fraction divided by the body weight and, if appropriate, the time, expressed as mg/kg for a single intake or mg/kg/day for multiple intakes. For dermal exposure, this is the amount of material applied to the skin, and is normally divided by the body mass and expressed as mg/kg.

Absorbed Dose, Radiation—The mean energy imparted to the irradiated medium, per unit mass, by ionizing radiation. Units: rad (rad), gray (Gy).

Absorbed Fraction—A term used in internal dosimetry. It is that fraction of the photon energy (emitted within a specified volume of material) which is absorbed by the volume. The absorbed fraction depends on the source distribution, the photon energy, and the size, shape and composition of the volume.

Absorption—The process by which a chemical penetrates the exchange boundaries of an organism after contact, or the process by which radiation imparts some or all of its energy to any material through which it passes.

Absorption Coefficient—Fractional absorption of the energy of an unscattered beam of x- or gamma-radiation per unit thickness (linear absorption coefficient), per unit mass (mass absorption coefficient), or per atom (atomic absorption coefficient) of absorber, due to transfer of energy to the absorber. The total absorption coefficient is the sum of individual energy absorption processes (see Compton Effect, Photoelectric Effect, and Pair Production).

Absorption Coefficient, Linear—A factor expressing the fraction of a beam of x- or gamma radiation absorbed in a unit thickness of material. In the expression $I=I_o e^{-\mu x}$, I_o is the initial intensity, I the intensity of the beam after passage through a thickness of the material x, and μ is the linear absorption coefficient.

Absorption Coefficient, Mass—The linear absorption coefficient per cm divided by the density of the absorber in grams per cubic centimeter. It is frequently expressed as μ/ρ, where μ is the linear absorption coefficient and ρ the absorber density.

Absorption Ratio, Differential—Ratio of concentration of a nuclide in a given organ or tissue to the concentration that would be obtained if the same administered quantity of this nuclide were uniformly distributed throughout the body.

Activation—The process of making a material radioactive by bombardment with neutrons or protons.

Activity—The number of radioactive nuclear transformations occurring in a material per unit time (see Curie, Becquerel). The term for activity per unit mass is specific activity.

Activity Median Aerodynamic Diameter (AMAD)—The diameter of a unit-density sphere with the same terminal settling velocity in air as that of the aerosol particle whose activity is the median for the entire size distribution of the aerosol.

Acute Exposure, Chemical—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Acute Exposure, Radiation—The absorption of a relatively large amount of radiation (or intake of a radioactive material) over a short period of time.

Acute Radiation Syndrome—The symptoms which taken together characterize a person suffering from the effects of intense radiation. The effects occur within hours or days.

***Ad libitum*—**Available in excess and freely accessible.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit surface area or per unit weight of organic carbon of a specific particle size in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)—See Distribution Coefficient.

Alpha Particle—A positively charged particle ejected spontaneously from the nuclei of some radioactive elements. It is identical to a helium nucleus, i.e., 2 neutrons and two protons, with a mass number of 4 and an electrostatic charge of +2.

Alpha Track—The track of ionized atoms (pattern of ionization) left in a medium by an alpha particle that has traveled through the medium.

Annihilation (Positron-Electron)—An interaction between a positive and a negative electron in which they both disappear; their rest mass, being converted into electromagnetic radiation (called annihilation radiation) with two 0.51 MeV gamma photons emitted at an angle of 180° to each other.

Annual Limit on Intake (ALI)—The derived limit for the amount of radioactive material taken into the body of an adult worker by inhalation or ingestion in a year. It is the smaller value of intake of a given radionuclide in a year by the reference man that would result in a committed effective dose equivalent of 5 rem or a committed dose equivalent of 50 rem to any organ or tissue.

Atom—The smallest particle of an element that cannot be divided or broken up by chemical means. It consists of a central core called the *nucleus*, which contains *protons* and *neutrons* and an outer shell of *electrons*.

Atomic Mass (u)—The mass of a neutral atom of a nuclide, usually expressed in terms of "atomic mass units." The "atomic mass unit" is one-twelfth the mass of one neutral atom of carbon-12; equivalent to 1.6604×10^{-24} g.

Atomic Mass Number—See Mass Number.

Atomic Number—The number of protons in the nucleus of an atom. The "effective atomic number" is calculated from the composition and atomic numbers of a compound or mixture. An element of this atomic number would interact with photons in the same way as the compound or mixture. (Symbol: Z).

Atomic Weight—The weighted mean of the masses of the neutral isotopes of an element expressed in atomic mass units.

Attenuation—A process by which a beam from a source of radiation is reduced in intensity by absorption and scattering when passing through some material.

Attenuation Coefficient—The fractional reduction in the intensity of a beam of radiation as it passes through an absorbing medium. It may be expressed as reduction per unit distance, per unit mass thickness, or per atom, and is called the linear, mass, or atomic attenuation coefficient, respectively.

Auger Effect—The emission of an electron from the extranuclear portion of an excited atom when the atom undergoes a transition to a less excited state.

Background Radiation—The amount of radiation to which a member of the general population is exposed from natural sources, such as terrestrial radiation from naturally occurring radionuclides in the soil, cosmic radiation originating from outer space, and naturally occurring radionuclides deposited in the human body.

Becquerel (Bq)—International System of Units unit of activity and equals that quantity of radioactive material in which one transformation (disintegration) occurs per second (see Units).

Terabecquerel (TBq)—One trillion becquerel.
Gigabecquerel (GBq)—One billion becquerel.
Megabecquerel (MBq)—One million becquerel.
Kilobecquerel (kBq))—One thousand becquerel.
Millibecquerel (mBq)—One-thousandth of a becquerel.
Microbecquerel (µBq)—One-millionth of a becquerel.

Beta Particle—An electron that is emitted from the nucleus of an atom during one type of radioactive transformation. A beta particle has a mass and charge equal in magnitude to that of the electron. The charge may be either +1 or -1. Beta particles with +1 charges are called positrons (symbolized β^+), and beta particles with -1 charges are called negatrons (symbolized β^-).

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biologic Effectiveness of Radiation—See Relative Biological Effectiveness.

Biological Half-time—The time required for a biological system, such as that of a human, to eliminate by natural process half of the amount of a substance (such as a chemical substance, either stable or radioactive) that has entered it.

Biomagnification—The progressive increase in the concentration of a bioaccumulated chemical in organisms as that chemical is passed from the bottom to the top of the food web.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Body Burden, Chemical—The total amount of a chemical found in an animal or human body.

Body Burden, Radioactivity—The amount of radioactive material found in an animal or human body.

Bone Seeker—Any compound or ion which migrates in the body and preferentially deposits into bone.

Branching—The occurrence of two or more modes by which a radionuclide can undergo radioactive decay. For example, ^{214}Bi can undergo alpha or beta minus decay, ^{64}Cu can undergo beta minus, beta plus, or electron capture decay. An individual atom of a nuclide exhibiting branching disintegrates by one mode only. The fraction disintegrating by a particular mode is the "branching fraction" for that mode. The "branching ratio" is the ratio of two specified branching fractions (also called multiple disintegration).

Bremsstrahlung—X rays that are produced when a charged particle accelerates (speeds up, slows down, or changes direction) in the strong field of a nucleus.

Buildup Factor—The ratio of the radiation intensity, including both primary and scattered radiation, to the intensity of the primary (unscattered) radiation.

Cancer Effect Level (CEL)—The lowest dose of chemical or radiation in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Capture, Electron—A mode of radioactive decay involving the capture of an orbital electron by its nucleus. Capture from a particular electron shell, e.g., K or L shells, is designated as "K-electron capture" or "L-electron capture."

Capture, K-Electron—Electron capture from the K shell by the nucleus of the atom. Also loosely used to designate any orbital electron capture process.

Carcinogen—A chemical or radiation that is capable of inducing cancer.

Carcinoma—Malignant neoplasm composed of epithelial cells, regardless of their derivation.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Cataract—A clouding of the crystalline lens of the eye which obstructs the passage of light.

Ceiling Value—A concentration of a substance that should not be exceeded, even temporarily.

Charged Particle—A nuclear particle, atom, or molecule carrying a positive or negative charge.

Chronic Exposure—A long-term, continuous exposure to a chemical or radioactive material. For example, exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Collective Dose—The sum of the individual doses received in a given period of time by a specified population from exposure to a specified source of radiation. Collective dose is expressed in units such as man-rem and person-sievert.

Compton Effect—An attenuation process observed for x- or gamma radiation in which an incident photon interacts with an orbital electron of an atom to produce a recoil electron and a scattered photon whose energy is less than the incident photon.

Containment—The confinement of a chemical or radioactive substance in such a way that it is prevented from being dispersed from its container or into the environment, or is released only at a specified rate.

Contamination—Deposition of a stable or radioactive substance in any place where it is not desired.

Cosmic Rays—High-energy particulate and electromagnetic radiations that originate outside the earth's atmosphere and interact with the atmosphere to produce a shower of secondary cosmic rays.

Count (Radiation Measurements)—The external indication of a radiation-measuring device designed to enumerate ionizing events. It refers to a single detected event. The term “count rate” refers to the total number registered in a given period of time. The term is sometimes erroneously used to designate a disintegration, ionizing event, or voltage pulse.

Counter, Gas-flow Proportional (GPC)—An instrument for detecting beta particle radiation. Beta particles are detected by ionization of the counter gas which results in an electrical impulse at an anode wire.

Counter, Geiger-Mueller (GM counter)—Highly sensitive, gas-filled radiation-measuring device that detects (counts) individual photons or particulate radiation.

Counter, Scintillation—The combination of a crystal or phosphor, photomultiplier tube, and associated circuits for counting light emissions produced in the phosphors by ionizing radiation. Scintillation counters generally are more sensitive than GM counters for gamma radiation.

Counting, Cerenkov—Relatively energetic β-particles pass through a transparent medium of high refractive index and a highly-directional, bluish-white light ("Cerenkov" light) is emitted. This light is detected using liquid scintillation counting equipment.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Curie (Ci)—A unit of radioactivity. One curie equals that quantity of radioactive material in which there are 3.7×10^{10} nuclear transformations per second. The activity of 1 gram of radium is approximately 1 Ci.

Attocurie (aCi)—One-thousandth of a femtocurie (3.7×10^{-8} disintegrations per second).
Femtocurie (fCi)—One-billionth of a microcurie (3.7×10^{-5} disintegrations per second).

Megacurie (MCi)—One million curies ($3.7x10^{16}$ disintegrations per second).
Microcurie (μCi)—One-millionth of a curie ($3.7x10^{4}$ disintegrations per second).
Millicurie (mCi)—One-thousandth of a curie ($3.7x10^{7}$ disintegrations per second).
Nanocurie (nCi)—One-billionth of a curie ($3.7x10^{1}$ disintegrations per second).
Picocurie (pCi)—One-millionth of a microcurie ($3.7x10^{-2}$ disintegrations per second).

Daughter Products—See Progeny and Decay Product

Decay Chain or Decay Series—A sequence of radioactive decays (transformations) beginning with one nucleus. The initial nucleus, the parent, decays into a daughter or progeny nucleus that differs from the first by whatever particles were emitted during the decay. If further decays take place, the subsequent nuclei are also usually called daughters or progeny. Sometimes, to distinguish the sequence, the daughter of the first daughter is called the granddaughter, etc.

Decay Constant (λ)—The fraction of the number of atoms of a radioactive nuclide which decay in unit time (see Disintegration Constant).

Decay Product, Daughter Product, Progeny—A new nuclide formed as a result of radioactive decay. A nuclide resulting from the radioactive transformation of a radionuclide, formed either directly or as the result of successive transformations in a radioactive series. A decay product (daughter product or progeny) may be either radioactive or stable.

Decay, Radioactive—Transformation of the nucleus of an unstable nuclide by spontaneous emission of radiation, such as charged particles and/or photons (see Disintegration).

Delta Ray—An electron removed from an atom of a medium that is irradiated, or through which radiation passes, during the process of ionization (also called secondary electron). Delta rays cause a track of ionizations along their path.

Derived Air Concentration (DAC)—The concentration of radioactive material in air that, if breathed by the reference man for a working year of 2000 hours under conditions of light work (at a rate of 1.2 liters of air per hour), would result in an intake of one ALI (see Annual Limit on Intake).
Deterministic Effect—A health effect, the severity of which varies with the dose and for which a threshold is believed to exist (also called a non-stochastic effect).

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical or radiation prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Disintegration Constant—Synonymous with decay constant. The fraction of the number of atoms of a radioactive material that decays per unit time (see Decay Constant.)

Disintegration, Nuclear—A spontaneous nuclear transformation (radioactivity) characterized by the emission of energy and mass from the nucleus. When large numbers of nuclei are involved, the process is characterized by a definite half-life (see Transformation, Nuclear).

Distribution Coefficient (K_d)—Describes the distribution of a chemical between the solid and aqueous phase at thermodynamic equilibrium, is given as follows:

$K_d = \frac{[C]_s}{[C]_w}$, Units = (L solution)/(kg solid),
where $[C]_s$ is the concentration of the chemical associated with the solid phase in units of (mg)/(kg solid), and $[C]_w$ is the concentration of the chemical in the aqueous phase in units of (mg)/(L solution). As the magnitude of K_d decreases, the potential mobility of the chemical to groundwater systems increases and vice versa.

Dose—A general term denoting the quantity of a substance, radiation, or energy absorbed. For special purposes it must be appropriately qualified. If unqualified, it refers to radiation absorbed dose.

> **Absorbed Dose—**The energy imparted to matter by ionizing radiation per unit mass of irradiated material at the place of interest. The unit of absorbed dose is the rad. One rad equals 100 ergs per gram. In SI units, the absorbed dose is the gray which is 1 J/kg (see Rad).
>
> **Cumulative Dose (Radiation)—**The total dose resulting from repeated or continuous exposures to radiation.

Dose Assessment—An estimate of the radiation dose to an individual or a population group usually by means of predictive modeling techniques, sometimes supplemented by the results of measurement.

Dose Equivalent (DE)—A quantity used in radiation safety practice to account for the relative biological effectiveness of the several types of radiation. It expresses all radiations on a common scale for calculating the effective absorbed dose. The NRC defines it as the product of the absorbed dose, the quality factor, and all other modifying factors at the location of interest. ICRP has changed its definition to be the product of the absorbed dose and the radiation weighting factor. (The unit of dose equivalent is the rem. In SI units, the dose equivalent is the sievert, which equals 100 rem.)

Dose, Fractionation—A method of administering therapeutic radiation in which relatively small doses are given daily or at longer intervals.

Dose, Protraction—A method of administering therapeutic radiation by delivering it continuously over a relatively long period at a low dose rate.

Dose, Radiation—The amount of energy imparted to matter by ionizing radiation per unit mass of the matter, usually expressed as the unit rad, or in SI units, the gray. 100 rad = 1 gray (Gy) (see Absorbed Dose).

> **Committed Dose Equivalent ($H_{T,50}$)—**The dose equivalent to organs or tissues of reference (T) that will be received from an intake of radioactive material by an individual during the 50 years following the intake.
>
> **Committed Effective Dose Equivalent ($H_{E,50}$)—**The sum of the products of the weighting factors applicable to each of the body organs or tissues that are irradiated and the committed dose equivalent to those organs or tissues.
>
> **Effective Dose —**A dose value that attempts to normalize the detriment to the body (for cancer mortality and morbidity, hereditary effects, and years of life lost) from a non-uniform exposure to

that of a uniform whole body exposure. Effective dose is calculated as the sum of products of the equivalent dose and the tissue weighting factor (w_T) for each tissue exposed. ($E = \sum D_{T,R}\ w_R\ w_T$).

Effective Dose Equivalent (H_E)—This dose type is limited to internal exposures and is the sum of the products of the dose equivalent to the organ or tissue (H_T) and the weighting factors (w_T) applicable to each of the body organs or tissues that are irradiated. ($H_E = \sum w_T\ H_T$).

Equivalent Dose—A dose quantity that places the biological effect of all radiation types on a common scale for calculating tissue damage. Alpha particles, for example, are considered to cause 20 times more damage than gamma rays. Equivalent dose is calculated as the sum of products of the average absorbed dose (in gray) in an organ or tissue ($_{DT,R}$) from each type of radiation and the radiation weighting factor (w_R) for that radiation ($\sum D_{T,R}\ w_R$).

External Dose—That portion of the dose equivalent received from radiation sources outside the body.

Internal Dose—That portion of the dose equivalent received from radioactive material taken into the body.

Limit—A permissible upper bound on the radiation dose.

Maximum Permissible Dose (MPD)—The greatest dose equivalent that a person or specified part thereof shall be allowed to receive in a given period of time.

Median Lethal Dose (MLD)—Dose of radiation required to kill, within a specified period (usually 30 days), 50% of the individuals in a large group of animals or organisms. Also called the LD_{50}, or $LD_{50/30}$ if for 30 days.

Threshold Dose—The minimum absorbed dose that will produce a detectable degree of any given effect.

Tissue Dose—Absorbed dose received by tissue in the region of interest, expressed in rad (see Dose, Gray, and Rad).

Dose Rate—The amount of radiation dose delivered per unit time. Generically, the rate at which radiation dose is delivered to any material or tissue.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Dosimetry—Quantification of radiation doses to cells, tissues, organs, individuals or populations resulting from radiation exposures.

Early Effects (of radiation exposure)—Effects that appear within 60 days of an acute exposure.

Electron—A stable elementary particle having an electric charge equal to $\pm 1.60210 \times 10^{-19}$ C (Coulombs) and a rest mass equal to 9.1091×10^{-31} kg. A positron is a positively charged "electron" (see Positron).

Electron Volt—A unit of energy equivalent to the energy gained by an electron in passing through a potential difference of one volt. Larger multiple units of the electron volt are frequently used: keV for thousand or kilo electron volts; MeV for million or mega electron volts (eV). 1 eV=1.6×10^{-12} erg.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Energy—Capacity for doing work. Gravitationally, "potential energy" is the energy inherent in a mass because of its spatial relation to other masses. Chemically or radiologically, “potential energy” is the energy released when a chemical reaction or radiological transformation goes to completion. "Kinetic energy" is the energy possessed by a mass because of its motion (SI unit: joules):

> **Binding Energy (Electron)—**The amount of energy that must be expended to remove an electron from an atom.
>
> **Binding Energy (Nuclear)—**The energy represented by the difference in mass between the sum of the component parts and the actual mass of the nucleus. It represents the amount of energy that must be expended to break a nucleus into its component neutrons and protons.
>
> **Excitation Energy—**The energy required to change a system from its ground state to an excited state. Each different excited state has a different excitation energy.
>
> **Ionizing Energy—**The energy required to knock an electron out of an atom. The average energy lost by electrons or beta particles in producing an ion pair in air or in soft tissue is about 34 eV.
>
> **Radiant Energy—**The energy of electromagnetic radiation, such as radio waves, visible light, x and gamma rays.

Enrichment, Isotopic—An isotopic separation process by which the relative abundances of the isotopes of a given element are altered, thus producing a form of the element that has been enriched in one or more isotopes and depleted in others. In uranium enrichment, the percentage of uranium-235 in natural uranium can be increased from 0.7% to >90% in a gaseous diffusion process based on the different thermal velocities of the constituents of natural uranium (^{234}U, ^{235}U, ^{238}U) in the molecular form UF_6.

EPA Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Equilibrium, Radioactive—In a radioactive series, the state which prevails when the ratios between the activities of two or more successive members of the series remains constant.

> **Secular Equilibrium—**If a parent element has a very much longer half-life than the daughters (so there is not appreciable change in its amount in the time interval required for later products to attain equilibrium) then, after equilibrium is reached, equal numbers of atoms of all members of

the series disintegrate in unit time. This condition is never exactly attained, but is essentially established in such a case as ^{226}Ra and its transformation series to stable ^{206}Pb. The half-life of ^{226}Ra is about 1,600 years; of ^{222}Rn, approximately 3.82 days, and of each of the subsequent members, a few minutes. After about a month, essentially the equilibrium amount of radon is present; then (and for a long time) all members of the series disintegrate the same number of atoms per unit time. At this time, the activity of the daughter is equal to the activity of the parent.

Transient Equilibrium—If the half-life of the parent is short enough so the quantity present decreases appreciably during the period under consideration, but is still longer than that of successive members of the series, a stage of equilibrium will be reached after which all members of the series decrease in activity exponentially with the period of the parent. At this time, the ratio of the parent activity to the daughter activity is constant.

Equilibrium, Electron—The condition in a radiation field where the energy of the electrons entering a volume equals the energy of the electrons leaving that volume.

Excitation—The addition of energy to a system, thereby transferring it from its ground state to an excited state. Excitation of a nucleus, an atom, or a molecule can result from absorption of photons or from inelastic collisions with other particles. The excited state of an atom is an unstable or metastable state and will return to ground state by radiation of the excess energy.

Exposure (Chemical)—Contact of an organism with a chemical or physical agent. Exposure is quantified as the amount of the agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut) and available for absorption.

Exposure (Radiation)—Subjection to ionizing radiation or to a radioactive material. For example, exposure in air is a measure of the ionization produced in air by x or gamma radiation; the sum of the electric charges on all ions of one sign produced in air when all electrons liberated by photons in a volume of air are completely stopped in air (dQ), divided by the mass of the air in the volume (dm). The unit of exposure in air is the roentgen, or coulomb per kilogram (SI units). One roentgen is equal to 2.58×10^{-4} coulomb per kilogram (C/kg).

Fission, Nuclear—A nuclear transformation characterized by the splitting of a nucleus into at least two other nuclei with emission of several neutrons, accompanied by the release of a relatively large amount of energy.

Gamma Ray, Penetrating—Short wavelength electromagnetic radiation of nuclear origin.

Genetic Effect of Radiation—Inheritable change, chiefly mutations, produced by the absorption of ionizing radiation by germ cells. Genetic effects have not been observed in any human population exposed at any dose level.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Gray (Gy)—SI unit of absorbed dose, 1 J/kg. One gray equals 100 rad (see Units).

Half-life, Effective—See Half-Time, Effective.

Half-life, Radioactive—Time required for a radioactive substance to lose 50% of its activity by decay. Each radio-nuclide has a unique physical half-life. Known also as physical half-time and symbolized as T_r or T_{rad}.

Half-time, Biological—Time required for an organ, tissue, or the whole body to eliminate one-half of any absorbed substance by regular processes of elimination. This is the same for both stable and radioactive isotopes of a particular element, and is sometimes referred to as half-time, symbolized as t_{biol} or T_b.

Half-time, Effective—Time required for a radioactive element in an organ, tissue, or the whole body to be diminished 50% as a result of the combined action of radioactive decay and biological elimination, symbolized as T_e or T_{eff}.

$$\text{Effective half-time} = \frac{\text{Biological half-time} \times \text{Radioactive half-life}}{\text{Biological half-time} + \text{Radioactive half-life}}$$

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube. Literally, “in glass.”

***In Vivo*—**Occurring within the living organism. Literally, “in life.”

Intensity—Amount of energy per unit time passing through a unit area perpendicular to the line of propagation at the point in question.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Internal Conversion—Process in which a gamma ray knocks an electron out of the same atom from which the gamma ray was emitted. The ratio of the number of internal conversion electrons to the number of gamma quanta emitted in the de-excitation of the nucleus is called the "conversion ratio."

Ion—Atomic particle, atom or chemical radical bearing a net electrical charge, either negative or positive.

Ion Pair—Two particles of opposite charge, usually referring to the electron and positive atomic or molecular residue resulting after the interaction of ionizing radiation with the orbital electrons of atoms.

Ionization—The process by which a neutral atom or molecule acquires a positive or negative charge.

> **Primary Ionization—**(1) In collision theory: the ionization produced by the primary particles as contrasted to the "total ionization" which includes the "secondary ionization" produced by delta

rays. (2) In counter tubes: the total ionization produced by incident radiation without gas amplification.

Specific Ionization—Number of ion pairs per unit length of path of ionizing radiation in a medium; e.g., per centimeter of air or per micrometer of tissue.

Total Ionization—The total electric charge of one sign on the ions produced by radiation in the process of losing its kinetic energy. For a given gas, the total ionization is closely proportional to the initial ionization and is nearly independent of the nature of the ionizing radiation. It is frequently used as a measure of absorption of radiation energy.

Ionization Density—Number of ion pairs per unit volume.

Ionization Path (Track)—The trail of ion pairs produced by an ionizing particle in its passage through matter.

Ionizing Radiation—Any radiation capable of knocking electrons out of atoms and producing ions. Examples: alpha, beta, gamma and x rays, and neutrons.

Isobars—Nuclides having the same mass number but different atomic numbers.

Isomers—Nuclides having the same number of neutrons and protons but capable of existing, for a measurable time, in different quantum states with different energies and radioactive properties. Commonly the isomer of higher energy decays to one with lower energy by the process of isomeric transition.

Isotopes—Nuclides having the same number of protons in their nuclei, and hence the same atomic number, but differing in the number of neutrons, and therefore in the mass number. Identical chemical properties exist in isotopes of a particular element. The term should not be used as a synonym for nuclide because isotopes refer specifically to different nuclei of the same element.

Stable Isotope—A nonradioactive isotope of an element.

Joule—The S.I. unit for work and energy. It is equal to the work done by raising a mass of one newton through a distance of one meter (J = Nm), which corresponds to about 0.7 ft-pound.

Kerma (k)—A measure of the kinetic energy transferred from gamma rays or neutrons to a unit mass of absorbing medium in the initial collision between the radiation and the absorber atoms. The SI unit is J/kg. The special name of this unit is the rad (traditional system of units) or Gray (SI).

Labeled Compound—A compound containing one or more radioactive atoms intentionally added to its structure. By observations of radioactivity or isotopic composition, this compound or its fragments may be followed through physical, chemical, or biological processes.

Late Effects (of radiation exposure)—Effects which appear 60 days or more following an acute exposure.

$LD_{50/30}$—The dose of a chemical or radiation expected to cause 50% mortality in those exposed within 30 days. For radiation, this is about 350 rad (3.5 gray) received by humans over a short period of time.

Lethal Concentration$_{(Lo)}$ (LC_{Lo})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population within a specified time, usually 30 days.

Lethal Dose$_{(Lo)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals within a specified time, usually 30 days.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Linear Energy Transfer (LET)—A measure of the energy that a charged particle transfers to a material per unit path length.

> **Average LET—**The energy of a charged particle divided by the length of the path over which it deposits all its energy in a material. This is averaged over a number of particles.
>
> **High-LET—**Energy transfer characteristic of heavy charged particles such as protons and alpha particles where the distance between ionizing events is small on the scale of a cellular nucleus.
>
> **Low-LET—**Energy transfer characteristic of light charged particles such as electrons produced by x and gamma rays where the distance between ionizing events is large on the scale of a cellular nucleus.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lung Clearance Class (fast, F; medium, M; slow, S)—A classification scheme for inhaled material according to its rate of clearance from the pulmonary region of the lungs to the blood and the gastrointestinal tract.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Mass Numbers (A)—The number of nucleons (protons and neutrons) in the nucleus of an atom.

Minimal Risk Level—An estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mutagen—A substance that causes changes (mutations) in the genetic material in a cell. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a substance.

Neutrino (ν)—A neutral particle of infinitesimally small rest mass emitted during beta plus or beta minus decay. This particle accounts for conservation of energy in beta plus and beta minus decays. It plays no role in damage from radiation.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a substance at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Nuclear Reactor—A power plant that heats the medium (typically water) by using the energy released from the nuclear fission of uranium or plutonium isotopes instead of burning coal, oil, or natural gas. All of these sources of energy simply heat water and use the steam which is produced to turn turbines that make electricity or propel a ship.

Nucleon—Common name for a constituent particle of the nucleus. Applied to a proton or neutron.

Nuclide—A species of atom characterized by the constitution of its nucleus. The nuclear constitution is specified by the number of protons (Z), number of neutrons (N), and energy content; or, alternatively, by the atomic number (Z), mass number A(N+Z), and atomic mass. To be regarded as a distinct nuclide, the atom must be capable of existing for a measurable time. Thus, nuclear isomers are separate nuclides, whereas promptly decaying excited nuclear states and unstable intermediates in nuclear reactions are not so considered.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Pair Production—An absorption process for x- and gamma radiation in which the incident photon is absorbed in the vicinity of the nucleus of the absorbing atom, with subsequent production of an electron and positron pair (see annihilation). This reaction can only occur for incident photon energies exceeding 1.02 MeV.

Parent—Any radionuclide nuclide which, upon disintegration, yields a new nuclide (termed the progeny or daughter), either directly or as a later member of a radioactive series.

Permissible Exposure Limit (PEL)—A maximum allowable atmospheric level of a substance in workplace air averaged over an 8-hour shift.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereas the physiologically-based model compartments represent real anatomic regions of the body.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A model comprising a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Photoelectric Effect—An attenuation process observed for x and gamma radiation in which an incident photon interacts with a tightly bound inner orbital electron of an atom delivering all of its energy to knock the electron out of the atom. The incident photon disappears in the process.

Photon—A quantum of electromagnetic energy (E) whose value is the product of its frequency (ν) in hertz and Planck's constant (h). The equation is: $E = h\nu$.

Population dose—See Collective dose.

Positron—A positively charged electron.

Potential, Ionization—The energy expressed as electron volts (eV) necessary to separate one electron from an atom, resulting in the formation of an ion pair.

Power, Stopping—A measure of the ability of a material to absorb energy from an ionizing particle passing through it; the greater the stopping power, the greater the energy absorbing ability (see Linear Energy Transfer).

Progeny—The decay product or daughter products resulting after a radioactive decay or a series of radioactive decays. The progeny can also be radioactive, and the chain continues until a stable nuclide is formed.

Proton—Elementary nuclear particle with a positive electric charge equal numerically to the charge of the electron and a rest mass of 1.007 mass units.

Quality—A term describing the distribution of the energy deposited by a particle along its track; radiations that produce different densities of ionization per unit intensity are said to have different "qualities."

Quality Factor (Q)—The linear-energy-transfer-dependent factor by which absorbed doses are multiplied to obtain (for radiation protection purposes) a quantity that expresses - on a common scale for all ionizing radiation - the approximate biological effectiveness of the absorbed dose.

Type of radiation	Quality Factor
X, gamma, or beta	1
Alpha particles	20
Neutrons of unknown energy	10
High energy protons	10

Rad—The traditional unit of absorbed dose equal to 100 ergs per gram, or 0.01 joule per kilogram (0.01 Gy) in any medium (see Absorbed Dose).

Radiation—The emission and propagation of energy through space or through a material medium in the form of waves (e.g., the emission and propagation of electromagnetic waves, or of sound and elastic waves). 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).

Radiation Weighting Factor (also called Quality Factor)—In radiation protection, a factor (1 for x-rays, gamma rays, beta particles; 20 for alpha particles) weighting the absorbed dose of radiation of a specific type and energy for its effect on tissue.

Radioactive Material—Material containing radioactive atoms.

Radioactivity—Spontaneous nuclear transformations that result in the formation of new elements. These transformations are accomplished by emission of alpha or beta particles from the nucleus or by the capture of an orbital electron. Each of these reactions may or may not be accompanied by a gamma photon.

Radioactivity, Artificial—Man-made radioactivity produced by particle bombardment or nuclear fission, as opposed to naturally occurring radioactivity.

Radioactivity, Induced—Radioactivity produced in a substance after bombardment with neutrons or other particles. The resulting activity is "natural radioactivity" if formed by nuclear reactions occurring in nature and "artificial radioactivity" if the reactions are caused by man.

Radioactivity, Natural—The property of radioactivity exhibited by more than 50 naturally occurring radionuclides.

Radioisotope—An unstable or radioactive isotope of an element that decays or disintegrates spontaneously, emitting radiation.

Radionuclide—Any radioactive isotope of any element. Approximately 5,000 natural and artificial radioisotopes have been identified.

Radiosensitivity—Relative susceptibility of cells, tissues, organs, organisms, or any living substance to the injurious action of radiation. Radiosensitivity and its antonym, radioresistance, are used comparatively, rather than absolutely.

Reference Dose (RfD)—An estimate of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to non-threshold effects such as cancer.

Relative Biological Effectiveness (RBE)—The RBE is a factor used to compare the biological effectiveness of absorbed radiation doses (i.e., rad) due to different types of ionizing radiation. More specifically, it is the experimentally determined ratio of an absorbed dose of a radiation in question to the absorbed dose of a reference radiation (typically ^{60}Co gamma rays or 200 kVp x rays) required to produce an identical biological effect in a particular experimental organism or tissue (see Quality Factor).

Rem—The traditional unit of dose equivalent that is used in the regulatory, administrative, and engineering design aspects of radiation safety practice. The dose equivalent in rem is numerically equal to the absorbed dose in rad multiplied by the quality factor (1 rem is equal to 0.01 sievert).

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Roentgen (R)—A unit of exposure (in air) to ionizing radiation. It is the amount of x or gamma rays required to produce ions carrying 1 electrostatic unit 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.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Self-Absorption—Absorption of radiation (emitted by radioactive atoms) by the material in which the atoms are located; in particular, the absorption of radiation within a sample being assayed.

Short-Term Exposure Limit (STEL)—The maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily TLV-TWA may not be exceeded.

SI Units—The International System of Units as defined by the General Conference of Weights and Measures in 1960. These units are generally based on the meter/kilogram/second units, with special quantities for radiation including the becquerel, gray, and sievert.

Sickness, Acute Radiation (Syndrome)—The complex symptoms and signs characterizing the condition resulting from excessive exposure of the whole body (or large part) to ionizing radiation. The earliest of these symptoms are nausea, fatigue, vomiting, and diarrhea, and may be followed by loss of hair (epilation), hemorrhage, inflammation of the mouth and throat, and general loss of energy. In severe cases, where the radiation dose is relatively high (over several hundred rad or several gray), death may occur within two to four weeks. Those who survive six weeks after exposure of a single high dose of radiation may generally be expected to recover.

Sievert (Sv)—The SI unit of any of the quantities expressed as dose equivalent. The dose equivalent in sieverts is equal to the absorbed dose, in gray, multiplied by the quality factor (1 sievert equals 100 rem). The sievert is also the SI unit for effective dose equivalent, which is the sum of the products of the dose equivalent to each organ or tissue and its corresponding tissue weighting factor.

Specific-Activity—Radioactivity per unit mass of a radionuclide, expressed, for example, as Ci/gram or Bq/kilogram.

Specific Energy—The actual energy per unit mass deposited per unit volume in a small target, such as the cell or cell nucleus, as the result of one or more energy-depositing events. This is a stochastic quantity as opposed to the average value over a large number of instance (i.e., the absorbed dose).

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Stochastic Effect—A health effect that occurs randomly and for which the probability of the effect occurring, rather than its severity, is assumed to be a linear function of dose without a threshold (also called a nondeterministic effect).

Stopping Power—The average rate of energy loss of a charged particle per unit thickness of a material or per unit mass of material traversed.

Surface-seeking Radionuclide—A bone-seeking internal emitter that deposits and remains on the bone surface for a long period of time, although it may eventually diffuse into the bone mineral. This contrasts with a volume seeker, which deposits more uniformly throughout the bone volume.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Target Theory (Hit Theory)—A theory explaining some biological effects of radiation on the basis that ionization, occurring in a discrete volume (the target) within the cell, directly causes a lesion which subsequently results in a physiological response to the damage at that location. One, two, or more "hits" (ionizing events within the target) may be necessary to elicit the response.

Teratogen—A chemical that causes birth defects.

Threshold Limit Value (TLV®)—The maximum concentration of a substance to which most workers can be exposed without adverse effect. TLV is a term used exclusively by the ACGIH. Other terms used to express similar concepts are the MAC (Maximum Allowable Concentration) and PEL (Permissible Exposure Limits).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Tissue Weighting Factor (W_t)—Organ- or tissue-specific factor by which the equivalent dose is multiplied to give the portion of the effective dose for that organ or tissue. Recommended values of tissue weighting factors are:

Tissue/Organ	Tissue Weighting Factor
Gonads	0.70
Bone marrow (red)	0.12
Colon	0.12
Lung	0.12
Stomach	0.12
Bladder	0.05
Breast	0.05
Liver	0.05
Esophagus	0.05
Thyroid	0.05
Skin	0.01
Bone surface	0.01
Remainder (adrenals, brain, upper large intestine, small intestine, pancreas, spleen, thymus, and uterus)	0.05

Toxic Dose (TD_{50})—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution and elimination of toxic compounds in the living organism.

Toxicosis—A diseased condition resulting from poisoning.

Transformation, Nuclear—The process of radioactive decay by which a nuclide is transformed into a different nuclide by absorbing or emitting particulate or electromagnetic radiation.

Transition, Isomeric—The process by which a nuclide decays to an isomeric nuclide (i.e., one of the same mass number and atomic number) of lower quantum energy. Isomeric transitions (often abbreviated I.T.) proceed by gamma ray and internal conversion electron emission.

Tritium—The hydrogen isotope with one proton and two neutrons in the nucleus (Symbol: ^{3}H). It is radioactive and has a physical half-life of 12.3 years.

Unattached Fraction—That fraction of the radon daughters, usually ^{218}Po and ^{214}Po, which has not yet attached to a dust particle or to water vapor. As a free atom, it has a high probability of being exhaled and not retained within the lung. It is the attached fraction which is primarily retained.

Uncertainty Factor (UF)—A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

Units, Prefixes—Many units of measure are expressed as submultiples or multiples of the primary unit (e.g., 10^{-3} curie is 1 mCi and 10^{3} becquerel is 1 kBq).

Factor	Prefix	Symbol	Factor	Prefix	Symbol
10^{-18}	atto	A	10^{3}	kilo	k
10^{-15}	femto	F	10^{6}	mega	M
10^{-12}	pico	p	10^{9}	giga	G
10^{-9}	nano	N	10^{12}	tera	T
10^{-6}	micro	M	10^{15}	peta	P
10^{-3}	milli	M	10^{18}	exa	E
10^{-2}	centi	C			

Units, Radiological—

Units	Equivalents
Becquerel* (Bq)	1 disintegration per second = 2.7×10^{-11} Ci
Curie (Ci)	3.7×10^{10} disintegrations per second = 3.7×10^{10} Bq
Gray* (Gy)	1 J/kg = 100 rad
Rad (rad)	100 erg/g = 0.01 Gy
Rem (rem)	0.01 sievert
Sievert* (Sv)	100 rem

*International Units, designated (SI)

Working Level (WL)—Any combination of short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^{5} MeV of potential alpha energy.

Working Level Month (WLM)—A unit of exposure to radon daughters corresponding to the product of the radon daughter concentration in Working Level (WL) and the exposure time in nominal months (1 nominal month = 170 hours). Inhalation of air with a concentration of 1 WL of radon daughters for 170 working hours results in an exposure of 1 WLM.

X rays—Penetrating electromagnetic radiations whose wave lengths are very much shorter than those of visible light. They are usually produced by bombarding a metallic target with fast electrons in a high vacuum. X rays (called characteristic x rays) are also produced when an orbital electron falls from a high energy level to a low energy level.

Zero-Threshold Linear Hypothesis (or No-Threshold Linear Hypothesis)—The assumption that a dose-response curve derived from data in the high dose and high dose-rate ranges may be extrapolated through the low dose and low dose range to zero, implying that, theoretically, any amount of radiation will cause some damage.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cobalt
CAS Number: 10026-24-1
Date: March 2004
Profile Status: Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Key to figure: 26
Species: human

Minimal Risk Level: $1x10^{-4}$ [ ] mg/kg/day [ ] ppm [x] mg/m^3

Reference:

Nemery B, Casier P, Roosels D, et al. 1992. Survey of cobalt exposure and respiratory health in diamond polishers. Am Rev Respir Dis 145:610-616.

Experimental design:

Nemery et al. (1992) conducted a cross-sectional study of cobalt exposure and respiratory effects in diamond polishers. The study group was composed of 194 polishers working in 10 different workshops. In two of these workshops (#1, 2), the workers used cast iron polishing disks almost exclusively, and in the others, they used cobalt-containing disks primarily. The number of subjects from each workshop varied from 6 to 28 and the participation rate varied from 56 to 100%. The low participation in some workshops reflects the fact that only workers who used cobalt disks were initially asked to be in the study, rather than a high refusal rate (only eight refusals were documented). More than a year after the polishing workshops were studied, an additional three workshops with workers engaged in sawing diamonds, cleaving diamonds, or drawing jewelry were studied as an unexposed control group (n=59 workers). Subjects were asked to fill out a questionnaire regarding employment history, working conditions, medical history, respiratory symptoms, and smoking habits, to give a urine sample for cobalt determination, and to undergo a clinical examination and lung function tests. Both area air samples and personal air samples were collected (always on a Thursday). Sampling for area air determinations started 2 hours after work began and continued until 1 hour before the end of the work day. Personal air samples were collected from the breathing zone of a few workers per workshop for four successive 1-hour periods. Air samples were analyzed for cobalt and iron. In addition, personal air samplers were used to sample the air 1 cm above the polishing disks. These samples were analyzed for the entire spectrum of mineral and metallic compounds. Air samples were not obtained at one of the polishing workshops (#4), but this workshop was reported to be almost identical to an adjoining workshop (#3) for which samples were obtained. Urinary cobalt levels were similar between workers in these two workshops, so exposure was considered to be similar as well. It is important to note that the study authors suggested that the available methods used for air sampling may have underestimated the exposure levels.

There was a good correlation (R=0.92) between the results of area and personal air sampling, with area air sampling reporting lower concentrations than personal air samples in all workshops except one (#9) (Nemery et al. 1992). In this workshop, personal air samples appeared to be artificially low in comparison to area air samples and urinary cobalt levels of the workers. When this workshop was excluded, there was a good correlation (R=0.85–0.88) between urinary cobalt and cobalt in the air. Based on urinary cobalt levels, the concentration of cobalt expected in personal air samples from workshop #9 was about 45 $\mu g/m^3$ (the mean value actually reported was 6 $\mu g/m^3$). The polishing workshops were divided into two groups: those with low exposure to cobalt (#1–5, n=102) and those with high exposure to

cobalt (#6–10, n=91). Mean cobalt exposure concentrations were 0.4, 1.6, and 10.2 μg/m^3 by area air sampling and 0.4, 5.3, and 15.1 μg/m^3 by personal air sampling in the control, low-exposure, and high-exposure groups, respectively. The inclusion of the apparently biased personal air samples from workshop #9 means that the reported mean cobalt exposure in the high-exposure group obtained by personal air sampling (15.1 μg/m^3) may be lower than the true value. Air concentrations of iron were highest in the two polishing workshops that used iron disks and the sawing workshop (highest value =62 μg/m^3), and were not correlated with cobalt levels. Analysis of samples taken near the disks showed the presence of cobalt, with occasional traces of copper, zinc, titanium, manganese, chromium, silicates, and silicon dioxide. No tungsten was detected. There is a possibility that some workers had previously been exposed to asbestos, since pastes containing asbestos had been used in the past to glue the diamonds onto holders. However, the degree of asbestos exposure had apparently been insufficient to produce functional impairment. The researchers considered cobalt to be the only relevant exposure. Smoking habits were similar in workers from the high-exposure, low-exposure, and control groups. Duration of exposure was not discussed.

Effects noted in study and corresponding doses:

Workers in the high-exposure group were more likely than those in the other groups to complain about respiratory symptoms; the prevalences of eye, nose, and throat irritation and cough, and the fraction of these symptoms related to work, were significantly increased in the high-exposure group (Nemery et al. 1992). Workers in the high-exposure group also had significantly reduced lung function compared to controls and low-exposure group workers, as assessed by FVC (forced vital capacity), FEV_1 (forced expiratory volume in 1 second), MMEF (forced expiratory flow between 25 and 75% of the FVC), and mean PEF (peak expiratory flow rate), although the prevalence of abnormal values did not differ significantly between exposure categories. Results in the low-exposure group did not differ from controls. Two-way analysis of variance was used to show that the effect on spirometric parameters in the high exposure group was present in both men and women. Women seemed to be affected more than men, but the interaction between exposure and sex was not significant. Smoking was found to exert a strong effect on lung function, but lung function level remained negatively correlated with exposure to cobalt, independently of smoking.

Dose and end point used for MRL derivation:

[x] NOAEL [ ] LOAEL
Nemery et al. (1992) established a NOAEL of 0.0053 mg cobalt/m^3 for effects on pulmonary function (decreased values upon spirometric examination).

Uncertainty Factors used in MRL derivation:

[x] 1 [ ] 3 [ ] 10 (for use of a NOAEL)
[x] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

The chronic inhalation MRL for cobalt is derived as follows:

$MRL = NOAEL_{[ADJ]} \div UF$
$MRL = 0.0013$ mg cobalt/m$^3 \div 10$
$MRL = 1x10^{-4}$ mg cobalt/m^3

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

Was a conversion used from intermittent to continuous exposure? If so, explain:

0.0053 mg cobalt/m^3 * (8 hours/24 hours) * (5 days/7 days) = 0.0013 mg cobalt/m^3 continuous exposure.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA.

Other additional studies or pertinent information which lend support to this MRL:

Necrosis and inflammation of the respiratory tract epithelium (larynx, trachea, bronchioles, nasal turbinates) were reported in rats exposed to 19 mg cobalt/m^3 and mice exposed to 1.9 mg cobalt/m^3 (and above) as cobalt sulfate over 16 days (NTP 1991). Exposure of rats and mice to cobalt as cobalt sulfate for 13 weeks resulted in adverse effects on all parts of the respiratory tract, with the larynx being the most sensitive part (NTP 1991). At concentrations of ≥0.11 mg cobalt/m^3, rats and mice had squamous metaplasia of the larynx. Histiocytic infiltrates in the lung were also reported at similar levels in both the rats and mice. In rats, chronic inflammation of the larynx was found at ≥0.38 mg cobalt/m^3, and more severe effects on the larynx, nose, and lung were reported at higher exposures. In mice, acute inflammation of the nose was found at ≥1.14 mg cobalt/m^3, and more severe effects on the larynx, nose, and lung were reported at higher exposures.

Exposure of rats and mice to aerosols of cobalt (as cobalt sulfate) at concentrations from 0.11 to 1.14 mg cobalt/m^3 for 2 years resulted in a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice (NTP 1998). Squamous metaplasia of the larynx occurred in rats and mice at exposure concentrations of ≥0.11 mg cobalt/m^3, with severity of the lesion increasing with increased exposure concentration. Hyperplastic lesions of the nasal epithelium occurred in rats at concentrations of ≥0.11 mg cobalt/m^3, and in mice at concentrations of ≥0.38 mg cobalt/m^3. Both sexes of rats had greatly increased incidences (>90% incidence) of alveolar lesions at all exposure levels, including inflammatory changes, fibrosis, and metaplasia. Similar changes were seen in mice at all exposure levels, though the changes in mice were less severe.

Both studies by NTP (1991, 1998) failed to define a NOAEL, with the lowest concentration examined (0.11 mg/m^3) a LOAEL for a variety of respiratory effects. If an MRL were to be calculated based upon these studies, it would be as follows:

Duration adjustment: 0.11 mg cobalt/m^3 * (6 h/24 h) * (5 d/7 d) = 0.020 mg cobalt/m^3 continuous exposure.
Calculation of human equivalent concentration:
If fractional depositions in humans and animals are assumed to be equal, then:
$RDDR = V_E(animal)/S_{ET}(animal) \div V_E(human)/S_{ET}(human)$ = 0.24 m^3/day / 15 cm^2 ÷ 20 m^3/day / 200 cm^2
RDDR = 0.16
$LOAEL_{[HEC]}$ = LOAEL[ADJ] * RDDR
= 0.020 mg cobalt/m^3 * 0.16 = 0.0032 mg cobalt/m^3

To the $LOAEL_{[HEC]}$, an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation, and 10 for human variability) to derive an MRL of $1x10^{-5}$ mg/m^3. This number is an order of magnitude lower than the number derived from the Nemery et al. (1992) data, reflecting the fact that it is derived from animal data, not from a human study, and is based on a LOAEL, not a NOAEL. As the Nemery et al. (1992) study was a well-performed study in humans that defined a NOAEL and LOAEL, it was selected as the basis for derivation of the MRL.

Agency Contact (Chemical Manager): Obaid Faroon D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cobalt
CAS Number: 10026-24-1
Date: March 2004
Profile Status: Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 30
Species: human

Minimal Risk Level: $1x10^{-4}$ [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference:

Davis, J.E. and Fields, J.P. 1958. Experimental production of polycythemia in humans by administration of cobalt chloride. Proc Soc Exp Biol Med 99:493-495.

Experimental design:

Six apparently normal men, ages 20–47, were administered a daily dose of cobalt chloride, administered as a 2% solution diluted in either water or milk, for up to 22 days. Five of the six received 150 mg cobalt chloride per day for the entire exposure period, while the sixth was started on 120 mg/day and later increased to 150 mg/day. Blood samples were obtained daily from free-flowing punctures of fingertips at least 2 hours after eating, and at least 15 hours after the last dosage of cobalt. Blood was analyzed for red blood cell counts, hemoglobin percentage, leukocyte counts, reticulocyte percentages, and thrombocyte counts.

Effects noted in study and corresponding doses:

Exposure to cobalt resulted in the development of polycythemia in all six subjects, with increases in red blood cell numbers ranging from 0.5 to 1.19 million (~16–20% increase above pre-treatment levels). Polycythemic erythrocyte counts returned to normal 9–15 days after cessation of cobalt administration. Hemoglobin levels were also increased by cobalt treatment, though to a lesser extent than the erythrocyte values, with increases of 6–11% over pretreatment values. In five of the six subjects, reticulocyte levels were elevated, reaching at least twice the pre-experiment values. Thrombocyte and total leukocyte counts did not deviate significantly from pretreatment values.

Dose end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

Davis and Fields (1958) identified a LOAEL of 150 mg cobalt chloride per day for increased levels of erythrocytes in volunteers. 150 mg cobalt chloride/day corresponds to ~1 mg Co/kg/day, assuming a reference body weight of 70 kg. Available animal studies, presented below, lend support to this LOAEL, having demonstrated LOAEL values within half an order of magnitude of that identified by Davis and Fields (1958).

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [x] 10 (for use of a LOAEL)

[x] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

The intermediate oral MRL for cobalt is derived as follows:

MRL = LOAEL ÷ UF
MRL = 1 mg cobalt/kg-day ÷ 100
MRL = $1x10^{-2}$ mg cobalt/kg-day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

Was a conversion used from intermittent to continuous exposure? If so, explain: No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Other additional studies or pertinent information that lend support to this MRL:

No other studies of the effect of intermediate oral cobalt exposure on erythrocyte levels in healthy human subjects were identified in a search of the literature. Treatment of pregnant women for 90 days with 0.5–0.6 mg cobalt/kg/day as cobalt chloride did not prevent the reduction in hematocrit and hemoglobin levels often found during pregnancy (Holly 1955). However, treatment of anephric patients (with resulting anemia) with 0.16–1.0 mg cobalt/kg/day daily as cobalt chloride for 3–32 weeks resulted in increased levels of circulating erythrocytes and a decreased need for transfusions (Duckham and Lee 1976b; Taylor et al. 1977). While these studies provide additional evidence that exposure to cobalt can increase erythrocyte levels in humans, the fact that the patients were anephric makes definitive interpretation of the results more difficult.

Roche and Layrisse (1956) exposed volunteers to similar levels (150 mg $CoCl_2$/day) of cobalt, and reported a reversible decrease in uptake of ^{131}I by the thyroid. The decreased uptake is believed to result from cobalt blocking the organic binding of iodine (Paley et al. 1958). This observation adds support to the choice of effect level, as a similar exposure resulted in measurable effects in volunteers, though whether the changes in iodine uptake operate through the same mechanisms as the changes in erythrocyte numbers has not been determined.

Stanley et al. (1947) exposed groups (n=4, 6 for controls) of 6 Sprague-Dawley rats to 0, 0.62, 2.5, or 10 mg cobalt/kg/day (0, 2.5, 10, or 40 mg/kg-day of $CoCl_2 \cdot 6H_2O$) in gelatin capsules for 8 weeks. Blood counts and hemoglobin levels were examined at the beginning of the experiment and at 2-week intervals. Rats exposed to 0.62 mg cobalt/kg-day showed no change in erythrocyte number. At 2.5 mg cobalt/kg-day, a progressive increase in erythrocyte number was seen, increasing up to a maximum of 17% above pretreatment values on week 6. At the highest exposure level, a progressive increase in erythrocyte numbers was seen, reaching 29% above pretreatment values at 8 weeks of exposure. Statistical analyses of the group means were not provided, and the study provided only mean values of the measurements, precluding statistical analysis. However, if a 10% change is assumed to be an effect level, exposure to 2.5 mg cobalt/kg-day was the LOAEL for this study, with a NOAEL of 0.62 mg cobalt/kg-day.

Krasovskii and Fridyland (1971) exposed groups of rats to 0, 0.05, 0.5, or 2.5 mg Co/kg/day for up to 7 months. In the 2.5 mg/kg-day group, a persistent increase in erythrocyte levels was seen. The increase was transient in the 0.5 mg/kg/day rats, and was not present in rats exposed to 0.05 mg/kg/day. However, numerical data were not presented and statistical significance was not reported.

A number of other studies in animals have reported increases in erythrocyte levels following intermediate oral administration of cobalt compounds (see the LSE table for further details of these studies). However, the majority of them have considerable methodological limitations, including examination of either very high exposure levels or only one exposure level, limited reporting of results, or limited or no statistical analysis.

Whether or not polycythemia, a condition wherein an excess of erythrocytes is produced, constitutes an adverse effect is open to interpretation. At the levels seen in the available studies, and in particular in the Davis and Fields (1958) study, the subjects would be expected to be asymptomatic. However, data on the long-term effects of elevated erythrocyte levels are not available. As such, this end point was considered an adverse effect as a health-protective assumption, and was utilized as a critical end point for MRL derivation.

Agency Contact (Chemical Manager): Obaid Faroon D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Radioactive Cobalt
CAS number: Multiple
Date:March 2004
Profile status: Final
Route: [ ] Inhalation [ ] Oral [x] External
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Species: Human

Minimal Risk Level: 4 [ ] mg/kg/day [ ] ppm [ ] mg/m^3 [x] mSv (400 mrem)

References:

Schull WJ, Otake M, Yoshimaru H. 1988. Effect on intelligence test score of prenatal exposure to ionizing radiation in Hiroshima and Nagasaki: A comparison of the T65DR and DS86 dosimetry systems. Radiation Effects Research Foundation (RERF) Technical Report No. 3-88. Hirroshima, Japan. NTIS Report Number: DE89-906462.

Burt C. 1966. The genetic determination of differences in intelligence: A study of monozygotic twins reared together and apart. Brit J Psychol 57(1&2):137-153.

Experimental design:

Schull et al. (1988) study: Schull et al. (1988) evaluated the quantitative effect of exposure to ionizing radiation on the developing fetal and embryonic human brain. The end point measured was changes in intelligence test scores. The effects on individuals exposed *in utero* to the atomic bombing of Hiroshima and Nagasaki were based on the original PE86 samples (n=1,759; data on available intelligence testing) and a clinical sample (n=1,598). The original PE86 sample included virtually all prenatally exposed individuals who received tissue-absorbed doses of 0.50 Gy or more. There were many more individuals in the dose range 0–0.49 Gy in the PE86 sample than in the clinical sample. The clinical sample does not include children prenatally exposed at distances between 2,000 and 2,999 m in Hiroshima and Nagasaki. Children exposed at greater distances or not present in the city were selected as controls. In 1955–1956, Tanaka-B (emphasis on word-sense, arithmetic abilities, and the like, which were associated with the more subtle processing of visual clues than their simple recognition and depended more on connectedness) and the Koga (emphasis on perception of spatial relationships) intelligence tests were conducted in Nagasaki and the Koga test in Hiroshima.

Burt (1966) study: This study determined differences in intelligence in monozygotic twins reared together (n=95) and apart (n=53). All tests conducted in school consisted of (1) a group test of intelligence containing both non-verbal and verbal items, (2) an individual test (the London Revision of the Terman-Binet Scale) used primarily for standardization and for doubtful cases, and (3) a set of performance tests, based on the Pitner-Paterson tests and standardization. The methods and standard remained much the same throughout the study. Some of the reasons for separation of the twins were given as follows: death of the mother (n=9), unable to bring them up properly, mother's poor health (n=12), unmarried (n=6), and economic difficulties. The children were brought up by parents or foster parents (occupation ranged from unskilled to professional). IQ scores in the study group ranged from 66 to 137. The standard deviation of the group of separated monozygotic twins was reported at 15.3 as compared to 15.0 of ordinary siblings. Twins brought up in different environments were compared with those brought up in similar circumstances.

Effects noted in study and corresponding doses:

Schull et al. (1986) study: No evidence of radiation-related effect on intelligence was observed among individuals exposed within 0–7 weeks after fertilization or in the 26th or subsequent weeks. The highest risk of radiation damage to the embryonic and fetal brain occurs 8–15-weeks after fertilization under both dosimetric systems. The regression of intelligence score on estimated DS86 uterine absorbed dose is linear with dose, and the diminution in intelligence score is 21–29 points per Gy for the 8–15-week group and 10–26 points per Gy for the 16–25-week group. The results for 8–15 weeks applies regardless whether or not the mentally retarded individuals were included. The cumulative distribution of test scores suggested a progressive shift downwards in individual scores with increasing exposure. The mean IQ scores decrease significantly and systematically with uterine or fetal tissue dose within the 8–15- and 16–25-week groups.

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

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

Burt (1966) study: The average intelligence of the twins measured on a conventional IQ scale (SD=15) was 97.8 for the separated monozygotes, 98.1 for monozygotes brought up together, 99.3 for the dizygotes as compared with 100.2 for the siblings, and 100.0 for the population as a whole. The difference of 0.3 IQ point between the separated and unseparated identical twins is considered a NOAEL for this study.

Dose endpoint used for MRL derivation:

[x] NOAEL [ ] LOAEL 0.3 IQ point reduction in twins, between those raised together and those raised apart.

Uncertainty factors (UF) used in MRL derivation:

[x] 1 [ ] 3 [ ] 10 (for use of a NOAEL)
[x] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [x] 3 [ ] 10 (for human variability/sensitive population)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? If so, explain: No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL:

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

Supporting evidence for the acute MRL is provided by Jacobi and Glauberman (1995). Children in the 1st, 3rd, and 5th grades born in Washington, DC were tested, and average IQ levels of 94.2, 97.6, and 94.6, respectively, were reported. The range of 3.4 IQ points is considered to be a LOAEL for this study, which, if used for MRL derivation, would yield an MRL of 0.004 Sv (3.4 IQ points x 1 Sv/25 IQ points ÷ 30 [10 for use of a LOAEL and 3 for a sensitive population]).

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

The USNRC set a radiation exposure limit of 0.5 rem (50 mSv) for pregnant working women over the full gestational period (USNRC 1991). For the critical gestational period of 8–15 weeks, ATSDR believes that the conservative acute MRL of 4 mSv is consistent with the USNRC limit and could be applied to either acute (0–14-day) or intermediate (15–365-day) exposure periods.

Calculations

Given: 0.3 IQ point is a NOAEL. A 1 Sv dose results in a 25 IQ point reduction (range=21–29 points; mean=25) and provides a conversion factor from IQ prediction to radiation dose. Assume that the radiation dose and the subsequent reduction in IQ is a linear relationship.
MRL = NOAEL x CF ÷ UF
MRL = 0.3 x 1/25 ÷ 3
MRL = 0.004 Sv = 4 mSv (400 mrem)

Agency Contact (Chemical Manager): Obaid Faroon D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Radioactive Cobalt
CAS Number: Multiple
Date: March 2004
Profile Status: Final
Route: [ ] Inhalation [ ] Oral [X] External
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Species: Human

Minimal Risk Level: 1 [ ] mg/kg/day [ ] ppm [ ] mg/m^3 [X] mSv/year (100 mrem/year)

Reference: BEIR V. 1990. Health effects of exposure to low levels of ionizing radiation. Committee on the Biological Effects of Ionizing Radiations, National Research Council. National Academy Press. Washington, DC.

Experimental design: Not applicable

Effects noted in study and corresponding doses: No individual studies were identified that could be used to base a chronic-duration external exposure MRL that did not result in a cancer-producing end point. However, two sources of information were identified that did provide doses of ionizing radiation that have not been reported to be associated with detrimental effects (NOAELs). These sources provide estimates of background levels of primarily natural sources of ionizing radiation that have not been implicated in producing cancerous or noncancerous toxicological endpoints. BEIR V states that the average annual effective dose to the U.S. population is 3.6 mSv/year. A total annual effective dose equivalent of 3.6 mSv (360 mrem)/year to members of the U.S. population is obtained mainly by naturally occurring radiation from external sources, medical uses of radiation, and radiation from consumer products. The largest contribution (82%) is from natural sources, two-thirds of which is from naturally occurring radon and its decay products. Specific sources of this radiation are demonstrated in Table A-1.

The annual dose of 3.6 mSv per year has not been associated with adverse health effects or increases in the incidences of any type of cancers in humans or other animals.

Dose and end point used for MRL derivation: 3.6 mSv/year

[X] NOAEL [ ] LOAEL 3.6 mSv/year

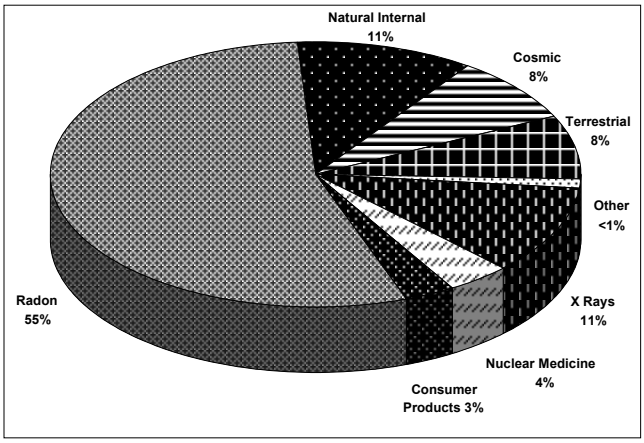
Uncertainty Factors used in MRL derivation:

[X] 1 [ ] 3 [ ] 10 (for use of a NOAEL)
[X] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [X] 3 [ ] 10 (for human variability)

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

Table A-1. Average Annual Effective Dose Equivalent from Ionizing Radiation to a Member of the U.S. Population[a]

	Effective dose equivalent	
Source	mSv	Percent of total dose
Natural		
Radon[b]	2.0	55
Cosmic	0.27	8.0
Terrestrial	0.28	8.0
Internal	0.39	11
Total natural	3.0	82
Artificial		
Medical		
X-ray	0.39	11
Nuclear	0.14	4.0
Consumer products	0.10	3.0
Other		
Occupational	<0.01	<0.3
Nuclear fuel cycle	<0.01	<0.03
Fallout	<0.01	<0.03
Miscellaneous[c]	<0.01	<0.03
Total artificial	0.63	18
Total natural and artificial	3.6	100



[a]Adapted from BEIR V, Table 1-3 , page 18.
[b]Dose equivalent to bronchi from radon daughter products
[c]DOE facilities, smelter, transportation, etc.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information which lend support to this MRL: ICRP has developed recommended dose limits for occupational and public exposure to ionizing radiation sources. The ICRP recommends limiting public exposure to 1 mSv/year (100 mrem/year), but does note that values at high altitudes above sea level and in some geological areas can sometimes be twice that value (≥2 mSv). In Annex C of ICRP 60, the commission provides data that suggests increasing the dose from 1 mSv to 5 mSv results in a very small, but detectable, increase in age-specific human mortality rate. ICRP states that the value of 1 mSv/year was chosen over the 5 mSv value because 5 mSv/year (500 mrem/year) causes this increase in age specific mortality rate, and 1 mSv/year (100 mrem/year) is typical of the annual effective dose from background, less radon (ICRP 1991). The 1 mSv estimate may underestimate the annual exposure to external sources of ionizing radiation to the U.S. population, as it does not include radiation from radon. Conversely, the 5 mSv estimate may be high, in that increases in mortality rate been reported. The most useful estimate appears to be the BEIR V estimate of 3.6 mSv, in that it accounts for an annual exposure to radon, is specific to the U.S. population, has not been associated with increases mortality, and it falls short of the 5 mSv value associated with small increases in human mortality.

Calculations:

$MRL = NOAEL_{(ADJ)} \div UF$
MRL = 3.6 mSv/year ÷ 3
MRL = 1.20 mSv/year
MRL = 1.0 mSv/year =100 mrem/year above background

Agency Contact (Chemical Manager): Obaid Faroon D.V.M., Ph.D.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.10, "Interactions with Other Substances," and Section 3.11, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.5, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38r is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

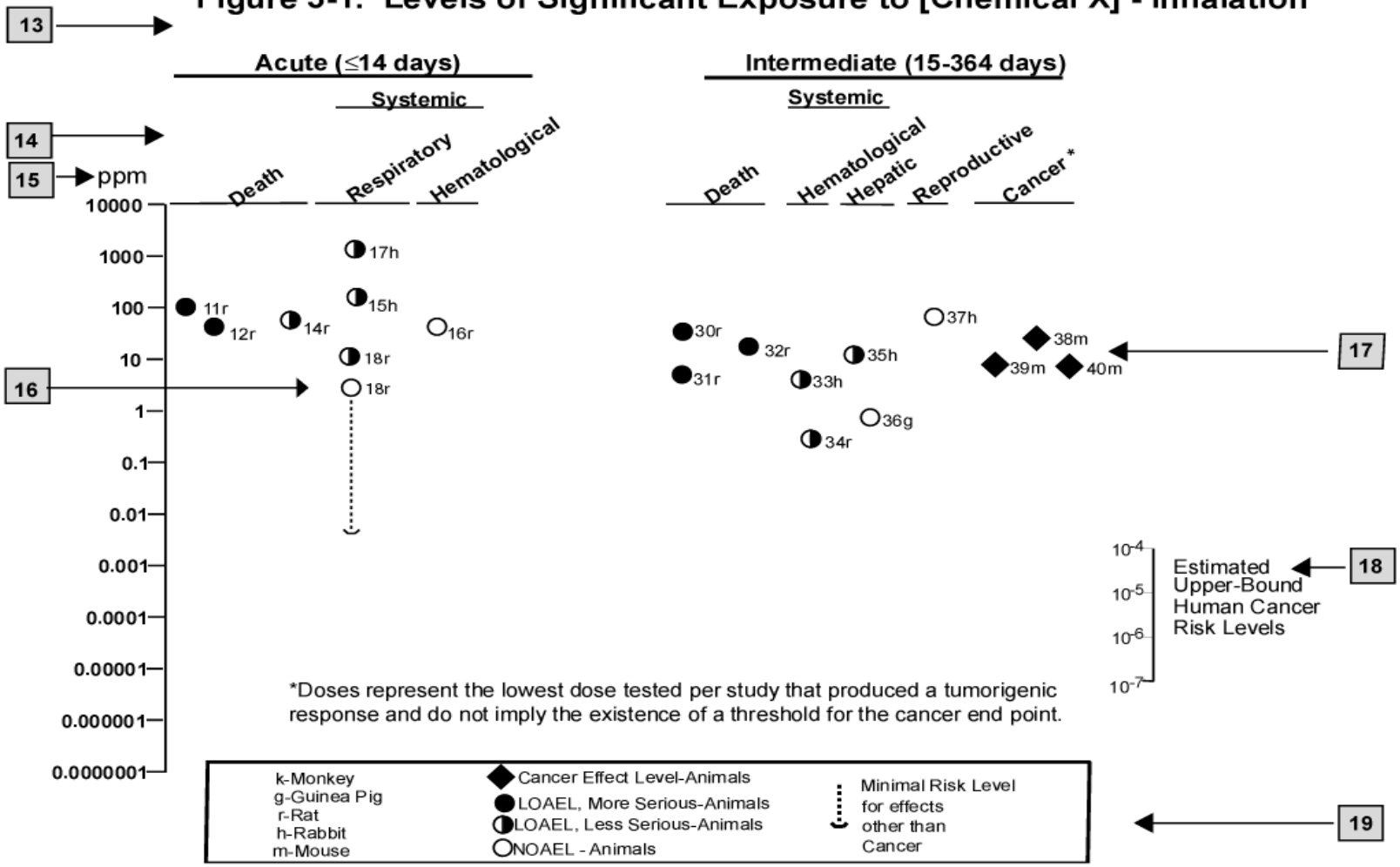
1 → **TABLE 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → a The number corresponds to entries in Figure 3-1.
b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5x10-3 ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

Some terms are generic and may not be used in this profile.

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALI	annual limit on intake
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DAC	derived air concentration
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense

DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid

MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration

OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	United States Nuclear Regulatory Commission
VOC	volatile organic compound

WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. OVERVIEW OF BASIC RADIATION PHYSICS, CHEMISTRY, AND BIOLOGY

Understanding the basic concepts in radiation physics, chemistry, and biology is important to the evaluation and interpretation of radiation-induced adverse health effects and to the derivation of radiation protection principles. This appendix presents a brief overview of the areas of radiation physics, chemistry, and biology and is based to a large extent on the reviews of Mettler and Moseley (1985), Hobbs and McClellan (1986), Eichholz (1982), Hendee (1973), Cember (1996), and Early et al. (1979).

D.1 RADIONUCLIDES AND RADIOACTIVITY

The substances we call elements are composed of atoms. Atoms in turn are made up of neutrons, protons and electrons: neutrons and protons in the nucleus and electrons in a cloud of orbits around the nucleus. Nuclide is the general term referring to any nucleus along with its orbital electrons. The nuclide is characterized by the composition of its nucleus and hence by the number of protons and neutrons in the nucleus. All atoms of an element have the same number of protons (this is given by the atomic number) but may have different numbers of neutrons (this is reflected by the atomic mass numbers or atomic weight of the element). Atoms with different atomic mass but the same atomic numbers are referred to as isotopes of an element.

The numerical combination of protons and neutrons in most nuclides is such that the nucleus is quantum mechanically stable and the atom is said to be stable, i.e., not radioactive; however, if there are too few or too many neutrons, the nucleus is unstable and the atom is said to be radioactive. Unstable nuclides undergo radioactive transformation, a process in which a neutron or proton converts into the other and a beta particle is emitted, or else an alpha particle is emitted. Each type of decay is typically accompanied by the emission of gamma rays. These unstable atoms are called radionuclides; their emissions are called ionizing radiation; and the whole property is called radioactivity. Transformation or decay results in the formation of new nuclides some of which may themselves be radionuclides, while others are stable nuclides. This series of transformations is called the decay chain of the radionuclide. The first radionuclide in the chain is called the parent; the subsequent products of the transformation are called progeny, daughters, or decay products.

In general there are two classifications of radioactivity and radionuclides: natural and artificial (man-made). Naturally-occurring radioactive materials (NORMs) exist in nature and no additional energy is necessary to place them in an unstable state. Natural radioactivity is the property of some naturally occurring, usually heavy elements, that are heavier than lead. Radionuclides, such as radium and uranium, primarily emit alpha particles. Some lighter elements such as carbon-14 and tritium (hydrogen-3) primarily emit beta particles as they transform to a more stable atom. Natural radioactive atoms heavier than lead cannot attain a stable nucleus heavier than lead. Everyone is exposed to background radiation from naturally-occurring radionuclides throughout life. This background radiation is the major source of radiation exposure to man and arises from several sources. The natural background exposures are frequently used as a standard of comparison for exposures to various artificial sources of ionizing radiation.

Artificial radioactive atoms are produced either as a by-product of fission of uranium or plutonium atoms in a nuclear reactor or by bombarding stable atoms with particles, such as neutrons or protons, directed at the stable atoms with high velocity. These artificially produced radioactive elements usually decay by emission of particles, such as positive or negative beta particles and one or more high energy photons (gamma rays). Unstable (radioactive) atoms of any element can be produced.

Both naturally occurring and artificial radioisotopes find application in medicine, industrial products, and consumer products. Some specific radioisotopes, called fall-out, are still found in the environment as a result of nuclear weapons use or testing.

D.2 RADIOACTIVE DECAY

D.2.1 Principles of Radioactive Decay

The stability of an atom is the result of the balance of the forces of the various components of the nucleus. An atom that is unstable (radionuclide) will release energy (decay) in various ways and transform to stable atoms or to other radioactive species called daughters, often with the release of ionizing radiation. If there are either too many or too few neutrons for a given number of protons, the resulting nucleus may undergo transformation. For some elements, a chain of daughter decay products may be produced until stable atoms are formed. Radionuclides can be characterized by the type and energy of the radiation emitted, the rate of decay, and the mode of decay. The mode of decay indicates how a parent compound undergoes transformation. Radiations considered here are primarily of nuclear origin, i.e., they arise from nuclear excitation, usually caused by the capture of charged or uncharged nucleons by a nucleus, or by the radioactive decay or transformation of an unstable nuclide. The type of radiation may be categorized as charged or uncharged particles, protons, and fission products) or electromagnetic radiation (gamma rays and x rays). Table D-1 summarizes the basic characteristics of the more common types of radiation encountered.

D.2.2 Half-Life and Activity

For any given radionuclide, the rate of decay is a first-order process that is constant, regardless of the radioactive atoms present and is characteristic for each radionuclide. The process of decay is a series of random events; temperature, pressure, or chemical combinations do not effect the rate of decay. While it may not be possible to predict exactly which atom is going to undergo transformation at any given time, it is possible to predict, on average, the fraction of the radioactive atoms that will transform during any interval of time.

The *activity* is a measure of the quantity of radioactive material. For these radioactive materials it is customary to describe the activity as the number of disintegrations (transformations) per unit time. The unit of activity is the curie (Ci), which was originally related to the activity of one gram of radium, but is now defined as that quantity of radioactive material in which there are:

1 curie (Ci) = 3.7×10^{10} disintegrations (transformations)/second (dps) or 2.22×10^{12} disintegrations (transformations)/minute (dpm).

The SI unit of activity is the becquerel (Bq); 1 Bq = that quantity of radioactive material in which there is 1 transformation/second. Since activity is proportional to the number of atoms of the radioactive material, the quantity of any radioactive material is usually expressed in curies, regardless of its purity or concentration. The transformation of radioactive nuclei is a random process, and the number of transformations is directly proportional to the number of radioactive atoms present. For any pure radioactive substance, the rate of decay is usually described by its radiological half-life, T_R, i.e., the time it takes for a specified source material to decay to half its initial activity. The specific activity is the activity of a radionuclide per mass of that radionuclide. If properly qualified, it can refer to activity per unit mass of related materials, such as the element itself or a chemical compound labeled with the radionuclide. The higher the specific activity of a radioisotope, the faster it is decaying.

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

$$A = A_o e^{-0.693t/Trad}$$

where A is the activity in dps or curies or becquerels, A_o is the activity at time zero, t is the time at which measured, and T_{rad} is the radiological half-life of the radionuclide (T_{rad} and t must be in the same units of time). The time when the activity of a sample of radioactivity becomes one-half its original value is the radioactive half-life and is expressed in any suitable unit of time.

Table D-1. Characteristics of Nuclear Radiations

Radiation	Rest mass[a]	Charge	Typical energy range	Path length[b]		Comments
				Air	Solid	
Alpha (α)	4.00 amu	+2	4–10 MeV	5–10 cm	25–80 μm	Identical to ionized He nucleus
Negatron (β^-)	$5.48x10^{-4}$ amu; 0.51 MeV	–1	0–4 MeV	0–10 m	0–1 cm	Identical to electron
Positron (β^+)	$5.48x10^{-4}$ amu; 0.51 MeV	+1	0-4 MeV	0–10 m	0–1 cm	Identical to electron except for sign of charge
Neutron	1.0086 amu; 939.55 MeV	0	0–15 MeV	b	b	Free half-life: 16 min
X ray (e.m. photon)	–	0	5 keV–100 keV	b	b	Photon from transition of an electron between atomic orbits
Gamma (ɣ) (e.m. photon)	–	0	10 keV–3 MeV	b	b	Photon from nuclear transformation

[a] The rest mass (in amu) has an energy equivalent in MeV that is obtained using the equation $E=mc^2$, where 1 amu = 932 MeV.
[b] Path lengths are not applicable to x- and gamma rays since their intensities decrease exponentially; path lengths in solid tissue are variable, depending on particle energy, electron density of material, and other factors.

amu = atomic mass unit; e.m. = electromagnetic; MeV = Megaelectron Volts

The specific activity is a measure of activity, and is defined as the activity of a radionuclide per mass of that radionuclide. This activity is usually expressed in curies per gram and may be calculated by

$$\text{curies/gram} = 1.3x10^8 / (T_{rad})\ (\text{atomic weight}) \quad \text{or}$$

$$[3.577 \times 10^5 \times \text{mass(g)}] / [T_{rad} \times \text{atomic weight}]$$

where T_{rad} is the radiological half-life in days.

In the case of radioactive materials contained in living organisms, an additional consideration is made for the reduction in observed activity due to regular processes of elimination of the respective chemical or biochemical substance from the organism. This introduces a rate constant called the biological half-life (T_{biol}) which is the time required for biological processes to eliminate one-half of the activity. This time is virtually the same for both stable and radioactive isotopes of any given element.

Under such conditions the time required for a radioactive element to be halved as a result of the combined action of radioactive decay and biological elimination is the effective clearance half-time:

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

Table D-2 presents representative effective half-lives of particular interest.

Table D-2. Half-Lives of Some Radionuclides in Adult Body Organs

		Half-life[a]		
Radionuclide	Critical organ	Physical	Biological	Effective
Uranium 238	Kidney	4,460,000,000 y	4 d	4 d
Hydrogen 3[b] (Tritium)	Whole body	12.3 y	10 d	10 d
Iodine 131	Thyroid	8 d	80 d	7.3 d
Strontium 90	Bone	28 y	50 y	18 y
Plutonium 239	Bone surface	24,400 y	50 y	50 y
	Lung	24,400 y	500 d	474 d
Cobalt 60	Whole body	5.3 y	99.5 d	95 d
Iron 55	Spleen	2.7 y	600 d	388 d
Iron 59	Spleen	45.1 d	600 d	42 d
Manganese 54	Liver	303 d	25 d	23 d
Cesium 137	Whole body	30 y	70 d	70 d

[a]d = days, y = years
[b]Mixed in body water as tritiated water

D.2.3 Interaction of Radiation with Matter

Both ionizing and nonionizing radiation will interact with materials; that is, radiation will lose kinetic energy to any solid, liquid or gas through which it passes by a variety of mechanisms. The transfer of energy to a medium by either electromagnetic or particulate radiation may be sufficient to cause formation of ions. This process is called ionization. Compared to other types of radiation that may be absorbed, such as ultraviolet radiation, ionizing radiation deposits a relatively large amount of energy into a small volume.

The method by which incident radiation interacts with the medium to cause ionization may be direct or indirect. Electromagnetic radiations (x rays and gamma photons) are indirectly ionizing; that is, they give up their energy in various interactions with cellular molecules, and the energy is then utilized to produce a fast-moving charged particle such as an electron. It is the electron that then may react with a target molecule. This particle is called a “primary ionizing particle. Charged particles, in contrast, strike the tissue or medium and directly react with target molecules, such as oxygen or water. These particulate radiations are directly ionizing radiations. Examples of directly ionizing particles include alpha and beta particles. Indirectly ionizing radiations are always more penetrating than directly ionizing particulate radiations.

Mass, charge, and velocity of a particle, as well as the electron density of the material with which it interacts, all affect the rate at which ionization occurs. The higher the charge of the particle and the lower the velocity, the greater the propensity to cause ionization. Heavy, highly charged particles, such as alpha particles, lose energy rapidly with distance and, therefore, do not penetrate deeply. The result of these

interaction processes is a gradual slowing down of any incident particle until it is brought to rest or "stopped" at the end of its range.

D.2.4 Characteristics of Emitted Radiation

D.2.4.1 Alpha Emission. In alpha emission, an alpha particle consisting of two protons and two neutrons is emitted with a resulting decrease in the atomic mass number by four and reduction of the atomic number of two, thereby changing the parent to a different element. The alpha particle is identical to a helium nucleus consisting of two neutrons and two protons. It results from the radioactive decay of some heavy elements such as uranium, plutonium, radium, thorium, and radon. The alpha particles emitted by a given radionuclide have the same energy and intensity combination. Most of the alpha particles that are likely to be found have energies in the range of about 4 to 8 MeV, depending on the isotope from which they came.

The alpha particle has an electrical charge of +2. Because of this double positive charge and their size, alpha particles have great ionizing power and, thus, lose their kinetic energy quickly. This results in very little penetrating power. In fact, an alpha particle cannot penetrate a sheet of paper. The range of an alpha particle (the distance the charged particle travels from the point of origin to its resting point) is about 4 cm in air, which decreases considerably to a few micrometers in tissue. These properties cause alpha emitters to be hazardous only if there is internal contamination (i.e., if the radionuclide is inside the body).

D.2.4.2 Beta Emission. A beta particle (β) is a high-velocity electron ejected from a disintegrating nucleus. The particle may be either a negatively charged electron, termed a negatron (β-) or a positively charged electron, termed a positron (β+). Although the precise definition of "beta emission" refers to both β- and β+, common usage of the term generally applies only to the negative particle, as distinguished from the positron emission, which refers to the β+ particle.

D.2.4.2.1 Beta Negative Emission. Beta particle (β-) emission is another process by which a radionuclide, with a neutron excess achieves stability. Beta particle emission decreases the number of neutrons by one and increases the number of protons by one, while the atomic mass number remains unchanged.[1] This transformation results in the formation of a different element. The energy spectrum of beta particle emission ranges from a certain maximum down to zero with the mean energy of the spectrum being about one-third of the maximum. The range of betas is much less in tissue than in air. Beta negative emitting radionuclides can cause injury to the skin and superficial body tissues, but mostly present an internal contamination hazard.

D.2.4.2.2 Positron Emission. In cases in which there are too many protons in the nucleus, positron emission may occur. In this case a proton may be thought of as being converted into a neutron, and a positron (β+) is emitted.1 This increases the number of neutrons by one, decreases the number of protons by one, and again leaves the atomic mass number unchanged. The gamma radiation resulting from the annihilation (see glossary) of the positron makes all positron emitting isotopes more of an external radiation hazard than pure β emitters of equal energy.

D.2.4.2.3 Gamma Emission. Radioactive decay by alpha, beta, or positron emission, or electron capture often leaves some of the energy resulting from these changes in the nucleus. As a result, the 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;

[1] Neutrinos also accompany negative beta particles and positron emissions

gamma emissions originate in the nucleus while x rays originate in the orbital electron structure or from rapidly changing the velocity of an electron (e.g., as occurs when shielding high energy beta particles or stopping the electron beam in an x ray tube).

D.3 ESTIMATION OF ENERGY DEPOSITION IN HUMAN TISSUES

Two forms of potential radiation exposures can result: internal and external. The term exposure denotes physical interaction of the radiation emitted from the radioactive material with cells and tissues of the human body. An exposure can be "acute" or "chronic" depending on how long an individual or organ is exposed to the radiation. Internal exposures occur when radionuclides, which have entered the body (e.g., through the inhalation, ingestion, or dermal pathways), undergo radioactive decay resulting in the deposition of energy to internal organs. External exposures occur when radiation enters the body directly from sources located outside the body, such as radiation emitters from radionuclides on ground surfaces, dissolved in water, or dispersed in the air. In general, external exposures are from material emitting gamma radiation, which readily penetrate the skin and internal organs. Beta and alpha radiation from external sources are far less penetrating and deposit their energy primarily on the skin's outer layer. Consequently, their contribution to the absorbed dose of the total body dose, compared to that deposited by gamma rays, may be negligible.

Characterizing the radiation dose to persons as a result of exposure to radiation is a complex issue. It is difficult to: (1) measure internally the amount of energy actually transferred to an organic material and to correlate any observed effects with this energy deposition; and (2) account for and predict secondary processes, such as collision effects or biologically triggered effects, that are an indirect consequence of the primary interaction event.

D.3.1 Dose/Exposure Units

D.3.1.1 Roentgen. The roentgen (R) is a unit of x or gamma-ray exposure and is a measured by the amount of ionization caused in air by gamma or x radiation. One roentgen produces 2.58×10^{-4} coulomb per kilogram of air. In the case of gamma radiation, over the commonly encountered range of photon energy, the energy deposition in tissue for a dose of 1 R is about 0.0096 joules (J) /kg of tissue.

D.3.1.2 Absorbed Dose and Absorbed Dose Rate. The absorbed dose is defined as the energy imparted by radiation to a unit mass of the tissue or organ. The unit of absorbed dose is the rad; 1 rad = 100 erg/gram = 0.01 J/kg in any medium. An exposure of 1 R results in a dose to soft tissue of approximately 0.01 J/kg. The SI unit is the gray which is equivalent to 100 rad or 1 J/kg. Internal and external exposures from radiation sources are not usually instantaneous but are distributed over extended periods of time. The resulting rate of change of the absorbed dose to a small volume of mass is referred to as the absorbed dose rate in units of rad/unit time.

D.3.1.3 Working Levels and Working Level Months. Working level (WL) is a measure of the atmospheric concentration of radon and its short-lived progeny. One WL is defined as any combination of short-lived radon daughters (through polonium-214), per liter of air, that will result in the emission of 1.3×10^5 MeV of alpha energy. An activity concentration of 100 pCi radon-222/L of air, in equilibrium with its daughters, corresponds approximately to a potential alpha-energy concentration of 1 WL. The WL unit can also be used for thoron daughters. In this case, 1.3×10^5 MeV of alpha energy (1 WL) is released by the thoron daughters in equilibrium with 7.5 pCi thoron/L. The potential alpha energy exposure of miners is commonly expressed in the unit Working Level Month (WLM). One WLM corresponds to exposure to a concentration of 1 WL for the reference period of 170 hours, or more generally

WLM = concentration (WL) x exposure time (months) (one “month” = 170 working hours).

D.3.2 Dosimetry Models

Dosimetry models are used to estimate the dose from internally deposited to radioactive substances. The models for internal dosimetry consider the amount of radionuclides entering the body, the factors affecting their movement or transport through the body, distribution and retention of radionuclides in the body, and the energy deposited in organs and tissues from the radiation that is emitted during spontaneous decay processes. The dose pattern for radioactive materials in the body may be strongly influenced by the route of entry of the material. For industrial workers, inhalation of radioactive particles with pulmonary deposition and puncture wounds with subcutaneous deposition have been the most frequent. The general population has been exposed via ingestion and inhalation of low levels of naturally occurring radionuclides as well as radionuclides from nuclear weapons testing.

The models for external dosimetry consider only the photon doses (and neutron doses, where applicable) to organs of individuals who are immersed in air or are exposed to a contaminated object.

D.3.2.1 Ingestion. Ingestion of radioactive materials is most likely to occur from contaminated foodstuffs or water or eventual ingestion of inhaled compounds initially deposited in the lung. Ingestion of radioactive material may result in toxic effects as a result of either absorption of the radionuclide or irradiation of the gastrointestinal tract during passage through the tract, or a combination of both. The fraction of a radioactive material absorbed from the gastrointestinal tract is variable, depending on the specific element, the physical and chemical form of the material ingested, and the diet, as well as some other metabolic and physiological factors. The absorption of some elements is influenced by age, usually with higher absorption in the very young.

D.3.2.2 Inhalation. The inhalation route of exposure has long been recognized as being a major portal of entry for both nonradioactive and radioactive materials. The deposition of particles within the lung is largely dependent upon the size of the particles being inhaled. After the particle is deposited, the retention will depend upon the physical and chemical properties of the dust and the physiological status of the lung. The retention of the particle in the lung depends on the location of deposition, in addition to the physical and chemical properties of the particles. The converse of pulmonary retention is pulmonary clearance. There are three distinct mechanisms of clearance which operate simultaneously. Ciliary clearance acts only in the upper respiratory tract. The second and third mechanisms act mainly in the deep respiratory tract. These are phagocytosis and absorption. Phagocytosis is the engulfing of foreign bodies by alveolar macrophages and their subsequent removal either up the ciliary "escalator" or by entrance into the lymphatic system. Some inhaled soluble particles are absorbed into the blood and translocated to other organs and tissues.

D.3.3 Internal Emitters

An internal emitter is a radionuclide that is inside the body. The absorbed dose from internally deposited radionuclide depends on the energy absorbed per unit mass by the irradiated tissue. For a radionuclide distributed uniformly throughout an infinitely large medium, the concentration of absorbed energy must be equal to the concentration of energy emitted by the radionuclide. An infinitely large medium may be approximated by a tissue mass whose dimensions exceed the range of the particle. All alpha and most beta radiation will be absorbed in the organ (or tissue) of reference. Gamma-emitting radionuclide emissions are penetrating radiation, and a substantial fraction of gamma energy may be absorbed in tissue. The dose to an organ or tissue is a function of the effective retention half-time, the energy released in the tissue, the amount of radioactivity initially introduced, and the mass of the organ or tissue.

D.4 BIOLOGICAL EFFECTS OF RADIATION

When biological material is exposed to ionizing radiation, a chain of cellular events occurs as the ionizing particle passes through the biological material. A number of theories have been proposed to describe the interaction of radiation with biologically important molecules in cells and to explain the resulting damage to biological systems from those interactions. Many factors may modify the response of a living organism to a given dose of radiation. Factors related to the exposure include the dose rate, the energy of the radiation, and the temporal pattern of the exposure. Biological considerations include factors such as species, age, sex, and the portion of the body exposed. Several excellent reviews of the biological effects of radiation have been published, and the reader is referred to these for a more in-depth discussion (Brodsky 1996; Hobbs and McClellan 1986; ICRP 1984; Mettler and Moseley 1985; Rubin and Casarett 1968).

D.4.1 Radiation Effects at the Cellular Level

According to Mettler and Moseley (1985), at acute doses up to 10 rad (100 mGy), single strand breaks in DNA may be produced. These single strand breaks may be repaired rapidly. With doses in the range of 50–500 rad (0.5–5 Gy), irreparable double-stranded DNA breaks are likely, resulting in cellular reproductive death after one or more divisions of the irradiated parent cell. At large doses of radiation, usually greater than 500 rad (5 Gy), direct cell death before division (interphase death) may occur from the direct interaction of free-radicals with essential cellular macromolecules. Morphological changes at the cellular level, the severity of which are dose-dependent, may also be observed.

The sensitivity of various cell types varies. According to the Bergonie-Tribondeau law, the sensitivity of cell lines is directly proportional to their mitotic rate and inversely proportional to the degree of differentiation (Mettler and Moseley 1985). Rubin and Casarett (1968) devised a classification system that categorized cells according to type, function, and mitotic activity. The categories range from the most sensitive type, "vegetative intermitotic cells", found in the stem cells of the bone marrow and the gastrointestinal tract, to the least sensitive cell type, "fixed postmitotic cells," found in striated muscles or long-lived neural tissues.

Cellular changes may result in cell death, which if extensive, may produce irreversible damage to an organ or tissue or may result in the death of the individual. If the cell recovers, altered metabolism and function may still occur, which may be repaired or may result in the manifestation of clinical symptoms. These changes may also be expressed at a later time as tumors or cellular mutations, which may result in abnormal tissue.

D.4.2 Radiation Effects at the Organ Level

In most organs and tissues the injury and the underlying mechanism for that injury are complex and may involve a combination of events. The extent and severity of this tissue injury are dependent upon the radiosensitivity of the various cell types in that organ system. Rubin and Casarett (1968) describe and schematically display the events following radiation in several organ system types. These include: a rapid renewal system, such as the gastrointestinal mucosa; a slow renewal system, such as the pulmonary epithelium; and a nonrenewal system, such as neural or muscle tissue. In the rapid renewal system, organ injury results from the direct destruction of highly radiosensitive cells, such as the stem cells in the bone marrow. Injury may also result from constriction of the microcirculation and from edema and inflammation of the basement membrane, designated as the histohematic barrier, which may progress to fibrosis. In slow renewal and nonrenewal systems, the radiation may have little effect on the parenchymal cells, but ultimate parenchymal atrophy and death over several months result from fibrosis and occlusion of the microcirculation.

D.4.3 Low Level Radiation Effects

Cancer is the major latent harmful effect produced by ionizing radiation and the one that most people exposed to radiation are concerned about. The ability of alpha, beta, and gamma radiation to produce cancer in virtually every tissue and organ in laboratory animals has been well-demonstrated. The development of cancer is not an immediate effect. Radiation-induced leukemia has the shortest latent period at about 2 years, while other radiation induced cancers, such as osteosarcoma, have latent periods greater than 20 years. The mechanism by which cancer is induced in living cells is complex and is a topic of intense study. Exposure to ionizing radiation can produce cancer at any site within the body; however, some sites appear to be more common than others, such as the breast, lung, stomach, and thyroid.

DNA is the major target molecule during exposure to ionizing radiation. Other macromolecules, such as lipids and proteins, are also at risk of damage when exposed to ionizing radiation. The genotoxicity of ionizing radiation is an area of intense study, as damage to the DNA is ultimately responsible for many of the adverse toxicological effects ascribed to ionizing radiation, including cancer. Damage to genetic material is basic to developmental or teratogenic effects, as well. However, for effects other than cancer, there is little evidence of human effects at low levels of exposure.

D.5 UNITS IN RADIATION PROTECTION AND REGULATION

D.5.1 Dose Equivalent (or Equivalent Dose)

Dose equivalent (as measured in rem or sievert) is a special radiation protection quantity that is used for administrative and radiation safety purposes to express the absorbed dose in a manner which considers the difference in biological effectiveness of various kinds of ionizing radiation. ICRP (1990) changed this term to equivalent dose, but it has not yet been adopted by the USNRC or DOE.

The USNRC defines the dose equivalent, H, as the product of the absorbed dose, D, and the quality factor, Q, at the point of interest in biological tissue. This relationship is expressed as $H = D \times Q$. The dose equivalent concept is applicable only to doses that are not great enough to produce biomedical effects.

The quality factor or radiation weighting factor is a dimensionless quantity that depends in part on the stopping power for charged particles, and it accounts for the differences in biological effectiveness found among the types of radiation. Originally relative biological effectiveness (RBE) was used rather than Q to define the quantity, rem, which was of use in risk assessment. The generally accepted values for quality factors and radiation weighting factors for various radiation types are provided in Table D-3. The dose equivalent rate is the time rate of change of the dose equivalent to organs and tissues and is expressed as rem/unit time or sievert/unit time.

Table D-3. Quality Factors (Q) and Absorbed Dose Equivalencies

Type of radiation	Quality factor (Q)	Radiation weighting factor (w_r)*
X, gamma, or beta radiation	1	1
Alpha particles, multiple-charged particles, fission fragments and heavy particles of unknown charge	20	0.05
Neutrons (other than thermal >> 100 keV to 2 MeV), protons, alpha particles, charged particles of unknown energy	10	20
Neutrons of unknown energy	10	
High-energy protons	10	0.1
Thermal neutrons		5

*Absorbed dose in rad equal to 1 rem or the absorbed dose in gray equal to 1 sievert.

Source: USNRC. 2004. Standards for the protection against radiation, table 1004(b).1. 10 CFR 20.1004. U.S. Nuclear Regulatory Commission, Washington, D.C. NCRP 1993

D.5.2 Relative Biological Effectiveness

RBE is used to denote the experimentally determined ratio of the absorbed dose from one radiation type to the absorbed dose of a reference radiation required to produce an identical biologic effect under the same conditions. Gamma rays from cobalt-60 and 200–250 kVp x-rays have been used as reference standards. The term RBE has been widely used in experimental radiobiology, and the term quality factor (or radiation weighting factor) used in calculations of dose equivalents for radiation safety purposes (ICRP 1977; NCRP 1971; UNSCEAR 1982). Any RBE value applies only to a specific biological end point, in a specific exposure, under specific conditions to a specific species. There are no generally applicable values of RBE since RBEs are specific to a given exposure scenario.

D.5.3 Effective Dose Equivalent (or Effective Dose)

The absorbed dose is usually defined as the mean energy imparted per unit mass to an organ or tissue. This represents a simplification of the actual problem. Normally when an individual ingests or inhales a radionuclide or is exposed to external radiation that enters the body (gamma), the dose is not uniform throughout the whole body. The simplifying assumption is that the detriment will be the same whether the body is uniformly or non-uniformly irradiated. In an attempt to compare detriment from absorbed dose of a limited portion of the body with the detriment from total body dose, the ICRP (1977) has derived a concept of effective dose equivalent. ICRP (1990) changed this term to effective dose, but it has not yet been adopted by the USNRC or DOE.

The effective dose equivalent, H_E, is

$$H_E = (\text{the sum of}) \; W_t \, H_t$$

where H_t is the dose equivalent (or equivalent dose) in the tissue t, W_t is the tissue weighting factor in that tissue, which represents the estimated proportion of the stochastic risk resulting from tissue, t, to the stochastic risk when the whole body is uniformly irradiated for occupational exposures under certain conditions (ICRP 1977). Tissue weighting factors for selected tissues are listed in Table D-4.

D.5.4 SI Units

The ICRU (1980), ICRP (1984), and NCRP (1985) now recommend that the rad, roentgen, curie, and rem be replaced by the SI units: gray (Gy), Coulomb per kilogram (C/kg), Becquerel (Bq), and sievert (Sv), respectively. The relationship between the customary units and the international system of units (SI) for radiological quantities is shown in Table D-5.

Table D-4. Tissue Weighting Factors for Calculating Effective Dose Equivalent and Effective Dose for Selected Tissues

	Tissue weighting factor	
Tissue	NCRP115/ ICRP60	USNRC/ICRP26
Bladder	0.05	–
Bone marrow	0.12	0.12
Bone surface	0.01	0.03
Breast	0.05	0.15
Colon	0.12	–
Esophagus	0.05	–
Gonads	0.20	0.25
Liver	0.05	–
Lung	0.12	0.12
Skin	0.01	–
Stomach	0.12	–
Thyroid	0.05	0.03
Remainder	0.05	0.30
Total	1.00	1.00

ICRP60 = International Commission on Radiological Protection, 1990 Recommendations of the ICRP
NCRP115 = National Council on Radiation Protection and Measurements. 1993. Risk Estimates for Radiation Protection, Report 115. Bethesda, Maryland
USNRC = Nuclear Regulatory Commission, Title 10, Code of Federal Regulations, Part 20

Table D-5. Comparison of Common and SI Units for Radiation Quantities

Quantity	Customary units	Definition	SI units	Definition
Activity (A)	curie (Ci)	3.7×10^{10} transformations s^{-1}	becquerel (Bq)	s^{-1}
Absorbed dose (D)	rad	10^{-2} Jkg^{-1}	gray (Gy)	Jkg^{-1}
Absorbed dose rate (Ď)	rad per second (rad s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	gray per second (Gy s^{-1})	Jkg^{-1} s^{-1}
Dose equivalent (H)	rem	10^{-2} Jkg^{-1}	sievert (Sv)	Jkg^{-1}
Dose equivalent rate ( )	rem per second (rem s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	sievert per second (Sv s^{-1})	Jkg^{-1} s^{-1}
Effective dose	rem	10^{-2} Jkg^{-1}	Sievert (Sv)	Jkg^{-1}
Equivalent dose (H)	rem	10^{-2} Jkg^{-1}	Sievert (Sv)	Jkg^{-1}
Linear energy transfer (LET)	kiloelectron volts per micrometer (keV μm^{-1})	1.602×10^{-10} Jm^{-1}	kiloelectron volts per micrometer (keV μm^{-1})	1.602×10^{-10} Jm^{-1}

Jkg^{-1} = Joules per kilogram; $Jkg^{-1}s^{-1}$ = Joules per kilogram per second; Jm^{-1} = Joules per meter; s^{-1} = per second

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APPENDIX E. INDEX