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 cesium, existing naturally as the stable (nonradioactive) isotope ^{133}Cs and in the form of radioactive isotopes produced during nuclear fission, the most abundant of which are ^{137}Cs and ^{134}Cs. This chapter 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 cesium; radiation toxicity associated with exposure to radiocesium (primarily ^{137}Cs and ^{134}Cs) is discussed in Section 3.3. The chemical properties of stable and radioactive cesium 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.

Since the average concentration of stable cesium in the earth's crust is low (on average about 1 ppm) and stable cesium is used only in small quantities in electronic and energy production industries, the risk of significant exposure to stable cesium via inhalation, oral, or dermal routes is expected to be small. Limited information is available on monitoring (or detection) of stable cesium in the environment and on health effects from exposure to stable cesium.

Decreased appetite, nausea, and diarrhea were reported in a man who ingested about 34 mg Cs/kg (as cesium chloride) after morning and evening meals for 36 days; this man also experienced apparent neurological changes within 15 minutes of dosing (Neulieb 1984). Prolonged QT syndrome and associated cardiac arrhythmias have been described in patients who have ingested cesium chloride as a component of homeopathic remedies (Bangh et al. 2001; Harik et al. 2002; Saliba et al. 2001).

Animal studies indicate that cesium is of relatively low toxicity. Acute oral LD_{50} values for rats and mice range from 800 to 2,000 mg Cs/kg, cesium hydroxide being more toxic than cesium iodide or cesium chloride. Single oral doses of cesium chloride, administered to female mice at dose levels ranging from 125 to 500 mg/kg, have been shown to result in significant increases in chromosomal breaks in bone marrow cells (Ghosh et al. 1990, 1991).

No reports were located regarding adverse effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation or dermal exposure to stable cesium.

Radioactive isotopes of cesium are a greater health concern than stable cesium. The most important exposure routes are external exposure to the radiation emitted by the radioisotope and ingestion of radioactive cesium-contaminated food sources. Vascular plants do not accumulate large levels of cesium through root uptake because cesium is strongly adsorbed to soils. However, the deposition of radioactive debris on flora with large surface areas such as lichens or moss is significant. Animals that feed on this vegetation, such as reindeer and caribou, may ingest large quantities of radiocesium (and other radionuclides found in fallout). Human consumption of meat from such animals results in the internalization of these radionuclides (see Section 6.7 for more detailed information on the lichen-caribou-human food chain). Radioactive cesium particles may be found in the air following the release of nuclear fission products; however, no reports were located in which adverse health effects from inhalation of radioactive cesium were discussed. Dermal absorption has been observed in rats, as evidenced by traces of ^{137}Cs in the blood a few minutes following dermal application of ^{137}CsCl (Pendic and Milivojevic 1966), but no data were located on relative amounts and absorption rates.

Limited human data are available regarding health effects that can be exclusively associated with exposure to radioactive cesium sources such as ^{137}Cs and ^{134}Cs. These radionuclides are products of either neutron activation or nuclear fission and may, therefore, be released from sites where nuclear fission occurs, from radioactive material removed from such sites, or from leakage of radioactive cesium sources. Both ^{137}Cs and ^{134}Cs emit beta radiation (that travels short distances and can penetrate the skin and superficial body tissues) and gamma radiation (that penetrates the entire body). The radiation dose from these radionuclides can be classified as either external (if the source is outside the body) or internal (if the source is inside the body).

The external dose from cesium radionuclides arises primarily from the penetrating gamma rays that travel great distances in air. Beta radiation emitted outside the body is normally of little health concern unless the radioactive material contacts the skin. Skin contact can allow the beta radiation to pass through the epidermis to live dermal tissue where it becomes a major contributor to a radiocesium-generated radiation dose to the skin. At very high doses, the beta and gamma radiation can cause such adverse effects as erythema, ulceration, or even tissue necrosis.

Once radioactive cesium is internalized, it is absorbed, distributed, and excreted in the same manner as stable cesium. The internal radiation dose from cesium is a measure of the amount of energy that the beta and gamma emissions deposit in tissue. The short-range beta radiation produces a localized dose while the more penetrating gamma radiation contributes to a whole body dose. Molecular damage results from the direct ionization of atoms that are encountered by beta and gamma radiation and by interactions of resulting free radicals with nearby atoms. Tissue damage results when the molecular damage is extensive and not sufficiently repaired in a timely manner.

In radiation biology, the term *absorbed dose* is the amount of energy deposited by radiation per unit mass of tissue, expressed in units of rad or gray (Gy) (see Appendix D for a detailed description of principles of ionizing radiation. The term *dose equivalent* refers to the biologically significant dose, which is determined by multiplying the absorbed dose by radiation weighting factors for the type and energy of the radiations involved. Dose equivalent is expressed in units of rem or sievert (Sv). The radiation weighting factors are considered to be unity for the beta and gamma radiation emitted from ^{134}Cs and ^{137}Cs, so for these radionuclides, the absorbed dose (in rad or Gray) is equal to the dose equivalent (in rem or sievert). The dose equivalent from internalized cesium radionuclides is estimated using the quantity of material entering the body (via ingestion or inhalation), the biokinetic parameters for cesium (retention, distribution, and excretion), the energies and intensities of the beta and gamma radiation emitted, and parameters describing the profile of absorbed radiation energy within the body. If, for example, a person ingests a given activity of radiocesium (measured in curies [Ci] or becquerels [Bq]), the tissues of the body will absorb some of the energy of the emitted beta and gamma radiation in a pattern reflecting the kinetics of distribution and elimination of the ingested radiocesium, the rate at which the radioactive isotope decays to a stable form, and the age of the person at the time of ingestion, which affects both the biokinetics of the radiocesium as well as the potential length of time over which the tissues can be exposed to the radiation. The biodistribution of cesium will vary somewhat for uptake in muscle, fat, various organs, and the skeleton. Therefore, each tissue may receive a different dose equivalent. The total dose equivalent for the body will reflect the integration of the dose equivalents for the various tissues using a weighting scheme for the relative sensitivities of tissues and organs to short- and long-term effects.

The EPA has published a set of internal dose conversion factors for standard persons of various ages (newborn; 1, 5, 10, or 15 years of age; and adult) in its Federal Guidance Report No. 13 supplemental CD (EPA 2000). For example, the EPA has estimated that the dose equivalent following ingestion of 1 Bq of ^{137}Cs is 1.30×10^{-8} Sv (assuming an integration time of 50 years for an adult following the initial

exposure). Age-specific dose coefficients for inhalation and ingestion of any of the radioactive isotopes of cesium by the general public can be found in ICRP publications 71 (ICRP 1995) and 72 (ICRP 1996), respectively. Dose coefficients for inhalation, ingestion, and submersion in a cloud of cesium radionuclides can be found in U.S. EPA Federal Guidance Report No. 11 (EPA, 1993a). Dose coefficients for external exposure to radioisotopes of cesium in air, surface water, or soil contaminated to various depths can be found in U.S. EPA Federal Guidance Report No. 12 (EPA, 1993b).

Adverse health effects resulting from external exposure to beta or gamma emissions from radioisotopes of cesium would be the same as those from other radioactive elements that release beta or gamma radiation, and would not be the result of exposure to cesium *per se* (refer to Section 2.2 for a discussion of dose-related symptoms of acute radiation exposure). Developmental and carcinogenic effects have been reported in Japanese survivors of acute high-dose external radiation from the atomic bombs detonated over Hiroshima and Nagasaki (see Agency for Toxic Substances and Disease Registry 1999 for a detailed description of the health effects related to ionizing radiation in general). Exposure to lower levels of radiation would be expected to result in decreased health risk. Although developmental and carcinogenic effects would be expected in individuals subjected to high radiation doses from any source of gamma radiation, non-accidental exposure to a level of significant health risk via a radiocesium source is not likely to occur.

Symptoms typical of cutaneous radiation syndrome (initial dermal erythema and subsequent ulceration) occurred among Russian military recruits who were accidentally exposed to a sealed source of ^{137}Cs (Gottlöber et al. 2000). Some of the exposed men also described symptoms of nausea, vomiting, and headache, which occurred at the onset of the dermal effects.

A number of individuals in Goiânia, Brazil, who experienced mixed external, dermal, and oral exposure to an opened ^{137}CsCl source, exhibited classic symptoms of acute radiation syndrome including vomiting, diarrhea, and nausea, as well as skin lesions from radiation burns, orofacial lesions, ocular injury, hematological effects (bone marrow aplasia, leukopenia, thrombocytopenia, lymphopenia, neutropenia), mild elevations of some liver enzymes, reduced sperm counts, and death (in four cases, attributed to infections resulting from reduced resistance) (Brandão-Mello et al. 1991; Gomes et al. 1990). External exposure was estimated based on frequencies of chromosomal aberrations in lymphocytes of exposed individuals at various times following exposure, while internal doses were estimated based on whole-body radiation counting and excretory levels of ^{137}Cs. The adverse effects were the result of beta and gamma radiation, not cesium *per se*.

Information regarding adverse effects in animals exposed to radioactive isotopes of cesium via natural routes (inhalation, oral, or dermal) is limited to observations of significantly reduced fertility and temporary sterility in male mice following single or repeated oral administration of radioactive cesium nitrate (Ramaiya et al. 1994). Postmating embryo mortality was associated with increased frequency of dominant lethal mutations. Studies of animals exposed to radiocesium via natural routes are not usually performed because levels great enough to cause significant adverse health effects would also pose a severe health risk to investigators. However, it has been shown that distribution patterns of ^{137}Cs are similar in animals exposed to relatively nontoxic levels of ^{137}CsCl by parenteral injection, inhalation exposure, or oral administration (Boecker et al. 1969a; Stara 1965). Therefore, the occurrence of depressed blood factors, severe bone marrow depression, germinal cell damage, early death, and increased incidences of benign and malignant neoplasms in a variety of tissues in dogs exposed to ^{137}CsCl via intravenous injection provide the most reasonable indication of health effects that would be expected in animals exposed to ^{137}CsCl by inhalation or oral exposure (Nikula et al. 1995, 1996).

Adverse neurological, developmental, reproductive, genotoxic, and cancer effects have been observed in animal studies employing external exposure to sealed radioactive cesium sources, and are the result of the external gamma radiation, not the cesium *per se*. Impaired motor activity, decreased thickness of cortical layers of the brain, and increased aggressive behavior were observed after the birth of rats that had been briefly exposed *in utero* to relatively high levels of external radiation from a ^{137}Cs source (Minamisawa et al. 1992; Norton and Kimler 1987, 1988). The most vulnerable developmental period was around gestational days 14–15. In another study, adverse developmental effects in fetal rats irradiated on gestational day 12 included reduced litter size, smaller head size, retarded odontogenesis, and cleft palate when examined on gestational day 18 (Saad et al. 1991, 1994). Significant increases in the formation rate of micronuclei were seen in blood cells of other fetal rats following irradiation of pregnant dams via a sealed ^{137}Cs source on gestational day 14 (Koshimoto et al. 1994). Significantly reduced fertility (including temporary sterility) was reported in male mice exposed to an external ^{137}Cs source for almost 20 days; an increased frequency of dominant lethal mutations was also indicated by increased postmating embryo mortality (Ramaiya et al. 1994). Increased lifetime risk of mammary tumors was noted in female rats that were exposed, between the ages of 8 and 36 weeks, to single whole-body doses of radiation from a ^{137}Cs source (Bartstra et al. 1998). Irradiation at 64 weeks, however, yielded fewer carcinomas than unirradiated controls.

3.2 DISCUSSION OF HEALTH EFFECTS OF STABLE CESIUM BY ROUTE OF EXPOSURE

Section 3.2 discusses the chemical toxicity of cesium. Radiation toxicity resulting from exposure to radiocesium 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 cesium. 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 1990b), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

3.2.1 Inhalation Exposure

No reports were located regarding the following health effects in humans or animals following inhalation exposure to stable cesium:

3.2.1.1 Death

3.2.1.2 Systemic Effects

3.2.1.3 Immunological and Lymphoreticular Effects

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

3.2.2 Oral Exposure

Limited information is available regarding health effects following oral exposure of humans to stable cesium compounds. Symptoms of decreased appetite, nausea, diarrhea, and cardiac arrhythmia have been associated with consumption of cesium chloride (Bangh et al. 2001; Harik et al. 2002; Neulieb 1984; Saliba et al. 2001). Death was reported laboratory animals following oral administration of large doses of cesium compounds (Ghosh et al. 1990; Johnson et al. 1975; Khosid 1967).

3.2.2.1 Death

No reports were located regarding death in humans following acute-, intermediate-, or chronic-duration oral exposure to stable cesium.

No studies were located regarding death in animals following intermediate- or chronic-duration oral exposure to stable cesium. However, acute oral administration of cesium at high dose levels has resulted in observed mortality in rats and mice. In female mice administered cesium chloride, reported oral LD_{50} values range from 2,300 to 2,500 mg/kg (Ghosh et al. 1990; Khosid 1967). An acute oral LD_{50} value for cesium iodide is 2,386 mg/kg in rats (Johnson et al. 1975). Cesium hydroxide appears to be more highly toxic to rats than cesium chloride and cesium iodide, as evidenced by a lower LD_{50} value of 1,026 mg/kg (Johnson et al. 1975). Some of the toxic effects can be attributed to the strong alkaline nature of cesium hydroxide. Khosid (1967) estimated an acute oral LD_{50} value of 800 mg/kg for mice that were administered cesium hydroxide. No information was located regarding mortality in animals following oral administration of other compounds of stable cesium.

3.2.2.2 Systemic Effects

Decreased appetite, nausea, and diarrhea were reported in a man who ingested about 34 mg Cs/kg (as stable cesium chloride) after morning and evening meals for 36 days; this man also experienced apparent neurological changes within 15 minutes of dosing (Neulieb 1984). Prolonged QT syndrome and associated cardiac arrhythmias have been described in patients who have ingested cesium chloride as a

component of homeopathic remedies (Bangh et al. 2001; Harik et al. 2002; Saliba et al. 2001). No additional information was located regarding systemic effects in humans following oral exposure to stable cesium.

No animal studies were located in which the systemic effects that were observed following oral administration of compounds of stable cesium could be attributed to the presence of cesium. Gastrointestinal and respiratory effects noted in rats administered acute oral doses of cesium hydroxide may have been due to the alkaline properties of the compound rather than the biochemical behavior of cesium.

No data were located regarding, hematological, musculoskeletal, endocrine, dermal, ocular, or metabolic effects in humans or animals following oral exposure to stable cesium.

Respiratory Effects. No reports were located regarding respiratory effects in humans following acute-, intermediate-, or chronic-duration oral exposure to stable cesium.

No reports were located regarding respiratory effects in animals following intermediate- or chronic-duration exposure to stable cesium. Congested, cyanotic lungs with petechial hemorrhages were observed in rats following oral treatment with single cesium iodide doses large enough to cause death. A bloody nasal exudate was seen in some relatively high-dose rats (Johnson et al. 1975).

Cardiovascular Effects. Individual case reports describe prolonged QT syndrome and associated cardiac arrhythmia in patients who consumed cesium chloride as a component of homeopathic remedies for cancer prevention (Saliba et al. 2001), tumor reduction (Harik et al. 2002), and cyst reduction (Bangh et al. 2001. No reports were located regarding cardiovascular effects in animals following acute-, intermediate-, or chronic-duration oral exposure to stable cesium.

Gastrointestinal Effects. No reports were located regarding gastrointestinal effects in humans following acute- or chronic-duration oral exposure to stable cesium, and only one report of intermediate-duration exposure was located. An investigator who voluntarily ingested about 34 mg Cs/kg (as cesium chloride, assuming 70 kg body weight) after each morning and evening meal (68 mg Cs/kg/day) for 36 days reported gradually decreased appetite, prenausea feelings, and diarrhea. The observations were self-described and effects were correlated to dietary habits during the course of the study (Neulieb 1984).

No reports were located regarding gastrointestinal effects in animals following intermediate- or chronic-duration oral exposure to stable cesium. In an acute lethality study of rats, administration of cesium hydroxide or cesium iodide at dose levels up to 910 or 1,217 mg Cs/kg, respectively, resulted in stomach and intestinal hemorrhage, bloody fluid exudate within the peritoneal cavity, and adhesions of abdominal organs. Rats receiving lethal doses of cesium iodide exhibited fluid-filled stomach (Johnson et al. 1975).

Hepatic Effects. No reports were located regarding hepatic effects in humans following acute-, intermediate-, or chronic-duration oral exposure to stable cesium.

No reports were located regarding hepatic effects in animals following acute- or chronic-duration oral exposure to stable cesium. No significant effect on maternal liver weight was noted in rats consuming 115 mg Cs/kg/day (as cesium chloride in the drinking water) during gestation and 40 mg Cs/kg/day during lactation (Messiha 1988b).

Renal Effects. No reports were located regarding renal effects in humans following acute-, intermediate-, or chronic-duration oral exposure to stable cesium.

No reports were located regarding renal effects in animals following acute- or chronic-duration oral intake of stable cesium, and one report was located regarding intermediate-duration intake. In that study, no significant effect on maternal kidney weight was noted in mice consuming 115 mg Cs/kg/day (as cesium chloride in the drinking water) during gestation and 40 mg Cs/kg/day during lactation (Messiha 1988b).

Body Weight Effects. No reports were located regarding body weight effects in humans following acute-, intermediate-, or chronic-duration oral exposure to stable cesium.

No reports were located regarding body weight effects in animals following acute- or chronic-duration oral exposure to stable cesium. One intermediate-duration study found no significant effect on maternal body weight in mice consuming 115 mg Cs/kg/day (as cesium chloride in the drinking water) during gestation and 40 mg Cs/kg/day during lactation (Messiha 1988b).

3.2.2.3 Immunological and Lymphoreticular Effects

No reports were located regarding immunological or lymphoreticular effects in humans following acute-, intermediate-, or chronic-duration oral exposure to stable cesium.

No reports were located regarding immunological or lymphoreticular effects in animals following acute- or chronic-duration oral exposure to stable cesium. In one study of intermediate-duration, no significant effect on maternal spleen weight was noted in mice consuming 115 mg Cs/kg/day (as cesium chloride in the drinking water) during gestation and 40 mg Cs/kg/day during lactation (Messiha 1988b).

3.2.2.4 Neurological Effects

No reports were located regarding neurological effects in humans following acute- or chronic-duration oral exposure to stable cesium. In one study of intermediate-duration exposure, an investigator, who voluntarily ingested about 34 mg Cs/kg/day (as stable cesium chloride) after morning and evening meals for 36 days, experienced general feelings of well-being, heightened sense perception, and tingling sensations in lips, cheeks, hands, and feet within 15 minutes of intake (Neulieb 1984). No self-reported adverse effects were noted in performance of mathematical tasks or in automobile driving skill.

No reports were located regarding neurological effects in animals following intermediate- or chronic-duration oral exposure to stable cesium. Rats administered unspecified acute gavage doses of cesium hydroxide exhibited initial signs of hyperexcitability followed by apathy and weakness during the course of 14 days of observation after dosing (Johnson et al. 1975).

3.2.2.5 Reproductive Effects

No reports were located regarding reproductive effects in humans or animals following acute-, intermediate-, or chronic-duration oral exposure to stable cesium.

3.2.2.6 Developmental Effects

No reports were located regarding developmental effects in humans following acute-, intermediate-, or chronic-duration oral exposure to stable cesium.

No reports were located regarding developmental effects in animals following acute- or chronic-duration oral exposure to stable cesium. In intermediate-duration studies, one investigator reported reduced body weight in offspring of mouse dams consuming approximately 115 mg Cs/kg/day during gestation and

40 mg Cs/kg/day during lactation (Messiha 1988b). Other observations included slight, but significant, changes in some organ weights and slight differences in activity of some hepatic enzymes among offspring of treated dams, relative to controls. Similar results were reported in the offspring of female mice consuming approximately 40 mg Cs/kg/day only during lactation (Messiha 1989b). However, gross and histopathologic examinations of the offspring, typical of well-designed developmental toxicity studies, were not performed in either of these studies, making them of little value for assessment of the developmental toxicity potential of cesium.

3.2.2.7 Cancer

No reports were located in which cancer in humans or animals could be associated with acute-, intermediate-, or chronic-duration oral exposure to stable cesium.

3.2.3 Dermal Exposure

3.2.3.1 Death

No reports were located regarding death in humans or animals following acute-, intermediate-, or chronic-duration dermal exposure to stable cesium.

3.2.3.2 Systemic Effects

No reports were located in which respiratory, cardiovascular, gastrointestinal, hematological, musculo-skeletal, hepatic, renal, endocrine, body weight, or metabolic effects in humans or animals could be associated with dermal exposure to stable cesium.

Dermal Effects. No reports were located regarding dermal effects in humans following acute-, intermediate-, or chronic-duration dermal exposure to stable cesium.

No reports were located regarding dermal effects in animals following intermediate- or chronic-duration dermal exposure to stable cesium. Cesium hydroxide was considered a nonirritant on intact skin and a mild irritant on abraded skin of rabbits 24 and 48 hours, respectively, following closed-patch application of a 5% solution; similar application of cesium iodide resulted in no observed irritation (Johnson et al. 1975).

Ocular Effects. No reports were located regarding eye irritation in humans resulting from ocular contact with stable cesium.

A 5% solution of cesium hydroxide was extremely irritating and caustic to the rabbit eye (Johnson et al. 1975). It is likely that this effect was the result of the caustic nature of the hydroxide rather than an effect due to cesium *per se*. Similar treatment with cesium iodide resulted in no evidence of ocular irritation.

3.2.3.3 Immunological and Lymphoreticular Effects

No reports were located regarding immunological or lymphoreticular effects in humans following acute-, intermediate-, or chronic-duration dermal exposure to stable cesium.

No reports were located regarding immunological or lymphoreticular effects in animals following acute- or chronic-duration dermal exposure to stable cesium. There was no indication of a sensitization response in guinea pigs following repeated intracutaneous injections of 0.1% solutions of cesium hydroxide or cesium iodide (Johnson et al. 1975).

No reports were located regarding the following health effects in humans or animals following dermal exposure to stable cesium:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

3.2.4.1 Death

No data were located regarding death in humans or animals following exposure to stable cesium via routes other than inhalation, oral, or dermal exposure.

3.2.4.2 Systemic Effects

No data were located regarding respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans or animals following exposure to stable cesium via routes other than inhalation, oral, or dermal exposure.

Cardiovascular Effects. Cardiac arrhythmias were elicited in experimental animals following the injection of stable cesium chloride directly into the circulatory system (Brachmann et al. 1983; Levine et al. 1985; Murakawa et al. 1997; Patterson et al. 1990; Senges et al. 2000).

No reports were located in which the following health effects in humans or animals could be associated with exposure to stable cesium via routes other than inhalation, oral, or dermal exposure:

3.2.4.3 Immunological and Lymphoreticular Effects

3.2.4.4 Neurological Effects

3.2.4.5 Reproductive Effects

3.2.4.6 Developmental Effects

3.2.4.7 Cancer

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

Section 3.3 discusses radiation toxicity associated with exposure to radionuclides of cesium 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, 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

During and after nuclear accidents, such as the steam explosion that occurred at the Chernobyl nuclear power plant in 1986, significant amounts of ^{137}Cs (and to a lesser extent ^{134}Cs) may be released to the atmosphere in suspended particles and be widely dispersed through the air. Although radioactive cesium, suspended in the air following such accidents or re-suspended later from ground-deposited fallout (USNRC 1998), may be internalized via inhalation, there was no indication that inhalation was a significant route of exposure to radioactive cesium among individuals exposed externally by either being in the vicinity of a release or in areas receiving substantial ground-deposited fallout, or those exposed by ingestion of radioactive cesium-contaminated food following the Chernobyl accident (Balonov 1993).

No reports were located regarding health effects in humans or animals following inhalation exposure to radioactive cesium. Available human case reports and animal studies involving inhaled radioisotopes of cesium deal exclusively with biokinetics. Parenteral injection of ^{137}CsCl in laboratory animals has resulted in distribution patterns and tissue doses of ^{137}Cs that are similar to those resulting from inhalation or oral exposure (Boecker et al. 1969a; Stara 1965). For these reasons, it has been proposed that adverse health effects, related to a soluble and readily absorbed compound such as ^{137}CsCl, should be similar across the three routes of exposure (Melo et al. 1996, 1997; Nikula et al. 1995, 1996). Therefore, depressed blood factors, severe bone marrow depression, germinal cell damage, early death, and increased incidences of benign and malignant neoplasms in a variety of tissues and organs, effects that have been observed in dogs following intravenous administration of ^{137}CsCl (Nikula et al. 1995, 1996; Redman et al. 1972), would be expected to occur following inhalation exposure to air concentrations of ^{137}CsCl that would result in comparable ^{137}Cs blood concentrations (see Section 3.3.4 for additional information regarding exposure other than inhalation, oral, dermal, or external exposure).

3.3.1.1 Death

Although no studies were located regarding death in humans or animals following acute-, intermediate-, or chronic-duration inhalation exposure to radioactive cesium, dose-related decreased survival was observed in beagle dogs that had received single intravenous injections of ^{137}CsCl in amounts resulting in average initial body burdens of 64–147 MBq/kg (1.7–4.0 mCi/kg) (Nikula et al. 1995, 1996). Similar

effects would be expected in animals exposed to air concentrations of ^{137}CsCl that would result in similar body burdens (see Section 3.3.4 for more detailed information regarding health effects in animals exposed to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure).

3.3.1.2 Systemic Effects

No data were located regarding systemic effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation exposure to radioactive cesium. However, hematological effects similar to those observed in dogs that had received single intravenous injections of ^{137}CsCl (Nikula et al. 1995, 1996; Redman et al. 1972) would be expected in animals exposed to air concentrations of ^{137}CsCl that would result in body burdens similar to those attained via intravenous injection.

Hematological Effects. Depressed blood cell counts and platelet levels, reduced packed-cell volume, and bone marrow aplasia were observed in dogs that had been administered single intravenous injections of ^{137}CsCl, which resulted in average initial body burdens ranging from 36.4 to 141.0 MBq/kg (1.0 to 3.8 mCi/kg) (Nikula et al. 1995; Redman et al. 1972). Severely depressed blood cell counts were observed in 23 dogs that died within 52 days following single intravenous administration of ^{137}CsCl at levels resulting in average initial body burdens in the range of 64–147 MBq/kg (1.7–4.0 mCi/kg) (Nikula et al. 1996). Similar effects would be expected in dogs exposed to air concentrations of ^{137}CsCl that would result in body burdens similar to those attained via intravenous injection (see Section 3.3.4 for more detailed information regarding health effects in animals exposed to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure).

3.3.1.3 Immunological and Lymphoreticular Effects

No data were located regarding immunological or lymphoreticular effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation exposure to radioactive cesium. However, severe bone marrow depression was observed in dogs exposed to ^{137}CsCl by intravenous injection at activity levels resulting in estimated total bone marrow doses of 7–24 Gy (700–2,400 rad) (Nikula et al. 1995). Similar effects would be expected in dogs exposed to air concentrations of ^{137}CsCl that would result in body burdens similar to those attained via intravenous injection (see Section 3.3.4 for more detailed information regarding health effects in animals exposed to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure).

3.3.1.4 Neurological Effects

No data were located regarding neurological effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation exposure to radioactive cesium.

3.3.1.5 Reproductive Effects

No data were located regarding reproductive effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation exposure to radioactive cesium. However, germinal epithelium damage and azoospermia were reported in dogs that had been administered ^{137}CsCl by intravenous injection at activity levels resulting in long-term total whole-body doses ranging from 7.42 to 16.40 Gy (742 to 1,640 rad) (Nikula et al. 1995, 1996). Similar effects would be expected in dogs exposed to air concentrations of ^{137}CsCl that would result in body burdens similar to those attained via intravenous injection (see Section 3.3.4 for more detailed information regarding health effects in animals exposed to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure).

3.3.1.6 Developmental Effects

No data were located regarding developmental effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation exposure to radioactive cesium.

3.3.1.7 Cancer

No data were located in which cancer in humans or animals could be associated with acute-, intermediate-, or chronic-duration inhalation exposure to radioactive cesium. However, benign and malignant neoplasms were found in a variety of tissues and organs of dogs administered single intravenous doses of ^{137}CsCl, which resulted in average initial body burdens ranging from 37 to 147 MBq/kg (1.0 to 4.0 mCi/kg) (Nikula et al. 1995, 1996). Similar effects would be expected in dogs exposed to air concentrations of ^{137}CsCl that would result in body burdens similar to those attained via intravenous injection (see Section 3.3.4 for more detailed information regarding health effects in animals exposed to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure).

3.3.2 Oral Exposure

No reports were located regarding health effects in humans or animals that could be exclusively associated with oral exposure to radioisotopes of cesium. Available human case reports and animal studies involving ingested radioisotopes of cesium deal with biokinetics. Parenteral injection of ^{137}CsCl in laboratory animals has resulted in distribution patterns and tissue doses of ^{137}Cs that are similar to those resulting from inhalation or oral exposure (Boecker et al. 1969a; Stara 1965). For these reasons, it has been proposed that adverse health effects, related to a soluble and readily absorbed compound such as ^{137}CsCl, should be similar across the three routes of exposure (Melo et al. 1996, 1997; Nikula et al. 1995, 1996). Therefore, depressed blood factors, severe bone marrow depression, germinal cell damage, early death, and increased incidences of benign and malignant neoplasms in a variety of tissues and organs, effects that have been observed in dogs following intravenous administration of ^{137}CsCl (Nikula et al. 1995, 1996; Redman et al. 1972), would be expected to occur following oral administration of ^{137}CsCl in amounts that would result in comparable ^{137}Cs blood concentrations (see Section 3.3.4 for additional information regarding exposure other than inhalation, oral, dermal, or external exposure).

3.3.2.1 Death

No reports were located regarding death in humans that could be exclusively associated with acute-, intermediate-, or chronic-duration oral exposure to radioactive cesium. In an event involving mixed external, dermal, and oral exposure of adults and children to an opened ^{137}CsCl source, significant short-term morbidity was followed in 50 patients and 4 deaths were reported within a few weeks among individuals with estimated radiation doses ranging from 4.5 to 6 Gy (450 to 600 rad) (Brandão-Mello et al. 1991).

Although no studies were located regarding death in humans or animals following acute-, intermediate-, or chronic-duration oral exposure to radioactive cesium, decreased survival was observed in young adult beagle dogs that had received single intravenous injections of ^{137}CsCl in amounts resulting in average initial body burdens of 64–147 MBq/kg (1.7–4.0 mCi/kg) (Nikula et al. 1995, 1996). Similar results would be expected in animals following oral exposure to ^{137}CsCl levels that would result in similar body burdens (see Section 3.3.4 for more detailed information regarding health effects in animals exposed to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure).

3.3.2.2 Systemic Effects

Acute radiation syndrome, characterized by nausea, vomiting, and diarrhea was reported in a number of individuals following mixed external, dermal, and oral exposure to an opened 50.9 TBq (1,375 Ci) ^{137}CsCl source in Goiânia, Brazil. Other adverse effects included skin lesions, ocular lesions, severe bone marrow depression, and mild elevations in the activities of some liver enzymes (Brandão-Mello et al. 1991; Gomes et al. 1990; Rosenthal et al. 1991). Hematological effects similar to those observed in dogs that had received single intravenous injections of ^{137}CsCl (Nikula et al. 1995, 1996; Redman et al. 1972) would be expected in animals following oral administration of ^{137}CsCl at levels that would result in body burdens similar to those attained via intravenous injection.

No data were located regarding, respiratory, cardiovascular, musculoskeletal, renal, endocrine, body weight, or metabolic effects in humans or animals following oral exposure to radioactive cesium.

Gastrointestinal Effects. Vomiting, diarrhea, and nausea were observed among eight patients treated for acute radiation exposure to an opened ^{137}CsCl source, both via external exposure and internal exposure (Brandão-Mello et al. 1991). These and other symptoms were classic symptoms of acute radiation syndrome. No reports were located regarding gastrointestinal effects in humans following intermediate- or chronic-duration oral exposure to radioactive cesium

No reports were located for animals regarding gastrointestinal effects following acute-, intermediate-, or chronic-duration oral exposure to radioactive cesium.

Hematological Effects. No reports were located for humans regarding hematological effects following intermediate- or chronic-duration oral exposure to radioactive cesium. In the 1987 incident of overexposure to a scavenged medical radiation source containing 50.9 TBq (1,375 Ci) ^{137}CsCl, approximately 250 persons were contaminated externally, many of whom also were contaminated internally. Twenty individuals developed the acute radiation syndrome, 14 of whom developed bone marrow failure after having received whole-body radiation doses ranging from 1 to 7.0 Gy (100 to 700 rad). Four of these 14 heavily contaminated individuals died. These effects are typical signs and symptoms of the hemopoietic (blood forming) syndrome in which the blood forming cells in the bone marrow are killed. This results in sharp decreases of all the blood cells and consequent impairment of the immune system and anemia (Brandão-Mello et al. 1991; Gomes et al. 1990).

No reports were located for animals regarding hematological effects following acute-, intermediate-, or chronic-duration oral exposure to radioactive cesium. However, depressed blood cell counts and platelet levels, reduced packed-cell volume, and bone marrow aplasia were observed in dogs that had been administered single intravenous injections of ^{137}CsCl, which resulted in average initial body burdens ranging from 36.4 to 141.0 MBq/kg (1.0 to 3.8 mCi) (Nikula et al. 1995; Redman et al. 1972). Severely depressed blood cell counts were observed in 23 dogs that died from 20 to 52 days following single intravenous administration of ^{137}CsCl at levels resulting in initial body burdens in the range of 122–164 MBq/kg (3.3–4.4 mCi/kg) (Nikula et al. 1996) and in 11 other dogs (Nikula et al. 1995) that died from 19 to 81 days following intravenous administration of ^{137}CsCl at levels resulting in initial body burdens in the range of 72–141 MBq/kg (1.9–3.8 mCi/kg). Similar effects would be expected in dogs following oral administration of ^{137}CsCl at levels that would result in body burdens similar to those attained via intravenous injection (see Section 3.3.4 for more detailed information regarding health effects in animals exposed to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure).

Hepatic Effects. No reports were located that associate acute-duration oral exposure to radioactive cesium with hepatic effects. Mild elevations of aminotransferases (ALT/AST) were seen in a few patients hospitalized following radiation exposure to an opened ^{137}CsCl source (Brandão-Mello et al. 1991). Exposures were both external and internal. No reports were located for humans regarding hepatic effects following intermediate- or chronic-duration oral exposure to radioactive cesium.

No reports were located for animals regarding hepatic effects following acute-, intermediate-, or chronic-duration oral exposure to radioactive cesium.

Dermal Effects. Reports of dermal effects are restricted to the accidental mixed external, dermal, and oral exposure of a number of individuals to an opened ^{137}CsCl source in which orofacial lesions, including oral bleeding and associated oral rash, mouth ulcers, acute oral candidiasis, and radiation dermatitis and depigmentation, were observed in 21 patients who had been acutely exposed at estimated radiation doses ranging from 1 to 7 Gy (100 to 700 rad) (Gomes et al. 1990). Some individuals exposed in the same incident exhibited typical radiation-induced skin lesions; the forearm was amputated in one individual with severe radiation injury (Brandão-Mello et al. 1991; Gomes et al. 1990).

No reports were located regarding dermal effects in animals following acute-, intermediate-, or chronic-duration oral exposure to radioactive cesium.

Ocular Effects. No reports were located regarding ocular effects in humans following intermediate- or chronic-duration oral exposure to radioactive cesium. Among 20 patients hospitalized following mixed external, dermal, and oral exposure to an opened ^{137}CsCl source, a few patients complained of lacrimation, hyperemia and edema of the conjunctiva, and ocular pain (Brandão-Mello et al. 1991). A few cases of protracted reduction in visual capacity were also reported, among which retinal injury was documented. In these cases, there was no change in lens transparency. These effects were due to the radiation, not to cesium *per se*.

No reports were located regarding ocular effects in animals following acute-, intermediate-, or chronic-duration oral exposure to radioactive cesium.

3.3.2.3 Immunological and Lymphoreticular Effects

No reports were located that associate immunological or lymphoreticular effects in humans with intermediate- or chronic-duration oral exposure to radioactive cesium. Severe bone marrow depression, characterized by a low white blood cell count and consequent immunodeficiency, developed in 14 patients hospitalized following mixed external, dermal, and oral exposure to an opened ^{137}CsCl source resulting in estimated absorbed doses ranging from 1 to 7 Gy (100 to 700 rad) (Brandão-Mello et al. 1991).

No reports were located regarding immunological or lymphoreticular effects in animals following acute-, intermediate-, or chronic-duration oral exposure to radioactive cesium. However, severe bone marrow depression was observed in dogs exposed to ^{137}CsCl by intravenous injection at activity levels resulting in estimated total bone marrow doses of 7–24 Gy (700–2,400 rad) (Nikula et al. 1995). Similar effects would be expected in dogs following oral exposure to ^{137}CsCl levels that would result in body burdens similar to those attained via intravenous injection (see Section 3.3.4 for more detailed information regarding health effects in animals exposed to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure).

3.3.2.4 Neurological Effects

No reports were located for humans or animals that associate neurological effects with acute-, intermediate-, or chronic-duration oral exposure to radioactive cesium.

3.3.2.5 Reproductive Effects

No reports were located that associate reproductive effects in humans with intermediate- or chronic-duration oral exposure to radioactive cesium. Spermatozoa were reduced or absent in the semen of nine males examined approximately 1 month following presumed acute radiation doses on the order of several hundred rad from an opened ^{137}CsCl source (Brandão-Mello et al. 1991). These individuals may have experienced mixed external, dermal, and oral exposure.

No reports were located regarding reproductive effects in animals following intermediate- or chronic-duration oral exposure to radioactive cesium. Significantly reduced fertility, expressed as the percentage of matings resulting in pregnancy (percent effective matings), was noted in male mice following a single oral administration of ^{137}Cs (as cesium nitrate) at activity levels that resulted in a total dose to the testis of approximately 3 Gy (300 rad) (Ramaiya et al. 1994). Complete, though temporary, sterility was evident at week 6 after dosing. By week 17, there were no significant differences in fertility between treatment and control groups. No significant reduction in male fertility was observed at activity levels resulting in cumulative doses to the testes ranging from 0.1 to 1 Gy (10 to 100 rad). Significantly reduced fertility was also evident in male mice administered daily oral doses of ^{137}Cs (as cesium nitrate) for 2 weeks that resulted in total testicular radiation doses of about 3.85 Gy (385 rad), measured at 5 weeks after treatment (Ramaiya et al. 1994).

Germinal epithelium damage and azoospermia were reported in dogs that had been administered ^{137}Cs (as cesium chloride) by intravenous injection at activity levels resulting in long-term total whole-body doses ranging from 7.42 to 16.40 Gy (742 to 1,640 rad) (Nikula et al. 1995, 1996). Similar effects would be expected in dogs following oral exposure to ^{137}CsCl levels that would result in body burdens similar to those attained via intravenous injection (see Section 3.3.4 for more detailed information regarding health effects in animals exposed to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure).

The highest NOAEL values and all reliable LOAEL values for reproductive effects from oral exposure to radioactive cesium are presented in Table 3-1 and plotted in Figure 3-1.

Table 3-1 Levels of Significant Exposure to Cesium - Radiation Toxicity - Oral

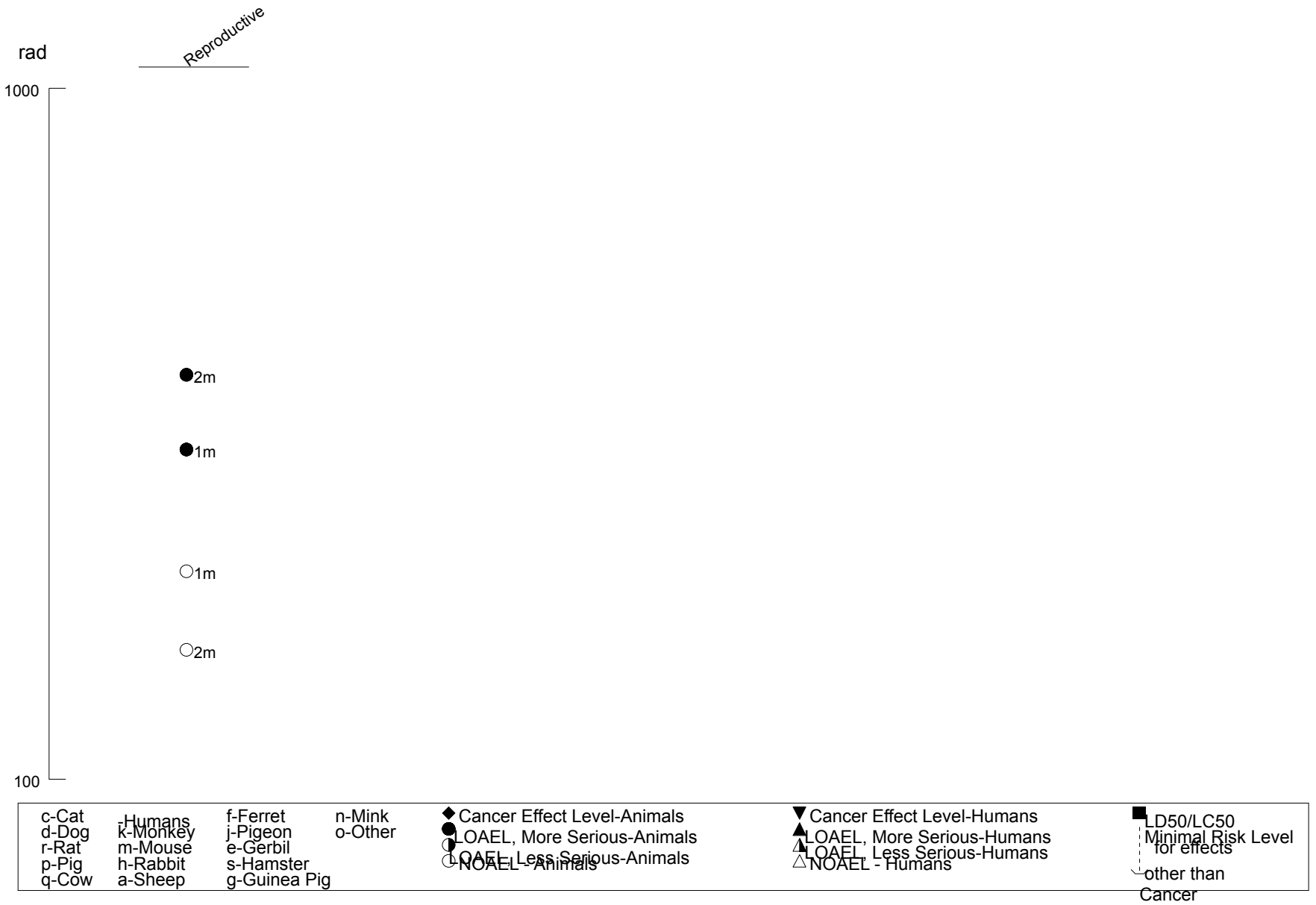
Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL		Reference Chemical Form
					Less Serious (rad)	Serious (rad)	
	ACUTE EXPOSURE						
	Reproductive						
1	Mouse (Hybrid)	Once (G)		200 M		300 M (temporary sterility)	Ramaiya et al. 1994 Cesium 137(as Cesium Nitrate)
2	Mouse (Hybrid)	2 wk 1x/d (G)		154 M		385 M (reduced fertility)	Ramaiya et al. 1994 Cesium 137(as Cesium Nitrate)

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

d=day(s); (G) = gavage; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; wk = week(s)

Figure 3-1. Levels of Significant Exposure to Cesium - Radiation Toxicity - Oral

Acute (≤14 day)



3.3.2.6 Developmental Effects

No reports were located that associate developmental effects in humans or animals with acute-, intermediate-, or chronic-duration oral exposure to radioactive cesium.

3.3.2.7 Cancer

No reports were located in which cancer in humans or animals could be associated with acute-, intermediate-, or chronic-duration oral exposure to radioactive cesium. However, benign and malignant neoplasms were found in a variety of tissues and organs of dogs administered single intravenous doses of ^{137}CsCl, which resulted in initial body burdens ranging from 37 to 147 MBq/kg (1.0 to 4.0 mCi/kg) (Nikula et al. 1995, 1996). Similar effects would be expected in dogs following oral exposure to ^{137}CsCl levels that would result in body burdens similar to those attained via intravenous injection (see Section 3.3.4 for more detailed information regarding health effects in animals exposed to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure).

3.3.3 External Exposure

This section contains information regarding health effects related to external exposure to radioactive cesium sources. Radionuclides of cesium, such as ^{137}Cs and ^{134}Cs, emit both beta particles and gamma rays, which are a health hazard in living organisms because they are capable of ionizing atoms that they encounter. Beta particles can travel appreciable distances in air, but travel only a few millimeters in tissues. External exposure to beta particles may result in damage to skin and superficial body tissues, but is not a threat to internal organs unless 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. Several feet of concrete or a few inches of lead or other high-density shielding are required for protection from gamma rays. Because it is so highly penetrating, external gamma radiation emitted by radionuclides such as cesium is a radiation hazard to internal organs (Agency for Toxic Substances and Disease Registry 1999; EPA 1998).

The purpose of this section is to provide information regarding health effects associated with external exposure to a radioactive cesium source. External exposure to radioactive cesium is simply exposure to beta and gamma radiation; there is nothing unique to cesium *per se*. The same hazards exist from

external exposure to any source of beta and gamma radiation. 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

There are no reports of deaths in humans that could be exclusively associated with acute-, intermediate-, or chronic-duration external exposure to radioactive cesium. Death was noted within a few weeks following mixed external, dermal, and oral exposure to an opened ^{137}CsCl source that resulted in estimated radiation doses ranging from 4 to 6 Gy (400 to 600 rad) (Brandão-Mello et al. 1991). See Section 3.3.2.1 for more detailed information.

Significantly reduced survival was noted in rat fetuses following whole-body irradiation (via a ^{137}Cs source) of pregnant dams on gestational day 14 at acute radiation doses ≤4 Gy (400 rad); an LD_{50} value was about 5 Gy (500 rad) (Koshimoto et al. 1994). No reports were located regarding death in animals following intermediate- or chronic-duration external exposure to radioactive cesium.

3.3.3.2 Systemic Effects

Symptoms typical of cutaneous radiation syndrome (initial dermal erythema and subsequent ulceration) occurred among Russian military recruits who were accidentally exposed to a sealed source of ^{137}Cs during training in 1996 and 1997 (Gottlöber et al. (2000). Some of the exposed men also described symptoms of acute radiation syndrome (nausea, vomiting, and headache), which occurred at the onset of the dermal effects. Nausea, vomiting, and diarrhea, were reported in a number of individuals following mixed external, dermal, and oral exposure to an opened ^{137}CsCl source in Goiânia, Brazil; other adverse effects included skin lesions, ocular lesions, severe bone marrow depression, and mild elevations in the activities of some liver enzymes (Brandão-Mello et al. 1991; Gomes et al. 1990; Rosenthal et al. 1991). See Section 3.3.2.2 for a more detailed description of systemic effects following mixed exposure to radioactive cesium.

No reports were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, ocular, body weight, metabolic, or other systemic effects in humans or animals that could be exclusively associated with external exposure to radioactive cesium.

Dermal Effects. Initial dermal erythema progressed to ulceration within a few weeks following initial accidental exposure of Russian military recruits to a sealed external source of ^{137}Cs gamma radiation (Gottlöber et al. 2000). However, there was no information regarding radiation doses to these individuals.

3.3.3.3 Immunological and Lymphoreticular Effects

No reports were located that associate immunological or lymphoreticular effects in humans with intermediate- or chronic-duration external exposure to radioactive cesium. Severe bone marrow depression, characterized by neutropenia and thrombocytopenia, developed in 14 patients hospitalized following mixed external, dermal, and oral exposure to an opened ^{137}CsCl source resulting in estimated absorbed doses ranging from 1 to 7 Gy (100 to 700 rad) (Brandão-Mello et al. 1991). This effect was the result of the radiation, not the presence of cesium *per se*.

No reports were located regarding immunological or lymphoreticular effects in animals following acute-, intermediate-, or chronic-duration external exposure to radioactive cesium.

3.3.3.4 Neurological Effects

No reports were located that associate neurological effects in humans or animals with postnatal acute-, intermediate-, or chronic-duration external exposure to radioactive cesium. Neurological effects associated with *in utero* exposure are discussed in Section 3.3.3.6, Developmental Effects.

3.3.3.5 Reproductive Effects

No reports were located that associate reproductive effects in humans with intermediate- or chronic-duration external exposure to radioactive cesium. Spermatozoa were reduced or absent in the semen of nine males examined approximately 1 month following presumed acute exposure to an opened ^{137}CsCl source (Brandão-Mello et al. 1991). These individuals may have experienced mixed external, dermal, and oral exposure.

No reports were located regarding reproductive effects in animals following acute- or chronic-duration external exposure to radioactive cesium. Significantly reduced fertility, expressed as the percentage of matings resulting in pregnancy (% effective matings), was noted in male mice following external

exposure to a ^{137}Cs source 23 hours a day for 19.5 days at a dose rate of 0.675 mGy/hour (6.75 mrad/hour), resulting in a total dose of 3Gy (300 rad) (Ramaiya et al. 1994). Complete sterility was evident in males by the third week following exposure termination. During weeks 1 and 2 after the cessation of treatment, significantly increased total and postimplantation embryo mortality was noted. These effects were the result of the radiation, not the presence of cesium *per se*.

All reliable LOAEL values for reproductive effects from external exposure to radioactive cesium are presented in Table 3-2 and plotted in Figure 3-2.

3.3.3.6 Developmental Effects

No reports were located that associate developmental effects in humans with acute-, intermediate-, or chronic-duration external exposure to radioactive cesium. Cells of the developing central nervous system are among the most sensitive to the effects of ionizing radiation in the developing fetus (Agency for Toxic Substances and Disease Registry 1999). Schull and Otake (1999) cite numerous reports in which impaired cognitive function was observed in atomic bomb survivors of Hiroshima and Nagasaki prenatally exposed (during weeks 8–15 or 16–25 after ovulation) to ionizing radiation from the bombs. The small number (38) of mentally-impaired survivors makes it difficult to generalize a dose-response relationship. However, the data are compatible with either a threshold dose of 20–40 rad (0.2–0.4 Gy) or zero threshold linear response. Although such effects would be expected in individuals exposed to similar levels of external radiation from any source of gamma radiation, it is unlikely that such high levels would be achieved from any radiocesium source under situations of normal use.

No reports were located regarding developmental effects in animals following intermediate- or chronic-duration external exposure to radioactive cesium. Significantly reduced postnatal body weight, impaired motor activity, and decreased thickness within cortical layers of the brain were observed in young rats (7–21 days postpartum) exposed during gestation by whole-body radiation of pregnant dams via a sealed ^{137}Cs gamma radiation source at a rate of approximately 0.5 Gy/minute (50 rad/minute) for a total radiation dose of 0.75 or 1 Gy (75 or 100 rad) (Norton and Kimler 1987, 1988). The effects were of larger magnitude when the fetal rats were exposed on gestation day 15 rather than earlier (gestation days 11 or 13) or later (gestation day 17). Significantly smaller litter size, smaller head size, and retarded odontogenesis were observed in fetuses of pregnant mice exposed on gestation day 12 to whole-body irradiation from a sealed ^{137}Cs gamma radiation source for 4.9 minutes (resulting in a total radiation dose

Table 3-2 Levels of Significant Exposure to Cesium - Radiation Toxicity - External Radiation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)		LOAEL Serious (rad)		Reference Chemical Form
	ACUTE EXPOSURE								
	Developmental								
1	Rat (Wistar)	Once Gd 13, 14, or 15			50	(increased micronuclei in hematocytes)	400	(31.5% fetal mortality)	Koshimoto et al. 1994 Cesium 137
2	Rat (Sprague-Dawley)	Once Gd 11 or 17					100	(altered motor function, decreased cortical thickness)	Norton and Kimler 1987 Cesium 137
3	Rat (Sprague-Dawley)	Once Gd 13, 15, or 17					75	(altered motor function, decreased cortical thickness, most prominent when exposed on Gd 15)	Norton and Kimler 1988 Cesium 137
4	Mouse (C57BL/6)	Once Gd 14			100 M	(6% lower body weight, 9% lower brain weight, reduced brain size)			Minamisawa et al. 1990 Cesium 137
5	Mouse (C57BL/6)	Once Gd 14			100 M	(16% lower body weight, increased aggressive behavior)			Minamisawa et al. 1992 Cesium 137
6	Mouse Swiss albino	Once Gd 12			400	(retarded odontogenesis)			Saad et al. 1991 Cesium 137

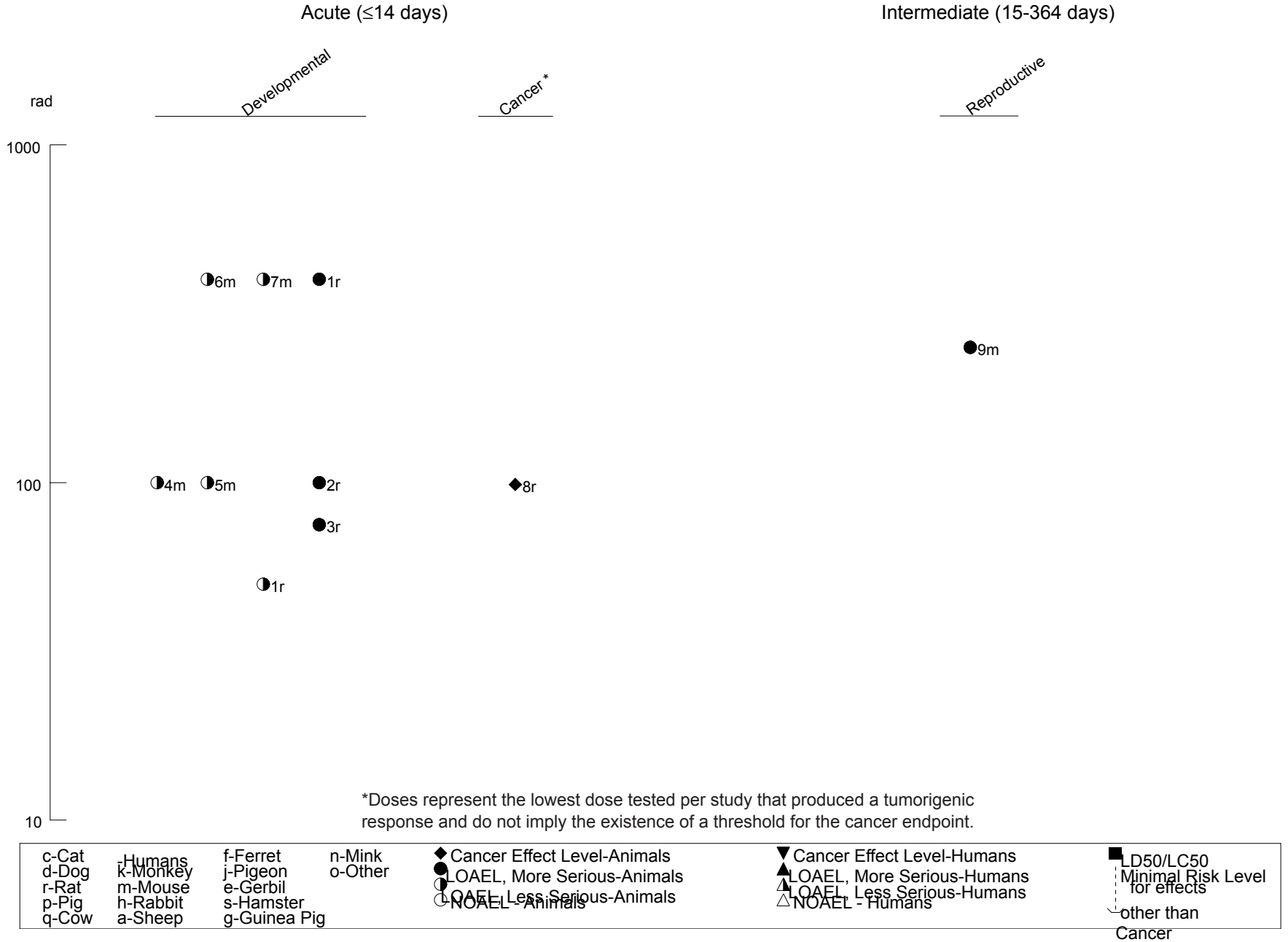
Table 3-2 Levels of Significant Exposure to Cesium - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
7	Mouse Swiss albino	Once Gd 12			400 (smaller litter size, smaller head size, delayed palatogenesis)		Saad et al. 1994 Cesium 137
	Cancer						
8	Rat WAG/Rij	Once at 8, 12, 16, 22, 36, or 64 wk of age				100 F (mammary carcinoma in 57/200 rats)	Bartstra et al. 1998 Cesium 137
	INTERMEDIATE EXPOSURE						
	Reproductive						
9	Mouse (Hybrid)	19.5 d 23 hr/d				300 M (reduced fertility)	Ramaiya et al. 1994 Cesium 137

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

d=day(s); F = Female; Gd = gestational day; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; wk = week(s).

Figure 3-2. Levels of Significant Exposure to Cesium - Radiation Toxicity - External Radiation



of 4 Gy or 400 rad) and examined on gestation day 18. Additionally, all exposed fetuses exhibited cleft palate on examination while normal closure was observed in all unexposed control fetuses (Saad et al. 1991, 1994). Significantly reduced survival was observed in rat fetuses following whole-body irradiation (via a sealed ^{137}Cs gamma radiation source) of pregnant dams on gestation day 14 at acute radiation doses of 4 Gy (400 rad) or greater. An LD_{50} value for fetuses was about 5 Gy (500 rad) (Koshimoto et al. 1994). Aggressive behavior was studied in male mice (100–135 days of age) exposed *in utero* on gestation day 14 through whole-body irradiation of pregnant dams via an external sealed ^{137}Cs gamma radiation source at total radiation doses of 1 or 2 Gy (100 or 200 rad) (Minamisawa et al. 1992). Incidences of aggressive behavior were significantly higher among irradiated groups, relative to untreated controls. The intensity of aggressive behavior was significantly higher only in the 2 Gy (200 rad) exposure group. Minamisawa et al. (1990) found dose-related significantly decreased brain weight in 6-month-old mice that had been irradiated on gestation day 14 at doses of 1–3 Gy (100–300 rad). In each of these studies (Koshimoto et al. 1994; Minamisawa et al. 1990, 1992; Norton and Kimler 1987, 1988), the observed developmental effects were the result of radiation exposure, not the presence of cesium *per se*.

Kusama and Hasegawa (1993) designed a study to examine the relationship between fetal developmental stage at the time of external exposure to a sealed ^{137}Cs gamma radiation source and the occurrence of external malformations and growth retardation. Groups of pregnant ICR mice were irradiated once with 1.5 Gy (150 rad) at a dose rate of 0.2 Gy/minute (20 rad/minute) on 6-hour intervals during the period of organogenesis (gestation days 6.5–14). Fetuses were examined on gestation day 18. The authors reported peaks in the occurrence of exencephaly among fetuses irradiated during gestation days 6.5–8.75 and 10.25–10.75, and the highest peak occurred at gestation day 7.5. Peaks in the occurrence of cleft palate were seen in fetuses irradiated at gestation days 8.75 and 10.75. The most apparent reduction in body weight of irradiated fetuses, relative to controls, occurred in groups irradiated between gestation days 9.75 and 11. The observed developmental effects were the result of radiation exposure, not the presence of cesium *per se*.

All reliable LOAEL values for developmental effects from external exposure to radioactive cesium are presented in Table 3-2 and plotted in Figure 3-2.

3.3.3.7 Cancer

No reports were located regarding cancer in humans following acute-, intermediate-, or chronic-duration external exposure to radioactive cesium in particular. Due to the nature of ionizing radiation in general, carcinogenic effects similar to those observed in Japanese survivors of the 1945 atomic bombing incidents might be expected among individuals acutely exposed to high levels of radiation from a radioactive cesium source. In the only available reports of adverse health effects in humans following exposure to radioactive cesium (^{137}Cs, the accidental human exposures in Goiânia, Brazil in 1987 and Russia in 1996 and 1997), the incidents are too recent for meaningful data on the potential for carcinogenicity. No reports were located in which increased cancer risk could be associated with long-term exposure to low levels of ionizing radiation.

No reports were located regarding cancer in animals following intermediate- or chronic-duration external exposure to radioactive cesium. Increased lifetime risk of mammary tumors was observed in female WRG/Rij rats exposed to single whole-body doses of 1 or 2 Gy (100 or 200 rad) of ^{137}Cs gamma radiation at a dose rate of 75 rad/minute (0.75 Gy/minute) between the ages of 8 and 36 weeks (Bartstra et al. 1998). The excess normalized risk values for carcinoma were 0.9 and 2.2 for 1 and 2 Gy (100 and 200 rad) doses, respectively, with no significant differences between the age groups of 8, 12, 16, 22, or 36 weeks. Irradiation at 64 weeks, however, yielded fewer carcinomas than unirradiated controls. The excess normalized risk values were found to be -0.7 and -0.3 for 1 and 2 Gy (100 and 200 rad) doses, respectively. These effects were the result of the gamma radiation, not the presence of cesium *per se*.

3.3.4 Other Routes of Exposure

Although parenteral injection is not considered to be an exposure route of concern for the general population, it has been considered to be a good indicator of adverse health effects that would be expected in laboratory animals following the absorption of ^{137}CsCl into the blood if such animals were to be exposed via inhalation or oral routes (Boecker et al. 1969a; Melo et al. 1996, 1997; Nikula et al. 1995, 1996). This argument is based on the results of biokinetic studies in dogs (Boecker et al. 1969a) in which intravenous injections of ^{137}CsCl resulted in temporal and tissue distribution patterns and tissue doses of ^{137}Cs that were similar to those resulting from inhalation exposure (Boecker et al. 1969a). Similar tissue distribution and retention kinetics were also shown in guinea pigs whether exposure to ^{137}CsCl had been via intraperitoneal, inhalation, or oral routes (Stara 1965).

In dogs, intravenous administration of soluble ^{137}CsCl has resulted in depression of a number of blood factors, severe bone marrow depression, germinal cell damage (males), and early death (Nikula et al. 1995, 1996; Redman et al. 1972). Long-term surviving dogs exhibited increased incidences of benign and malignant neoplasms in a variety of tissues and organs, with no apparent single target organ of toxicity.

3.3.4.1 Death

Dose-related decreased survival was observed in young adult beagle dogs that had received single intravenous injections of ^{137}CsCl in amounts resulting in average initial body burdens of 71.7–141 MBq/kg (1.9–3.8 mCi/kg) (Nikula et al. 1995). All six dogs in the highest exposure group died between 19 and 33 days following injection. The total whole body radiation dose to death in this group of dogs averaged 11.8 Gy (1,180 rad). Deaths were attributed to severe pancytopenia resulting from hematopoietic cell damage. In a study of 63 other beagle dogs, intravenous injection of ^{137}CsCl resulted in initial body burdens of approximately 64–147 MBq/kg (1.7–4.0 mCi/kg) (Nikula et al. 1996). These dogs, grouped according to age, were juveniles (142–151 days old), young adults (388–427 days old), or middle-aged adults (1,387–2,060 days old) at the time of injection. Early mortality, within 52 days following injection, was noted in 10/10 middle-aged dogs, 10/38 young adults, and 3/15 juveniles. Average initial ^{137}Cs body burdens among the early deaths were in the range of 133–147 MBq/kg (3.6–4.0 mCi/kg). The middle-aged dogs died significantly earlier ($p=0.002$) than the juvenile or young adult dogs, and middle-aged female dogs died significantly earlier ($p=0.002$) than middle-aged male dogs.

3.3.4.2 Systemic Effects

No data were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans or animals following exposure to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure.

Hematological Effects. Hematological dyscrasia, characterized by severe thrombocytopenia and leukopenia, and death within 81 days were observed in 11 of 54 dogs that had been administered single intravenous injections of ^{137}CsCl (Nikula et al. 1995; Redman et al. 1972). The early deaths occurred in groups with average initial body burdens ranging from 71.7 to 141 MBq/kg (1.9 to 3.8 mCi) and cumulative doses to death in the range of 11.8–14.0 Gy (1,180–1,400 rad). Moderately to severely depressed blood cell counts were observed among 25 surviving dogs, some of which had been injected with lower levels of ^{137}CsCl that resulted in average initial body burdens of 36.4 or 51.7 MBq/kg (1.0 or

1.4 mCi/kg). Other treatment-related hematological effects included bone marrow aplasia, decreased platelet levels, and reduced packed-cell volume. In long-term surviving dogs, depressed blood values returned toward normal within during the first year after radiocesium injection. Severely depressed blood cell counts were observed in 23 dogs that died within 52 days following single intravenous administration of ^{137}CsCl at levels resulting in average initial body burdens in the range of 64–162 MBq/kg (1.7–4.4 mCi/kg) (Nikula et al. 1996).

3.3.4.3 Immunological and Lymphoreticular Effects

Severe bone marrow depression was observed in dogs administered ^{137}CsCl by intravenous injection at activity levels resulting in estimated total bone marrow doses of 7–24 Gy (700–2,400 rad) (Nikula et al. 1995).

3.3.4.4 Neurological Effects

No data were located regarding neurological effects in humans or animals following exposure to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure.

3.3.4.5 Reproductive Effects

Persistent germinal epithelium damage and azoospermia were reported in all long-term surviving dogs that had been administered ^{137}CsCl by intravenous injection at activity levels resulting in long-term total whole-body doses ranging from 7.42 to 16.40 Gy (742 to 1,640 rad) (Nikula et al. 1995, 1996).

3.3.4.6 Developmental Effects

No data were located regarding developmental effects in humans or animals following exposure to radioactive cesium via routes other than inhalation, oral, dermal, or external exposure.

3.3.4.7 Cancer

Benign and malignant neoplasms were found in a variety of tissues and organs of beagle dogs that had been administered single intravenous injections of ^{137}CsCl (Nikula et al. 1995, 1996). Fifty-four young adult dogs at the Inhalation Toxicology Research Institute (ITRI) received amounts of ^{137}CsCl that resulted in average initial body burdens ranging from 37 to 141 MBq/kg (1.0 to 3.8 mCi/kg) (Nikula et al. 1995). In a study initiated at the Argonne National Laboratory (ANL), 63 beagle dogs, grouped according to age at study initiation (juveniles, 142–151 days old; young adults, 388–427 days old; and middle-aged adults, 1,387–2,060 days old), were administered single intravenous injections of ^{137}CsCl that resulted in initial body burdens of approximately 64–147 MBq/kg (1.7–4.0 mCi/kg) (Nikula et al. 1996). In both studies, dose-related increased incidences were observed for malignant neoplasms, malignant neoplasms excluding mammary neoplasms, all sarcomas considered as a group, all nonmammary carcinomas considered as a group, and malignant liver neoplasms. An increased risk for malignant thyroid neoplasms was seen in the ANL male dogs, but not in the ITRI males or females. In the ITRI (but not ANL) dogs, an increased relative risk for benign neoplasms excluding mammary neoplasms was observed. The occurrence of neoplasms in a diversity of tissues and organs results from the widespread distribution of cesium in the body.

3.4 GENOTOXICITY

Genotoxicity data for stable and radioactive cesium are summarized in Tables 3-3 and 3-4, respectively.

Evidence for genotoxic effects of stable cesium is limited to studies in which cesium chloride induced significantly increased incidences of chromosomal aberrations in human lymphocytes *in vitro* (Ghosh et al. 1993) (see Table 3-3) and mouse bone marrow *in vivo* (Ghosh et al. 1990, 1991; Santos-Mello et al. 2001) (see Table 3-4). Cesium sulfate was not mutagenic in *Escherichia coli (E. coli)* tester strains PQ37 and PQ35 either with or without metabolic activation in the SOS Chromotest (a bacterial colorimetric assay) at doses up to those resulting in significant toxicity (Olivier and Marzin 1987).

Increased frequency of point mutations in T-lymphocytes was observed in individuals in Goiânia, Brazil who had been exposed to an opened ^{137}CsCl source approximately 2.5 years prior to testing (Skandalis et al. 1997). The estimated dose from external radiation was 1.7 Gy (170 rad). The authors estimated internal doses based on whole-body counts and measured activity in urine and feces; however, realistic estimates were not reported. Among individuals exposed in the same incident, frequencies of

Table 3-3. Genotoxicity of Cesium *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Stable Cesium				
Mammalian cells:				
Human lymphocytes	Chromosomal aberrations	No data	+	Ghosh et al. 1993
Human lymphocytes	Micronuclei	No data	–	Santos-Mello et al. 1999
Prokaryotic organisms:				
Escherichia coli (PQ 37 and PQ 35)	Mutations	–	–	Olivier and Marzin 1987
Radioactive Cesium				
Mammalian cells:				
Human peripheral blood lymphocytes	Micronuclei	No data	+	Balasem and Ali 1991
Human peripheral blood lymphocytes	Chromosomal aberrations	No data	+	Doggett and McKenzie 1983
Human peripheral blood lymphocytes	Chromosomal aberrations	No data	+	Hintenlang 1993
Human peripheral blood lymphocytes	Chromosomal aberrations	No data	+	Iijima and Morimoto 1991
Human peripheral blood lymphocytes	Sister chromatid exchange	No data	–	Iijima and Morimoto 1991
Human spermatozoa	Chromosomal aberrations	No data	+	Mikamo et al. 1990, 1991
Human spermatozoa and zona-free hamster oocytes fertilization system	Micronuclei	No data	+	Kamiguchi et al. 1991
Mouse (BALB/c, SC3T3/W, Scid/St cells)	DNA double-strand breaks	No data	+	Biedermann et al. 1991
Chinese hamster ovary cells	Chromosomal aberrations, sister chromatid exchange	No data	+	Arslan et al. 1986

DNA = deoxyribonucleic acid; – = negative results; + = positive results

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

Species (test system)	End point	Results	Reference
Stable Cesium			
Mammalian cells:			
Mouse bone marrow	Chromosomal aberrations	+	Ghosh et al. 1990, 1991
Mouse bone marrow	Micronuclei	+	Santos-Mello et al. 2001
Mouse bone marrow	Micronuclei	–	Santos-Mello et al. 1999
Radioactive Cesium			
Mammalian cells:			
Human peripheral blood lymphocytes	Chromosomal aberrations	+	Natarajan et al. 1998
Human peripheral blood lymphocytes	Chromosomal aberrations	+	Padovani et al. 1993
Monkey germ cells (male)	Reciprocal translocations	+	Tobari et al. 1988
Monkey germ cells (male)	Reciprocal translocations	+	Ramaiya et al. 1994
Mouse germ cells (male)	Reciprocal translocations	+	Ramaiya et al. 1994
Mouse germ cells (male)	Dominant lethal mutations	+	Ramaiya et al. 1994

+ = positive results; – = negative results

chromosomal aberrations were used to estimate external radiation doses (Natarajan et al. 1998). No human reports were located in which genotoxic effects could be associated with specific radiation exposure levels, nor was there any information regarding potential for route-specific differences in observed genotoxic effects related to radioactive cesium exposure. Five years after the initial exposure to radioactive fallout from the Chernobyl accident of 1986, slightly greater frequencies of chromosomal aberrations were observed in peripheral blood lymphocytes of three groups of Byelorussian children (41 total) living in areas with ground contamination from ^{137}Cs fallout than in those of an Italian control group of 10 children (Padovani et al. 1993). Whole-body counts found an internally deposited ^{137}Cs activity range of 0.46–2.8 kBq (12-75 nCi) in children from Navrovl'a, an area (70 km from Chernobyl) exhibiting ^{137}Cs contamination of 550-1,500 GBq/km^2 (15–40 Ci/km^2). Internally deposited ^{137}Cs activity ranges of 0.044–0.4 kBq (1.2-10.8 nCi) and 7.7–32.3 kBq (208–872 nCi) were reported for children evacuated from the Chernobyl area soon after the accident to areas 200–300 km from Chernobyl with ^{137}Cs ground contamination of 40-400 GBq/km^2 (1–10 Ci/km^2), and children living in the Stolin area (250 km from Chernobyl) with ^{137}Cs ground contamination of 40–550 GBq/km^2 (1–5 Ci/km^2), respectively. Internalized activity was presumably from the consumption of ^{137}Cs-contaminated food. Although a small increase in the frequency of chromosomal aberrations in lymphocytes was observed, no pathology was apparent. These genotoxic effects were the result of the radiation, not the presence of cesium *per se*.

A dose-related increased frequency of micronuclei was observed in human peripheral blood lymphocytes exposed *in vitro* to gamma radiation from a sealed ^{137}Cs source at doses ranging from 0.05 to 6.00 Gy (5 to 600 rad) (Balasem and Ali 1991). This effect was the result of the radiation, not the presence of cesium *per se*.

In mice, genotoxic effects resulting from repeated oral exposure (daily administration for 2 weeks) to ^{137}Cs (as cesium nitrate) were compared with those elicited from external whole-body irradiation (23 hours/day for 19.5 days) using a ^{137}Cs source (Ramaiya et al. 1994). At comparable total radiation doses (approximately 3–4 Gy or 300–400 rad), both exposure scenarios resulted in similar increases in dominant lethal mutations among exposed male mice. Significant increases in the frequency of reciprocal translocations have been reported in spermatogonia of mice orally administered single doses of ^{137}Cs (as cesium chloride) that resulted in absorbed total body doses of approximately 3 Gy (300 rad) (Ramaiya et al. 1994).

Significant (dose-related) increases in the formation rate of micronuclei were seen in blood cells of fetal rats following irradiation of pregnant dams to total radiation doses of 0.5–4 Gy (50–400 rad), from a sealed ^{137}Cs gamma source, on gestation day 14 (Koshimoto et al. 1994). In crab-eating monkeys exposed to gamma radiation from an external ^{137}Cs source, increases in reciprocal translocations in spermatogonia were dose-related through the total absorbed dose range of 0.3–1.5 Gy (30–150 rad); it was also noted that the induction rate of translocations after acute high-dose-rate (0.25 Gy/minute or 25 rad/minute) exposure was about 10 times higher than that resulting from longer-term low-dose-rate ($1.8x10^{-7}$ Gy/minute or $1.8x10^{-5}$ rad/minute) exposure (Tobari et al. 1988). These effects were the result of the radiation, not the presence of cesium *per se*.

Additional assays, performed *in vitro*, have also indicated that radioisotopes of cesium are genotoxic; specific end points include chromosomal aberrations and breaks, sister chromatid exchanges, and micronuclei (Arslan et al. 1986; Biedermann et al. 1991; Doggett and McKenzie 1983; Hintenlang 1993; Iijima and Morimoto 1991; Kamiguchi et al. 1991; Mikamo et al. 1990, 1991). Refer to Agency for Toxic Substances and Disease Registry (1999) for more information on the genotoxic effects of ionizing radiation.

3.5 TOXICOKINETICS

Numerous biokinetic studies have been performed in animals exposed internally to small amounts of the radioisotope ^{137}Cs. The biokinetic behavior of cesium has also been studied in humans either given tracer amounts of radiocesium or accidentally exposed to larger amounts.

Fractional absorption of inhaled or ingested cesium to the blood decreases with decreasing solubility of the carrier. Cesium taken into the body in soluble form is almost completely absorbed to blood. Cesium entering the respiratory or gastrointestinal tract as relatively insoluble particulates is mostly excreted in the feces. Cesium that comes into contact with the skin may be absorbed to some extent through the skin.

Following uptake by the blood, widespread distribution of cesium to all major soft tissues is observed in humans and animals. Cesium levels are slightly higher in skeletal muscle than other tissues. Distribution patterns in animals have been shown to be similar following exposure to soluble cesium compounds by inhalation, oral, and parenteral routes of exposure. Cesium crosses the placenta to the fetus. Cesium is also found in breast milk of a mother with an internal deposition.

Cesium is a close chemical analogue of potassium. Cesium has been shown to compete with potassium for transport through potassium channels and can also substitute for potassium in activation of the sodium pump and subsequent transport into the cell.

Excretion rates for ^{137}Cs have been studied in numerous populations exposed to nuclear fallout following incidents such as the Chernobyl accident. Biologically based pharmacokinetic models have been developed to describe relationships between intake and elimination. Experimental human studies have also been performed using tracer amounts of ^{134}Cs and ^{137}Cs. Urinary excretion is the primary route of elimination of cesium, and is independent of the route of exposure. Urinary to fecal ratios for cesium in humans have been found to range from 2.5:1 to 10:1. Radiocesium excretion rates were higher in males with muscular dystrophy than in normal, age-matched controls, and higher in pregnant women than in others who were not pregnant.

The elimination of cesium in humans appears to be age and sex related; long-term retention is principally a function of muscle mass. Elimination half-times are shorter in children than in adults, and shorter in women than in men.

3.5.1 Absorption

3.5.1.1 Inhalation Exposure

Inhalation exposure to relatively soluble cesium compounds will result in absorption of cesium in humans, although no reports were located that measured absorption of cesium following inhalation exposure. Evidence for absorption was presented by Miller (1964) via whole-body counts of ^{137}Cs (taken periodically for up to 285 days) in two men following occupational exposure to ^{137}Cs (as cesium sulfate) that was presumed to have been by inhalation. Distribution of ^{137}Cs was relatively uniform throughout the body, and steadily decreasing whole-body counts indicated that ^{137}Cs was eliminated from the body with a biological half-time of approximately 73–84 days. Additional indirect evidence of absorption was reported for an adult male who had been accidentally exposed to airborne ^{137}Cs twice in a 13-month period (Hölgye and Malý 2002). In this case, biological half-times for elimination of ^{137}Cs were 72 and 73 days.

Inhaled soluble cesium compounds are readily absorbed and distributed systemically in animals. Approximately 80% cesium absorption was observed in dogs acutely exposed to small amounts of aerosolized ^{137}Cs (as cesium chloride) (Boecker 1969a, 1969b). Deposition and distribution of cesium

following inhalation exposure to radiolabeled cesium chloride was also observed in rats (Lie 1964; Stara and Thomas 1963) and guinea pigs (Stara 1965). Absorption was rapid following inhalation exposure.

3.5.1.2 Oral Exposure

It is generally accepted that cesium ingested as soluble cesium compounds is well absorbed by the gastrointestinal tract of humans and animals. Observations indicating that soluble cesium compounds were absorbed after ingestion by humans include: (1) low fecal excretory rates, (2) urinary excretory rates 4–10 times higher than those of fecal excretion, and (3) elimination half-times ranging from 45 to 147 days (Henrichs et al. 1989; Iinuma et al. 1965; Richmond et al. 1962; Rosoff et al. 1963). Henrichs et al. (1989) estimated an average cesium absorption of 78% in a group of 10 adult (5 male, 5 female) volunteers ingesting a meal of venison that was highly contaminated with ^{137}Cs and ^{134}Cs. Results from other controlled studies on human subjects indicate that absorption represented >90% of the cesium ingested in soluble form (Rosoff et al. 1963; Rundo 1964; Yamataga et al. 1966).

Absorption of ^{137}Cs from ingestion of radioactive fallout particles was found to be in the range of only 3%, indicating that such particles are relatively insoluble in biological fluids (LeRoy et al. 1966). Measurable amounts of ^{137}Cs were found in breast milk of women living in areas contaminated with radioactive fallout from the Chernobyl nuclear accident (Johansson et al. 1998). Based on whole body measurements of radioactivity in mothers and nursing infants and measured radioactivity in breast milk samples, it was estimated that 15% of the mothers' daily ^{137}Cs intake from contaminated food was transferred to the infant.

Animal studies support the findings in humans. Rapid absorption and widespread distribution of cesium was reported in guinea pigs administered single oral doses of soluble ^{137}Cs (as cesium chloride); fractional absorption data were not reported (Stara 1965). In rats orally administered single doses of highly insoluble irradiated fuel particles (mean diameter of 0.93 μm) containing ^{137}Cs and other radioactive elements, absorption of ^{137}Cs was found to be <10% (Talbot et al. 1993).

3.5.1.3 Dermal Exposure

Dermal absorption has been demonstrated in rats (Pendic and Milivojevic 1966). Traces of ^{137}Cs were observed in the blood of rats within a few minutes following the dermal application of ^{137}CsCl in aqueous

solution. Approximately 3% of ^{137}CsCl applied to a surface area of several cm^2 was absorbed within 6 hours.

3.5.2 Distribution

3.5.2.1 Inhalation Exposure

Once absorbed, cesium is rapidly distributed throughout the body. Separate measurements of radioactivity from head, chest, upper abdomen, lower abdomen, thighs, legs, and feet indicated that ^{137}Cs was widely distributed throughout the bodies of two men who were occupationally exposed to ^{137}Cs (Miller 1964). Proportions of radioactivity in these body segments remained relatively constant from days 9 to 285 after exposure, indicating that ^{137}Cs was not likely to have been selectively accumulating in a particular region.

Animal studies also indicate a relatively uniform distribution of cesium following inhalation exposure to soluble cesium compounds (Boecker 1969a, 1969b; Stara 1965). Within 2 hours following exposure to aerosols of ^{137}Cs (as cesium chloride), up to 60% of the total body burden of ^{137}Cs was found in tissues other than respiratory or gastrointestinal tracts of dogs (Boecker 1969a). At 32 days post exposure, concentrations of ^{137}Cs in skeletal muscles, diaphragm, kidneys, and mandibular salivary gland were slightly higher than the whole-body average; concentrations in lung, skin, bone (femur, ribs), fat, and blood were somewhat lower (Boecker 1969b). Other tissues exhibited concentrations approximating the whole-body average. A relatively uniform distribution of ^{137}Cs in numerous body tissues, with the highest concentrations in skeletal muscle, was also observed in guinea pigs and rats exposed by inhalation (Lie 1964; Stara 1965; Stara and Thomas 1963).

3.5.2.2 Oral Exposure

Widespread distribution of cesium was observed in humans following oral exposure to soluble cesium compounds. In two human subjects orally administered ^{137}Cs (as cesium chloride), whole blood levels of ^{137}Cs within the first hour after administration amounted to approximately 2–3% of the amount administered, indicating that ^{137}Cs was rapidly absorbed and well distributed via the circulation (Rosoff et al. 1963).

Animal studies also showed relatively uniform distribution following oral exposure to soluble cesium compounds. Guinea pigs exhibited ^{137}Cs in numerous body tissues after receiving single oral doses of ^{137}Cs (as cesium chloride). The highest concentrations were found in skeletal muscle (Stara 1965). After the first day post administration, no significant differences in ^{137}Cs distribution patterns were observed between groups of guinea pigs exposed by inhalation, oral administration, or intraperitoneal injection of ^{137}Cs (as cesium chloride) (Stara 1965). Dogs and mice exhibited relatively uniform distribution of cesium throughout body tissues following chronic oral administration of ^{137}Cs (as cesium chloride) (Furchner et al. 1964). Cesium also crossed the placenta of animals and was found in breast milk. Newborn lambs exhibited lower tissue levels of ^{134}Cs than their mothers following oral administration of radiolabeled cesium chloride during pregnancy (Vandecasteele et al. 1989). The concentrations of ^{134}Cs in nursing lambs eventually exceeded the levels in their mothers.

3.5.2.3 Dermal Exposure

One report was located regarding distribution of cesium in animals following dermal exposure (Pendic and Milivojevic 1966). The investigators found widespread distribution of ^{137}Cs in rats within a few minutes following application of $^{137}CsCl$ solution to the skin. Although cesium was distributed throughout the body, it was deposited mainly in the kidneys, muscular tissues (particularly cardiac muscle), and liver.

3.5.2.4 Other Routes of Exposure

Comparative human and animal studies have shown that parenteral exposure to cesium compounds results in cesium distribution patterns similar to those observed following inhalation or oral exposure (Rosoff et al. 1963; Stara 1965). By 3 days following administration, ^{137}Cs was found to be distributed relatively uniformly among the body tissues of five cancer patients who died at various times following intravenous injection of a single tracer dose of ^{137}Cs (as cesium chloride). Time-related decreases were observed in ^{137}Cs retention by all tissues surveyed (Rosoff et al. 1963). Transfer of ^{137}Cs from pregnant dam to fetus has been shown in rats following intraperitoneal injection of radiolabeled cesium chloride (Mahlum and Sikov 1969).

3.5.3 Metabolism

Absorbed cesium behaves in a manner similar to that of potassium (Rundo 1964; Rundo et al. 1963). Both potassium and cesium are alkali metals that distribute throughout the body as cations, and are incorporated into intracellular fluids by active transport mechanisms. Cesium has been shown to compete with potassium for transport through potassium channels and can also substitute for potassium in activation of the sodium pump and subsequent transport into the cell (Cecchi et al. 1987; Edwards 1982; Hodgkin 1947; Latorre and Miller 1983; Sjodin and Beauge 1967). In both types of transport, movement of cesium is sluggish compared with that of potassium (Blatz and Magleby 1984; Coronado et al. 1980; Cukierman et al. 1985; Edwards 1982; Gay and Stanfield 1978; Gorman et al. 1982; Hille 1973; Reuter and Stevens 1980); that is, transport mechanisms generally favor potassium over cesium. Discrimination between potassium and cesium generally is greater for passive transport out of cells (selectivity ratios of Cs:K for a variety of tissues ranging from <0.02 to approximately 0.2) than for active transport into cells (selective Cs:K ratio approximating 0.25) (Leggett et al. 2003). This results in a greater residence time of cesium than potassium in muscle cells and hence in the whole body, since skeletal muscle contains most of the body's potassium or cesium at equilibrium. However, cesium appears to compete somewhat more favorably with potassium during transport out of red blood cells (Forth et al. 1963) or across or between epithelial cells (Cereijido et al. 1981; Greger 1981; Wright 1972).

3.5.4 Elimination and Excretion

3.5.4.1 Inhalation Exposure

Urinary excretion is the major route of elimination of cesium taken into the body in soluble form. In dogs exposed to ^{137}Cs (as cesium chloride) by inhalation, rates of excretion of ^{137}Cs in the urine and feces were highest in the first 3 days after exposure, accounting for approximately 12 and 3% of the initial body burden, respectively. Urinary and fecal excretion of ^{137}Cs continued at lower rates through 130 days of analysis. Rates of elimination were determined by measuring the cesium remaining in the organs of rats sacrificed at 9 time points during 120 days following treatment. The elimination rates for specific tissues (muscle, kidney, liver, and lung) were similar to the whole-body rates, indicating that cesium did not selectively accumulate in any particular tissues (Boecker 1969b). Within 2.5 days following inhalation exposure to ^{137}Cs (as cesium chloride), guinea pigs had eliminated approximately 50% of the initial ^{137}Cs body burden in the urine and feces (Stara 1965). The urinary to fecal ratio for excretion was approximately 3:1 throughout 60 days of post-exposure measurements, by which time, virtually all of the initial ^{137}Cs body burden had been eliminated. The urinary to fecal ratio for elimination of cesium in rats

was about 3.5:1, with a biological half-time of elimination of approximately 4 days; 99% had been eliminated within 65 days following exposure (Stara and Thomas 1963).

No reports were located regarding routes of elimination and excretion of cesium in humans following inhalation exposure. However, kinetics of ^{137}Cs elimination in two adult males, accidentally exposed to ^{137}Cs (as cesium sulfate), were studied by whole-body measurements of gamma emission. The measured biological half-times were 73 and 84 days (Miller 1964). In the case of another adult male, accidentally exposed to airborne ^{137}Cs twice in a 13-month period, biological half-times for elimination were 72 and 73 days (Hölgye and Malý 2002).

In dogs exposed by inhalation, elimination rates of ^{137}Cs from specific tissues were similar to the rate of whole-body elimination, indicating that ^{137}Cs did not selectively accumulate in certain tissues, but was relatively uniformly eliminated from the body with a half-time of approximately 36–42 days (Boecker 1969b). Elimination rates of ^{137}Cs in guinea pigs and rats exposed by inhalation also did not vary significantly according to tissue type, although much shorter half-times of ^{137}Cs elimination (2.5 and 4 days) were observed for guinea pigs and rats, respectively (Stara 1965; Stara and Thomas 1963).

Relatively insoluble inhaled particles containing cesium were not absorbed in significant amounts and were more slowly eliminated from the lungs.

3.5.4.2 Oral Exposure

Urinary excretion is the primary route of elimination for cesium in humans. Among seven cancer or pulmonary patients who were administered single oral doses of ^{137}Cs (as cesium chloride), 7-day cumulative excretion of ^{137}Cs ranged from 7.0 to 17.3% of the administered activity. The urinary to fecal excretion ratio ranged from 2.5:1 to 10:1 (Rosoff et al. 1963). In a study of four Japanese volunteers orally administered single doses of ^{137}Cs (as cesium chloride), urinary to fecal excretion ratios ranging from 4.57:1 to 8.75:1 were calculated for excretory data collected after day 4 post administration. During the first 4 days after administration, excretory rates were consistently higher and the urinary:fecal excretory ratio was also somewhat higher (Iinuma et al. 1965). Based on the results of numerous reports of urinary and fecal excretion of Cs in human subjects, Leggett et al. (2003) reported an average urinary fraction (i.e., the ratio of cumulative urinary Cs to cumulative Cs in urine plus feces) of 0.86. Other sources of information on excretion rates of ^{137}Cs include numerous studies of populations exposed via fallout following atmospheric testing of nuclear weapons and from the Chernobyl accident, and

mathematical models, such as those described in Section 3.5.5, have been developed to describe the relationships among intake, retention, and elimination of cesium.

Animal data support the findings in humans of urinary excretion as the major route of elimination of cesium following oral administration of soluble cesium compounds. Guinea pigs had eliminated approximately 50% of the initial ^{137}Cs body burden in the urine and feces within 2.5 days following administration (Stara 1965). The urinary to fecal ratio was within the range of 2–3:1 throughout 60 days of post exposure measurements, by which time, virtually all of the initial ^{137}Cs body burden had been eliminated.

Elimination half-times for cesium in the whole body, sometimes expressed in terms of whole-body radioactivity retention, have been reported by some investigators (Henrichs et al. 1989; Iinuma et al. 1967; Lloyd et al. 1973; Melo et al. 1997; Richmond et al. 1962; Rundo 1964). For example, among 10 volunteers who consumed ^{134}Cs- and ^{137}Cs-contaminated food, approximately 6% of the initial body burden was rapidly eliminated (average half-time of elimination of 0.3 days); the remaining 94% was eliminated more slowly (average half-time of elimination of 90 days) (Henrichs et al. 1989). In another oral study of four adult males, a mean elimination half-time was 135 days for ^{134}Cs and ^{137}Cs (Richmond et al. 1962).

Elimination rates for ^{137}Cs appear to be age- and sex-dependent, decreasing with age and lower in adult males than adult females. Results of studies of populations that consumed food containing ^{137}Cs from weapons testing fallout showed elimination half-times that varied from 15±5 days in infants to 100±50 days in adults (McCraw 1965). Similar studies after the Chernobyl accident found similar elimination half-times, which ranged from about 8 days for 1-year-old infants to about 110 days for adults (IAEA 1991). A 4-year study of 110 persons comprising a cross-section within an unspecified population indicated that children, 5–14 years of age, had the shortest elimination half-times (20 days, with no significant difference between males and females) (Boni 1969b). The elimination half-times in older groups were significantly longer (47 days for adolescent and adult females, 67 days in 15-year-old males, and 93 days in males 30–50 years of age). Melo et al. (1994) also reported age- and sex-related differences in elimination rates among individuals internally contaminated by ^{137}CsCl in the Goiânia, Brazil accident (see Agency for Toxic Substances and Disease Registry 1999 for a complete description of the incident). Elimination half-times for girls 1–4 years of age averaged 24 days. For 7–10-year-old girls and boys, the average elimination half-time was 37 days. Elimination half-times of 58 and 83 days were estimated for adolescent and adult males, respectively; compared with 46 and 66 days for adolescent

and adult females, respectively. In the study of Melo et al. (1994), a high correlation was found between biological half-time for ^{137}Cs and weight for all age groups and sexes, except adult females.

Elimination rates of cesium may be altered by potassium intake. Following the intraperitoneal injection of ^{137}Cs in rats, a basal diet supplemented with 8–11% potassium resulted in cesium clearance of 60 days compared to about 120 days for rats receiving the unsupplemented basal diet that contained 1% potassium (Richmond and Furchner 1961). After 20 days on the diets, rats receiving supplemental potassium had body burdens of ^{137}Cs that were one-half those of the rats not receiving supplemental potassium. This finding shows that supplemental potassium reduces the uptake and increases the elimination of ingested ^{137}Cs.

Retention of cesium was lower in males suffering from muscular dystrophy than in age-matched controls. Older males with advanced signs of muscular dystrophy had lower retention than younger males exhibiting earlier stages of the disease (Lloyd et al. 1973).

Cesium crosses the placenta from mother to fetus. Measurable amounts of ^{137}Cs have been detected in human placenta and fetal tissue (Toader et al. 1996; Yoshioka et al. 1976). Cesium concentrations are higher in older fetuses than in younger ones (Toader et al. 1996). Pregnancy may increase the removal of cesium from the mother, as indicated by shorter elimination half-times during pregnancy relative to measurements taken before or after pregnancy or among nonpregnant controls (Bengtsson et al. 1964; Rundo and Turner 1966; Thornberg and Mattsson 2000; Zundel et al. 1969). Cesium has also been detected in human breast milk (Thornberg and Mattsson 2000).

3.5.4.3 Dermal Exposure

No reports were located regarding elimination and excretion of cesium in humans or animals following dermal exposure.

3.5.4.4 Other Routes of Exposure

Evidence for age-related differences in cesium elimination rates was observed in rats injected with ^{134}Cs or ^{137}Cs (as cesium chloride) at various ages. Retention of radiocesium from a single intraperitoneal injection of 0.5 μCi of carrier-free $^{134}CsCl$ increased with increasing age of rats at the time of dosing (Lengemann 1970). For example, the amount of radiocesium retained at 49 days after dosing was

>14 times greater in rats dosed at 4 months of age than in rats dosed at 1 month of age. Retention in rats injected at 21 months of age was approximately 1.9 times greater than that of the rats dosed at 4 months of age. Long-term retention also appears to be age related in dogs injected intravenously with ^{137}CsCl; puppies 3–5 months of age exhibited elimination half-times that were shorter than those of adult dogs (Melo et al. 1997). Age-related increases in cesium retention rates were also observed in other young dogs from 61 to approximately 300 days old, after which cesium retention reached a plateau; the increases in cesium retention were similar to growth curves (Tyler et al. 1969). There is some indication, however, that retention of cesium is higher in neonatal rats than in weanling or adult rats (Lengemann 1969, 1970; Mahlum and Sikov 1969).

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 and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

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

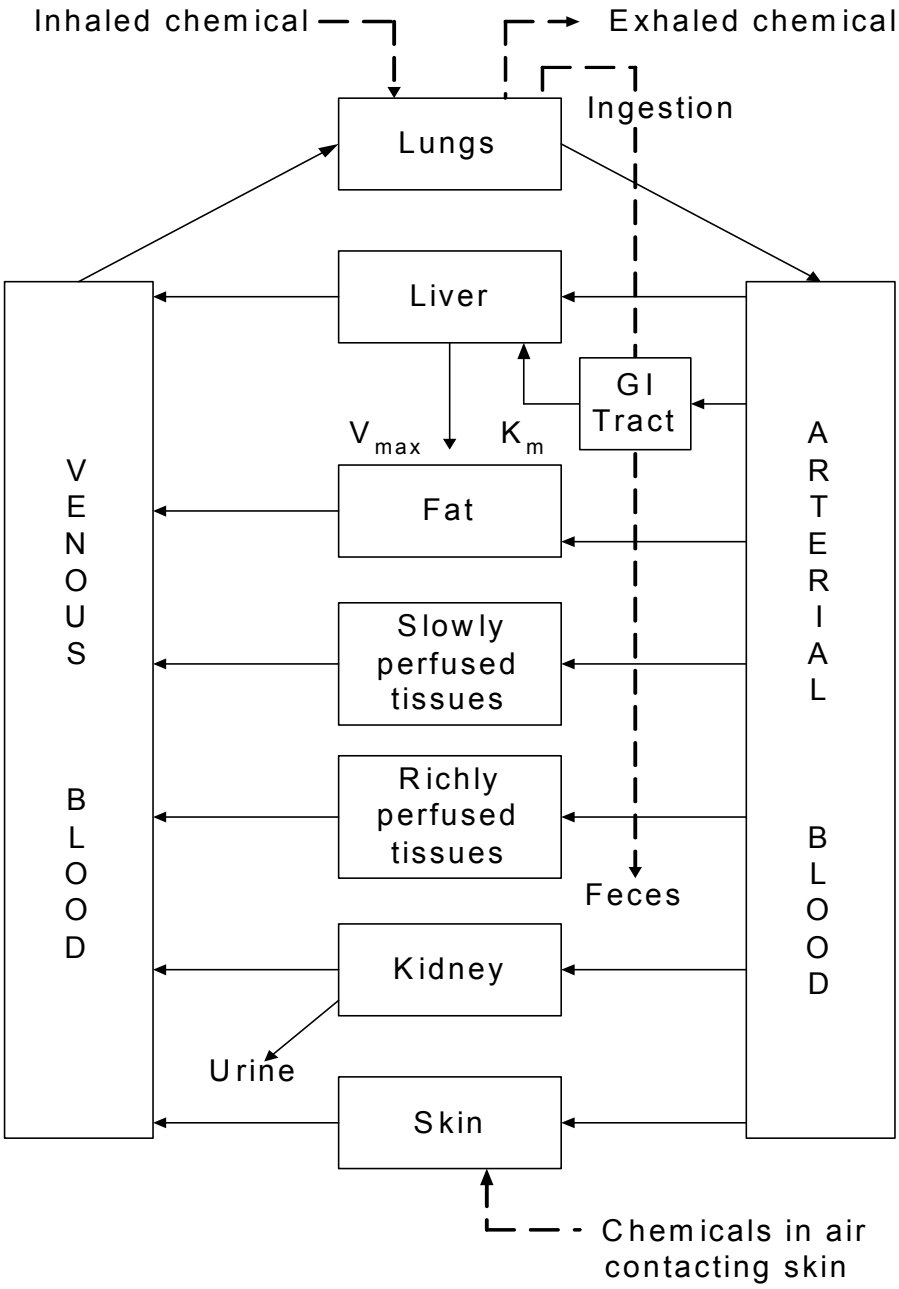
1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and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

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) 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 and radiation in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model. Figures 3-4 through 3-7 show models for radionuclides in general or specifically for cesium.

The International Commission on Radiological Protection (ICRP 1994, 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 cesium compounds. The ICRP (1979, 1989, 1993) also developed a 2-compartment biokinetic model for human oral exposure that applies to cesium. EPA (1998) adopted the ICRP (1993, 1994, 1995) models for assessment of radiologic risks from cesium exposures. The National Council on Radiation Protection and Measurements (NCRP) also developed a respiratory tract model for inhaled radionuclides (NCRP 1997). At this time, the NCRP recommends the use of the ICRP model for calculating radiation doses for 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

Figure 3-3. 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.

to the report, NCRP provides the animal testing clearance data and equations fitting the data that supported the development of the human model for cesium.

Human Respiratory Tract Model for Radiological Protection (ICRP 1994)

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

The ICRP deposition model may be used to estimate the amount of inhaled material that initially enters each compartment (see Figure 3-4). 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 the ET_1 region may be cleared either by dissolution and absorption into the blood or by nose-blowing. Particles deposited in each of the other regions may then be removed from each region and redistributed either upward into the respiratory tree by mucociliary clearance mechanisms, or to the lymphatic system and blood by different particle removal mechanisms.

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

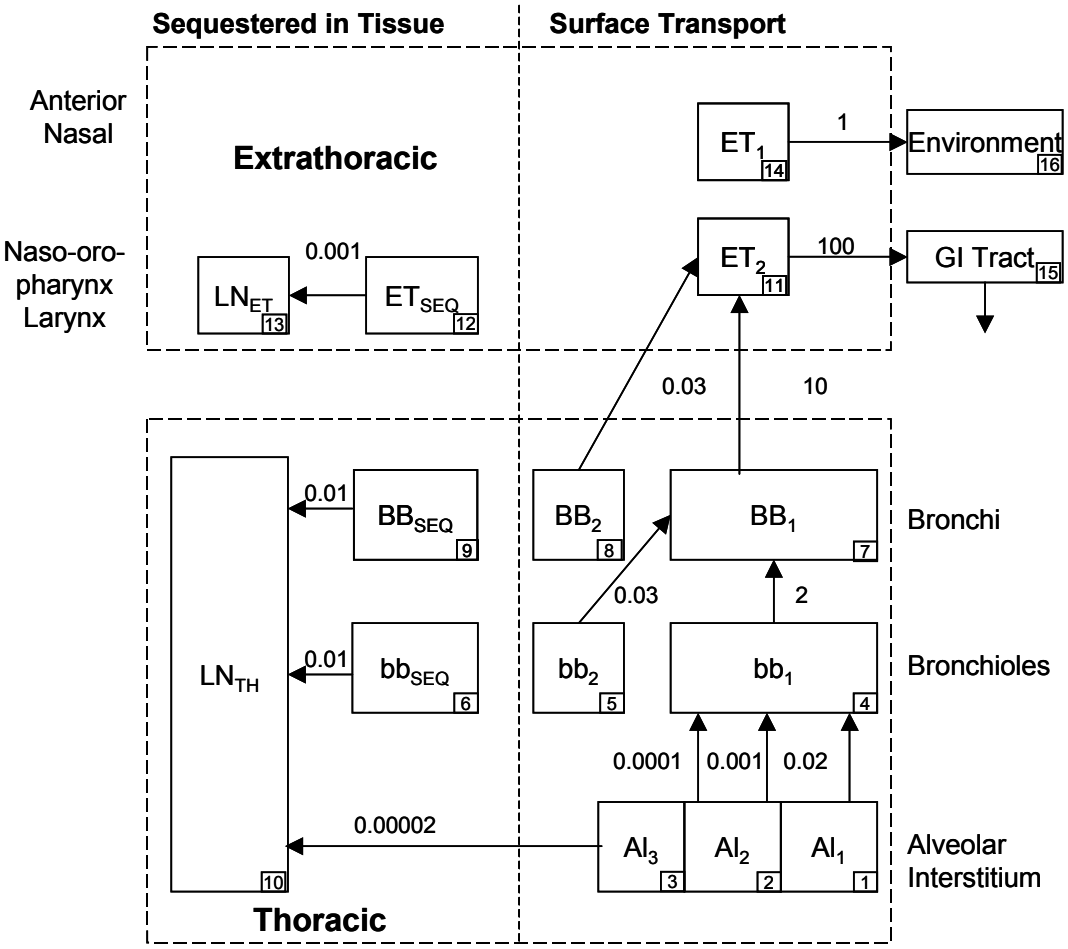
Table 3-5. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity[a]

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	Both:	0.3	0.31	17	0.33	0.38	19	0.58	1.12	32			
	Male:										0.841	2.22	44
	Female:										0.667	1.84	46
15 years	Male:	0.500	0.42	14	0.533	0.48	15	1.0	1.38	23	1.352	2.92	36
	Female:	0.417	0.35	14	0.417	0.40	16	0.903	1.30	24	1.127	2.57	38
Adult	Male:	0.625	0.45	12	0.750	0.54	12	1.25	1.5	20	1.923	3.0	26
	Female:	0.444	0.32	12	0.464	0.39	14	0.992	1.25	21	1.364	2.7	33

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

H = hour; L = liter; m = meter; min = minute; N/A = not applicable

Figure 3-4. Compartment Model to Represent Particle Deposition and Time-Dependent Particle Transport in the Respiratory Tract*



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

Source: ICRP 1994

Deposition of inhaled gases and vapors is modeled as a partitioning process that depends on the physiological parameters noted above as well as the solubility and reactivity of compounds in the respiratory tract (see Figure 3-5). 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 H_2, He). These compounds do not significantly interact with the respiratory tract tissues and essentially all the inhaled gas 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 compounds include sulfur dioxide (SO_2) and hydrogen fluoride (HF).

Respiratory Tract Mechanical (Particle) Clearance. The clearance portion of the model identifies the principal clearance pathways within the respiratory tract. The model was developed to predict the retention and clearance of various radioactive materials. The compartmental model is linked to the deposition model (see Figure 3-4) and to reference values presented in Table 3-6. Table 3-6 provides clearance rates by biological processes only, not by radioactive decay, and deposition fractions for each compartment for insoluble particles. The table provides rates of insoluble particle transport for each of the compartments, expressed as a fraction per day and also as half-time. ICRP (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 data, although particle retention in airway walls is based on experimental data from animal experiments.

The clearance of particles from the respiratory tract is a dynamic process. The rate of clearance generally changes with time from each region and by each route. Following deposition of large numbers of particles over a short time period (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. As particles dissolve, absorption rates also tend to change over time. By creating a model with compartments of different clearance rates within each region (e.g., BB_1, BB_2, BB_{seq}), the ICRP model

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

Part A: Clearance rates for insoluble particles

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

See next page for Part B

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

Part B: Partition of deposit in each region between compartments[b]

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

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

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

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

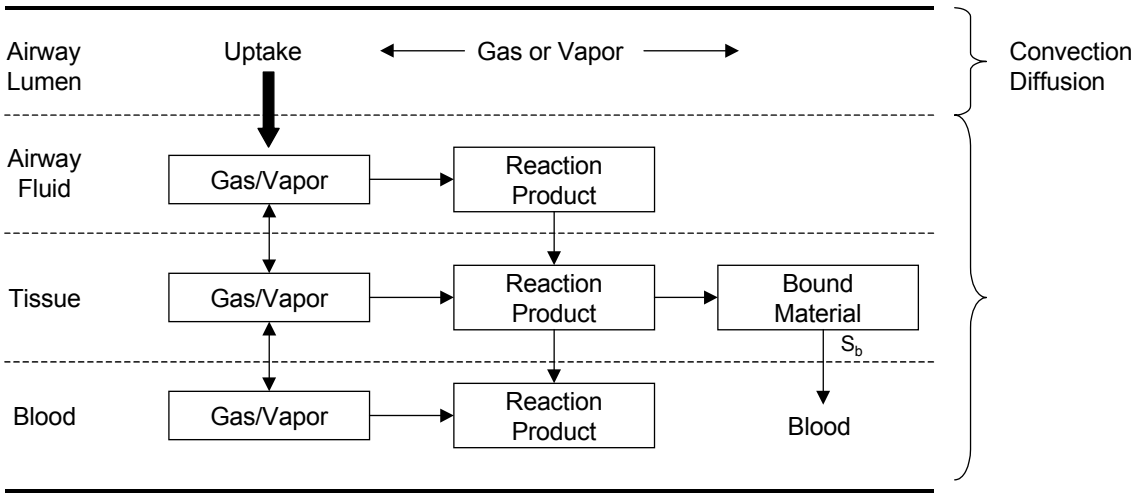
where:

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

AI = alveolar-interstitial region; BB = bronchial region; bb = bronchiolar region; BB_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchial region; bb_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchiolar region; d = day(s); ET = extrathoracic region; ET_{seq} = compartment representing prolonged retention in airway tissue of small fraction of particles deposited in the nasal passages; GI tract = gastrointestinal tract; 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

Figure 3-5. Reaction of Gases or Vapors at Various Levels of the Gas-Blood Interface



Source: ICRP 1994

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

Ciliary action removes deposited particles from the bronchi and bronchioles. Though mucociliary action rapidly transports most particles deposited here toward the pharynx, a fraction of these particles is cleared more slowly. Evidence for this clearance 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 movement is influenced by location. Movement is slower in areas closer to alveoli. It takes about 2 days for particles to travel from the bronchioles to the bronchi and 10 days from the bronchi to the pharynx. The second (slower) compartment is assumed to have approximately equal fractions deposited between BB_2 and bb_2 and both with clearance half-times estimated at 20 days. Particle size is a primary determinant of the fraction deposited in this slow thoracic compartment. A small fraction of particles deposited in the BB and bb regions may be retained in the airway wall for even longer periods (BB_{seq} and bb_{seq}).

If particles reach and become deposited in the alveoli, they tend to stay imbedded in the fluid on the alveolar surface or move into the lymph nodes. The 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 representing different slow 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, AI particle transport diminishes and some insoluble particles may remain 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. Absorption is essentially a 2-stage process, as shown in Figure 3-6. First, there is dissociation (dissolution) of particles. The dissolved molecules or ions then diffuse across capillary walls and are taken up by the blood. Immediately following dissolution, rapid absorption takes place. For some elements, rapid absorption does not occur because of binding to respiratory-tract components. In the absence of specific data for specific compounds, the model uses the following default absorption rate values for those specific compounds that are classified as Types F (fast), M (medium), S (slow), and V (instantaneous):

- For Type F, there is rapid 100% absorption within 10 minutes of the material deposited in the BB, bb, and AI regions, and 50% of material deposited in ET2. 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 ET2. 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.

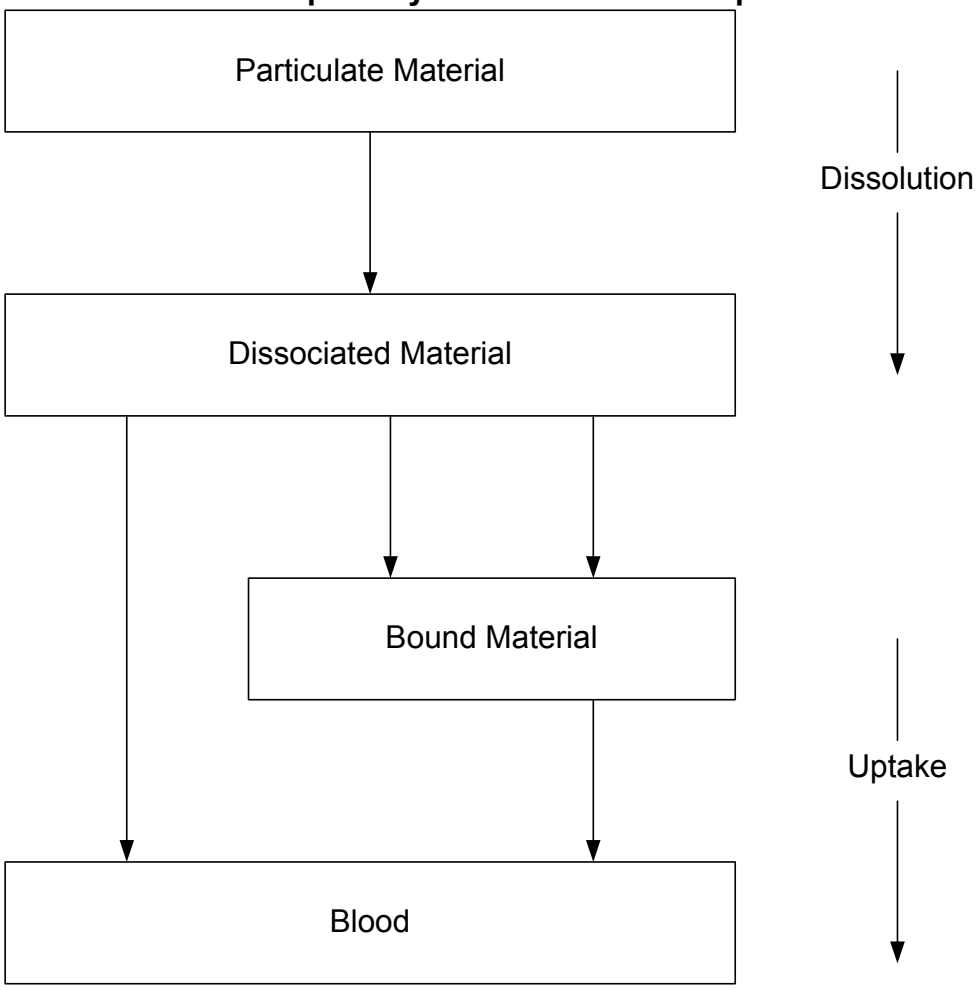
- For Type V, complete absorption (100%) is considered to occur instantaneously.

ICRP (1995) considers the experimental and human data to support the following classifications: cesium chloride and nitrate, Type F; cesium in irradiated fuel fragments, Type F or M; and cesium in fused aluminosilicate particles, M or S. ICRP (1995) recommends assigning all cesium aerosols to Type F in the absence of specific information supporting an alternative classification.

ICRP (1993) Cesium Biokinetic Model

Description of the Model. ICRP (1979, 1989, 1993) developed a 2-compartment model of the kinetics of ingested cesium in humans (Figure 3-6) that is applicable to infants, children, adolescents, and adults. The model is based on an age- and gender-specific model of Leggett (1986) in which compartment sizes and retention half-times were expressed as a function of the mass of potassium in the body. Ingested cesium is assumed to be completely absorbed into blood. Absorbed cesium is then assumed to distribute

Figure 3-6. The Human Respiratory Tract Model: Absorption into Blood



Source: ICRP 1994

uniformly in the body and to be eliminated from fast and slow elimination pools. The fraction of the total body cesium associated with the fast and slow pools, as well as the elimination half-times from each pool, are assumed to vary with age. The elimination half-times vary for ages 3 months, 1, 5, 10, 15 years, and adult (>15 years). The contribution of the fast pool decreases from 45% at age 5 years to 10% in adults. The elimination half-times of the fast pool decrease from 9.1 days at age 5 years to 2 days in adults, whereas the elimination half-times of the slow pool increase from 13–16 days in infants to 110 days in adults.

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

Risk Assessment. The ICRP biokinetic model has been used to establish radiation dose equivalents (Sv/Bq) of ingested ^{134}Cs, ^{136}Cs, and ^{137}Cs for ages 3 months to 70 years (ICRP 1993).

Target Tissues. The ICRP model is designed to calculate radiocesium intake limits based on radiation dose to all major organs.

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

Interroute Extrapolation. The ICRP model is designed to simulate oral exposure assuming 100% absorption of ingested cesium. The model is applicable to other routes of exposure if the extent of absorption for a particular exposure route is known.

Leggett et al. (2003) Cesium Biokinetics Model

Description of the Model. Leggett et al. (2003) developed a PBPK model of the kinetics of ingested or injected cesium in humans (Figure 3-7). The model includes compartments representing blood (plasma and red blood cells), brain, gastrointestinal tract, heart, kidney, liver, lung, pancreas, skin, and spleen. Transfers between plasma and tissues are simulated as first-order, flow-limited, rate constants (Table 3-7). Flow limitation is imposed by deriving the plasma-to-tissue rate constants in terms of tissue blood flows and empirically-derived arterial-venous extraction fractions (Table 3-8). Rate constants for transfers from tissues to plasma are derived from the product of the plasma-to-tissue rate constants and empirically-derived equilibrium ratios for cesium (fraction of body burden) in plasma and tissue (Table 3-9).

Table 3-7. Transfer Coefficients (d^{-1}) for a Reference Adult Male

Plasma to heart	14.128
Plasma to liver	19.515
Plasma to kidneys	67.108
Plasma to muscle	30.022
Plasma to gastrointestinal tract tissue	52.98
Plasma to stomach contents	4.516
Plasma to small intestine contents	1.0480
Plasma to large intestine contents	0.02
Plasma to spleen	5.298
Plasma to pancreas	1.766
Plasma to brain	0.424
Plasma to red marrow	5.298
Plasma to other skeleton	3.532
Plasma to skin	4.415
Plasma to lungs	4.415
Plasma to adipose tissue	8.83
Plasma to other 1[a]	8.826
Plasma to other 2[b]	0.00353
Plasma to red blood cells	1.8
Heart to plasma	8.073
Liver to plasma	2.204
Liver to small intestine	0.116
Kidneys to urinary bladder contents	1.678
Kidneys to plasma	31.876
Muscle to plasma	0.0751
Gastrointestinal tract tissue to plasma	8.191
Gastrointestinal tract tissue to liver	0.431
Gastrointestinal tract tissue to stomach contents	0.0333
Gastrointestinal tract tissue to small intestine contents	0.108
Gastrointestinal tract tissue to large intestine contents	0.0667
Spleen to plasma	5.033
Spleen to liver	0.265
Pancreas to plasma	1.678
Pancreas to liver	0.0883
Skin to plasma	0.867
Skin to excreta	0.0159
Brain to plasma	0.0848
Red marrow to plasma	0.706
Other skeleton to plasma	0.128
Lungs to plasma	1.472
Adipose tissue to plasma	1.766
Other 1[a] to plasma	0.692

Table 3-7. Transfer Coefficients (d^{-1}) for a Reference Adult Male

Other 2[b] to plasma	0.00141
Red blood cells to plasma	0.257
Urinary bladder contents to urine	12.0
Stomach to small intestine (contents)	40.0
Small intestine contents to plasma	28.215
Small intestine to large intestine (contents)	0.3
Small intestine contents to liver	1.485
Large intestine contents to feces	0.5

[a]Remaining tissues and fluids in the body with a relatively short turnover time.
[b]Small component of the remaining tissues and fluids in the body with a tenacious retention of Cs apparent in some long-term studies.

Source: Leggett et al. 2003

Table 3-8. Tissue-specific Extraction Fractions Assumed for Cesium

Tissues	Extraction fraction
Kidneys, gastrointestinal tract, heart	0.2
Liver, skin	0.05
Brain	0.002
All other tissues	0.1

Source: Leggett et al. 2003

Table 3-9. Tissue Masses, Cesium Equilibrium Distribution, and Tissue Blood Flow for a Reference Adult Male

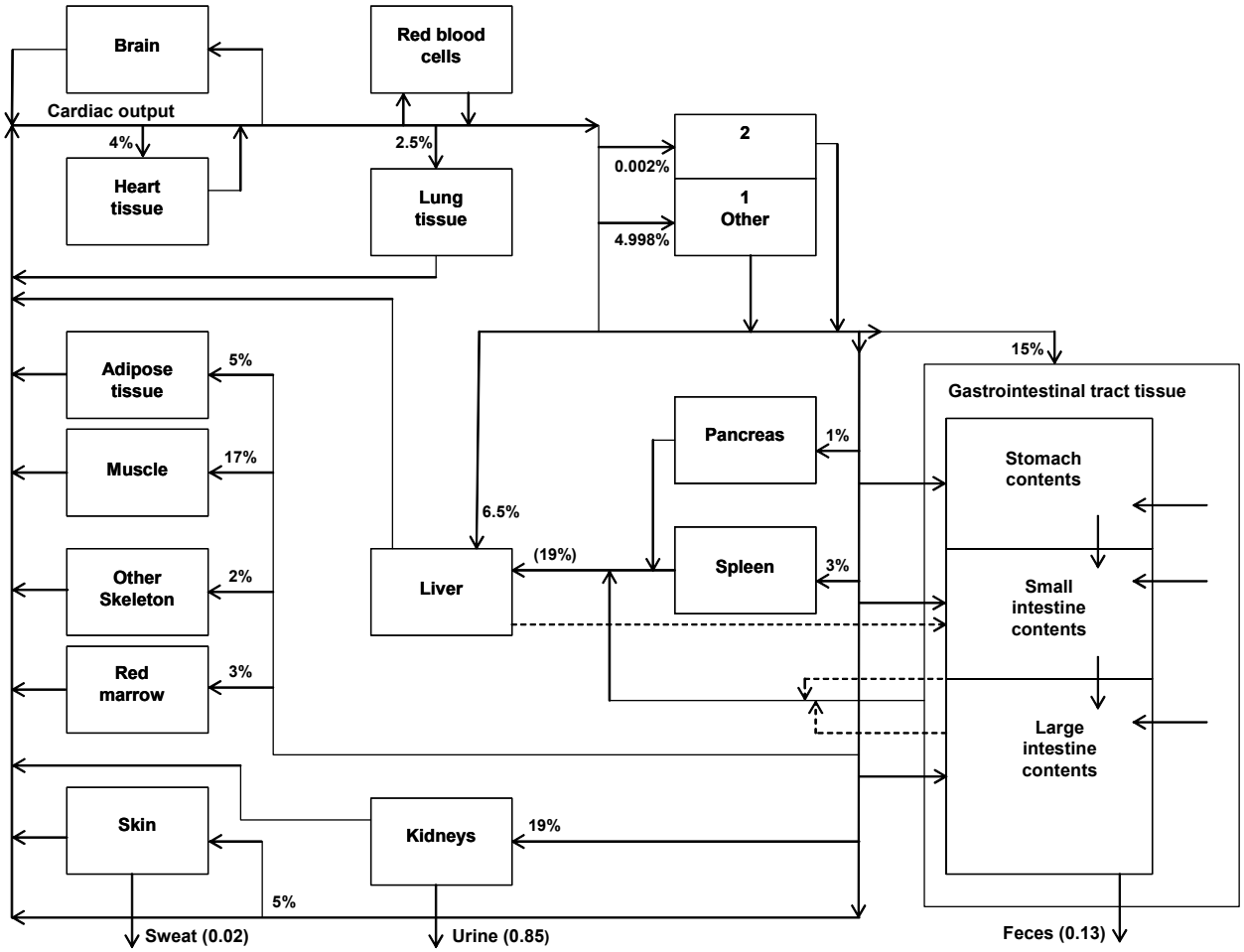
Compartment	Mass[a] (g)	Equilibrium cesium content[a] (fraction of total-body cesium)	Blood flow (FCO)
Adipose tissue[b]	12,000	0.01	0.05
Brain	1,450	0.01	0.12
Gastrointestinal contents	900	0.004	–
Gastrointestinal tract tissue	1,170	0.015	0.15
Heart	330	0.0035	0.04
Kidneys	310	0.004	0.19
Liver	1,800	0.02	0.065 (arterial) (0.19) (portal)
Lungs	500	0.006	0.025
Skeletal muscle	29,000	0.8	0.17
Plasma	3,100	0.002	–
Red blood cells	2,500	0.014	–
Skeleton	10,500	0.07	0.05
Red marrow		(0.015)	(0.03)
Bone and other tissue		(0.055)	(0.02)
Skin	3,300	0.01	0.05
Spleen	150	0.002	0.03
Pancreas	140	0.002	0.01
Other[c]	5,850	0.0305	0.05
Totals	73,000	1.00	1.00

[a]Without blood.
[b]Separable adipose tissue excluding yellow bone marrow.
[c]Remaining tissues and fluids in the body.

FCO = fraction of cardiac output

Source: Leggett et al. 2003

Figure 3-7. Directions of Flow of Cesium



Solid arrows represent plasma flow and broken arrows represent flow not involving plasma. Percentages indicate distribution of carbon monoxide. Numbers besides sweat, urine, and feces are fractions of cumulative excretion.

Source: Leggett et al. (2003).

Excretory pathways represented in the model include feces, sweat, and urine. Transfers between the central plasma flow and the gastrointestinal tract include secretion into the gastrointestinal tract and absorption to plasma.

Validation of the Model. The model has been evaluated for predicting observed blood and plasma cesium concentrations, whole-body retention of cesium, and urinary clearance of cesium in adults, following injections or ingestion of cesium (Leggett et al. 2003). Additional evaluations are reported, based on evaluations in rats and dogs. Model predictions corresponded reasonably well with observations.

Risk Assessment. The model is intended for predicting internal tissue doses to radiation following exposures to cesium for use in radiation risk assessment.

Target Tissues. The model is designed to calculate cesium concentrations in tissues, and includes major sites of accumulation (e.g., kidney, liver, and muscle).

Species Extrapolation. The model is designed for applications to human dosimetry and can be applied to other species (e.g., dog and rat) with modification of physiological parameters.

Interroute Extrapolation. The model is designed to simulate the intravenous or oral exposures to cesium and can be applied to other routes of exposure with the addition of simulations or estimates of the uptake of cesium into the central blood compartment.

3.6 MECHANISMS OF ACTION

3.6.1 Pharmacokinetic Mechanisms

Cesium is rapidly absorbed into blood following inhalation or oral exposure to soluble cesium compounds, as demonstrated by the rapid distribution of cesium activity after inhalation or ingestion. Approximately 80% absorption of ^{137}Cs was observed in dogs exposed to aerosols containing ^{137}Cs (as cesium chloride) (Boecker 1969a, 1969b). Oral ingestion of ^{134}Cs- and ^{137}Cs-contaminated food by volunteers resulted in approximately 78% absorption. Animal studies indicate that absorption rates from orally administered soluble cesium compounds are highest in the duodenum, followed in order by the jejunum, ileum, and colon. Very little absorption occurs in the stomach or caecum (Moore and Comar 1962, 1963). Absorption rates are higher in fasted rats than in fed rats, indicating that stomach contents

may influence the rate of cesium absorption. Relatively insoluble forms of cesium compounds, which may sometimes be associated with irradiated fuel particles, are poorly absorbed by inhalation and oral exposure routes (Boecker et al. 1974, 1977; LeRoy et al. 1966; Talbot et al. 1993). Dermal retention, but not transdermal absorption, has been qualitatively demonstrated in humans (Rundo 1964). Dermal absorption was observed following application of ^{137}CsCl in aqueous solution to the skin of rats (Pendic and Milivojevic 1966). Traces of ^{137}Cs were observed in the blood of rats within a few minutes following application.

Once absorbed, cesium is rapidly distributed throughout the body, becoming incorporated into the intracellular fluid of numerous tissues. Animal studies indicate that distribution patterns are similar following absorption from inhalation or oral exposure and that concentrations of cesium within muscle tissue are somewhat higher than the whole-body average (Stara 1965). Comparative human and animal studies have shown that parenteral exposure to cesium compounds results in cesium distribution patterns similar to those following inhalation or oral exposure (Rosoff et al. 1963; Stara 1965).

Absorbed cesium behaves in a manner similar to that of potassium. Both potassium and cesium are alkali metals that are distributed throughout the body as cations, becoming incorporated into intracellular fluids. Cesium has been shown to compete with potassium for transport through potassium channels and can also substitute for potassium in activation of the sodium pump and subsequent transport into the cell (Cecchi et al. 1987; Edwards 1982; Hodgkin 1947; Latorre and Miller 1983; Sjodin and Beauge 1967). In both types of transport, movement of cesium is sluggish compared with that of potassium (Blatz and Magleby 1984; Coronado et al. 1980; Cukierman et al. 1985; Edwards 1982; Gay and Stanfield 1978; Gorman et al. 1982; Hille 1973; Reuter and Stevens 1980). Discrimination between potassium and cesium generally is greater for passive transport out of cells than for active transport into cells (Leggett et al. 2003). This results in a greater residence time of cesium than potassium in muscle cells and hence in the whole body, since skeletal muscle contains most of the body's potassium or cesium at equilibrium. Although the biokinetics of potassium and cesium may vary somewhat in such characteristics as relative affinity for various cell types and differing retention rates, the similarities allow elimination rates for potassium to be used as an index of elimination rates for cesium (USNRC 1983). Urinary excretion is the major route of elimination of cesium.

3.6.2 Mechanisms of Toxicity

Earth contains relatively small amounts of stable (nonradioactive) cesium. Cesium has few industrial applications. At environmental levels, stable cesium is not chemically toxic in animals. Cesium is not likely to be of toxic concern to humans exposed to cesium by inhalation, oral, or dermal contact. Although a number of investigators have reported cesium-induced alterations in behavior or cardiac activity in animals systems exposed to cesium chloride by parenteral injection, underlying mechanisms are not yet fully understood.

Cesium may have both depressant and antidepressant properties in rodents, as it was shown to decrease the conditioned avoidance response of pole-climbing (Bose and Pinsky 1983b) and to reduce vertical and horizontal motor activity (Bose and Pinsky 1981, 1984; Bose et al. 1981; Pinsky et al. 1980), while enhancing amphetamine-induced hyperactivity and reducing the locomotor depressive action of reserpine (Messiha 1978).

Increased vertical activity (rearing), but not horizontal activity, was observed in mice given repeated injections of cesium chloride (Johnson 1972). Rastogi et al. (1980) found no increase in behavioral activity in rats repeatedly injected with cesium chloride, but noted a number of biochemical changes in the brain that included a statistically significant rise in tyrosine hydroxylase activity that resulted in a slight but statistically significant increase in tyrosine levels, markedly enhanced levels of the neurotransmitters norepinephrine and dopamine, and increased levels of a norepinephrine metabolite (4-hydroxy-3-methoxyphenylglycol). Cesium appeared to block the uptake of norepinephrine by synaptosomes.

Cesium was shown to alter normal cardiac rhythm, triggering short-lived early after depolarizations (EADs) and polymorphic ventricular tachyarrhythmias (VTs) in canine myocardial muscle fibers and Purkinje cells (Brachmann et al. 1983; Levine et al. 1985; Murakawa et al. 1997; Patterson et al. 1990), effects that are similar to those observed in humans with congenital and acquired long QT syndrome (Bonatti et al. 1983). Prolonged QT syndrome and associated cardiac arrhythmia have been observed in patients who consumed cesium chloride as a component of homeopathic remedies (Bangh et al. 2001; Harik et al. 2002; Saliba et al. 2001). Available animal data suggest that cesium-induced EADs and VTs were most likely the result of ionic imbalance due to reduced potassium permeability (Isenberg 1976) and imbalances of intra- and extracellular concentrations of calcium and sodium (Szabo et al. 1987).

Both ^{134}Cs and ^{137}Cs emit gamma radiation, and therefore, radioactive cesium is a health hazard. Highly penetrating gamma rays are the major cause of damage to tissues and internal organs following external overexposure to radioactive cesium. Once radioactive cesium is taken internally, cells of nearby tissues are at highest risk for damage due to the emission of beta particles. Radiation-induced damage in cells may be repaired quickly. Misrepaired damage may lead to permanent DNA changes and the potential for carcinogenesis. Very large acute radiation doses can damage or kill enough cells to cause the disruption of organ systems (acute radiation syndrome), harm to developing fetuses, and even death. Human and animal data indicate that radioactive cesium overexposure can result in adverse effects such as reduced fertility, abnormal neurological development, genotoxicity, and damage to blood-forming organs (Bartstra et al. 1998; Matsuda et al. 1985; Nikula et al. 1995, 1996; Padovani et al. 1993; Ramaiya et al. 1994; Skandalis et al. 1997; Tobari et al. 1988). 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

No data were located to indicate significant interspecies differences in pharmacokinetics or health effects associated with exposure to stable or radioactive cesium.

3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt

or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruptive effects resulting from exposure to stable or radioactive cesium.

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).

Soluble cesium compounds are readily absorbed into body fluids and bloodstream and are widely distributed throughout the body (see Section 3.5 for detailed information). PBPK models are used to simulate potential age-related differences in deposition of inhaled cesium, as well as differences in elimination rates for absorbed cesium (see Section 3.5.5 for more information on PBPK models). Although inhalation exposure to environmental levels of stable or radioactive cesium is not considered to be a major health concern, age-related differences in physical properties of the respiratory system and

ventilation patterns could result in differences in absorption rates of inhaled soluble or insoluble cesium compounds. Soluble cesium compounds are assumed to be completely absorbed in the gastrointestinal tract, with no adjustments for age. Available human and animal data do not indicate that age-related differences might exist for absorption and distribution of cesium following oral exposure. Since cesium is principally absorbed and distributed in ionic form (as Cs^+), any age-related differences in absorption following oral exposure would likely be the result of differences in diffusion rates and active transport mechanisms involved in the movement of cesium through extra- and intracellular fluids. Elimination rates for cesium appear to be age-related and may be most closely related to body mass. As described in detail in Section 3.5.4.2, young children exhibit whole-body biological elimination half-times that are much shorter than those of older children and adults (Boni 1969b; Melo et al. 1994). It is not known whether or not these age-related differences may be due to higher retention of cesium in adult tissues and lower rates of excretion.

Measurable amounts of ^{137}Cs have been found in the breast milk of women living in areas contaminated with radioactive fallout. Transfers to newborns and 1-year-old children were estimated to be approximately 40 and 50%, respectively (Johansson et al. 1998). Animal studies have shown that cesium crosses the placental barrier, but cesium is found in lower concentrations in the fetus than in maternal or placental tissues (Mahlum and Sikov 1969; Vandecasteele et al. 1989).

Although no information was located regarding age-related health effects in humans exposed to stable cesium, age-related differences in the pharmacokinetics of stable cesium could conceivably result in age-related differences in health effects. No studies were located regarding age-related differences in toxicity in animals exposed to stable cesium.

Most of the available information regarding age-related health effects from overexposure to cesium concern developmental effects related to *in utero* irradiation of human or animal fetuses from an external source of radiation. Impaired cognitive function was observed in atomic bomb survivors overexposed to ionizing radiation *in utero* during critical stages of neurological development (Schull and Otake 1999). Developmental toxicity studies employing external gamma radiation from a radioactive cesium source (or from any other gamma ray source) indicate that rats and mice are most sensitive to the effects of external radiation around gestation day 14. Effects observed following irradiation during this period include reduced survival, decreased brain size, smaller head size, and retarded odontogenesis (Koshimoto et al. 1994; Minamisawa et al. 1990; Norton and Kimler 1987, 1988; Saad et al. 1991, 1994). When tested as adults, animals irradiated during this developmental period exhibit increased aggressive behavior

(Minamisawa et al. 1992; Norton and Kimler 1987, 1988). Although comparative studies of neurological effects in animals first irradiated as juveniles or adults were not located, it is apparent that there are critical stages of fetal developmental during which there is increased susceptibility to the effects of radiation. In these studies, although cesium was used as the gamma source, the effects were not unique to cesium. Similar results would be elicited by any gamma source.

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 cesium 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 cesium 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 Cesium

Stable or radioactive isotopes of cesium may be measured in samples of urine, blood, feces, or body tissues by a number of methods outlined in Section 7.1. Stable cesium is of little toxicological concern. However, overexposure to radioactive isotopes of cesium may pose a significant health risk. Internal exposure may be quantified by direct counting (*in vivo* measurements) of radioactive emission from the body using whole-body counters capable of distinguishing the gamma emissions that are unique to radioactive isotopes of cesium. Radioactivity can be accurately measured in blood, excrement, and tissue samples using scintillation counting. The biomarkers that may help quantify exposure to stable or radioactive cesium are similar in children and adults.

3.9.2 Biomarkers Used to Characterize Effects Caused by Cesium

There are no known biomarkers of effect for exposure to stable cesium. High-level external or internal exposure to radioactive cesium can result in bone marrow aplasia, reduced white blood cell counts, decreased hemoglobin and platelet levels, and increased frequencies of chromosomal aberrations in lymphocytes. Frequencies of chromosomal aberrations were used to estimate external radiation doses among individuals in Goiânia, Brazil who had been exposed to an opened ^{137}CsCl source (Natarajan et al. 1998). These results are not unique to radioactive cesium. Similar results would be expected following overexposure to any source of ionizing radiation.

3.10 INTERACTIONS WITH OTHER CHEMICALS

No data were located regarding interactions of cesium with other chemicals that might influence the toxicity of cesium.

3.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to cesium than will most persons exposed to the same level of cesium 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 cesium, or compromised function of organs affected by cesium. Populations who are at greater risk due to their unusually high exposure to cesium are discussed in Section 6.7, Populations with Potentially High Exposures.

Increased susceptibility to the toxic effects resulting from exposure to high levels of stable or radioactive cesium might be indicated among individuals with abnormally low potassium intake, those with compromised kidney function, and patients taking stimulant or depressant drugs for the treatment of mental disorders (see Sections 3.5 and 3.6 for detailed information on the toxicokinetics and mechanisms of action of cesium). Individuals with compromised immune function might be more susceptible to the adverse effects of radiation overexposure from a radioactive cesium source (or from any other gamma emitting radioactive source).

Evidence for potential age-related differences in susceptibility to stable or radioactive cesium toxicity is provided by studies of elimination rates for ^{137}Cs in humans (Boni 1969b; Melo et al. 1994; Toader et al. 1996). Elimination rates are higher in young children than adults, and higher in adult females than adult males, indicating that lower elimination rates could result in greater retention and, therefore, increased toxicity for a given intake. Animal studies support these findings (Lengemann 1970; Mahlum and Sikov 1969; Melo et al. 1996, 1997; Tyler et al. 1969). There is some indication, however, that retention of cesium is higher in neonatal rats than in weanling or young adult rats (Lengemann 1969, 1970; Mahlum and Sikov 1969) (see Sections 3.5.4.2 and 3.5.4.4 for more detailed information.

Pregnant women (Zundel et al. 1969) and individuals suffering from muscular dystrophy (Lloyd et al. 1973) exhibited decreased cesium retention, which may decrease susceptibility to stable or radioactive cesium-induced toxicity.

3.12 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to cesium. 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 cesium. 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 cesium:

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.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical management of poisoning and drug overdose. 3rd edition. Philadelphia, PA: WB Saunders, 413-425.

NCRP Report No. 65. 1980. Management of persons accidentally contaminated with radionuclides. Bethesda MD: National Council on Radiation Protection and Measurements.

3.12.1 Reducing Peak Absorption Following Exposure

Because soluble cesium compounds are rapidly absorbed into blood following inhalation, oral, and dermal exposure, there are no prescribed methods for reducing peak absorption following exposure. Early counter measures that may aid in reducing peak absorption following oral exposure to stable or radioactive cesium include oral administration of insoluble Prussian blue (ferric hexacyanoferrate) that exchanges potassium for cesium, forming an insoluble complex that is eliminated through the feces (Oak Ridge Associated Universities 2003). Animal studies indicate that absorption of cesium may also be reduced by the administration of excess potassium (Richmond and Furchner 1961). Cathartics such as magnesium sulfate, as well as gastric lavage, will shorten the transit time of ingested cesium in the gastrointestinal tract (Ellenhorn et al. 1997; Gerber et al. 1992; Haddad et al. 1998). Countermeasures attempt to reduce the body burden of cesium following inadvertent exposure (see Section 3.12.2).

3.12.2 Reducing Body Burden

Oral administration of Prussian blue (potassium ferricyanoferrate) may enhance the fecal excretion of absorbed cesium (Ducousso et al. 1975; Ellenhorn et al. 1997; Gerber et al. 1992; Haddad et al. 1998;

Melo et al. 1996). Animal studies indicate that excretion of cesium may also be enhanced by the administration of excess potassium (Richmond and Furchner 1961). Higher plasma concentrations of potassium may increase the mobilization of cesium from tissues, and thus increase excretion.

3.12.3 Interfering with the Mechanism of Action for Toxic Effects

No data were located regarding reduction of the toxic effects of cesium through interfering with mechanisms of action.

3.13 ADEQUACY OF THE DATABASE

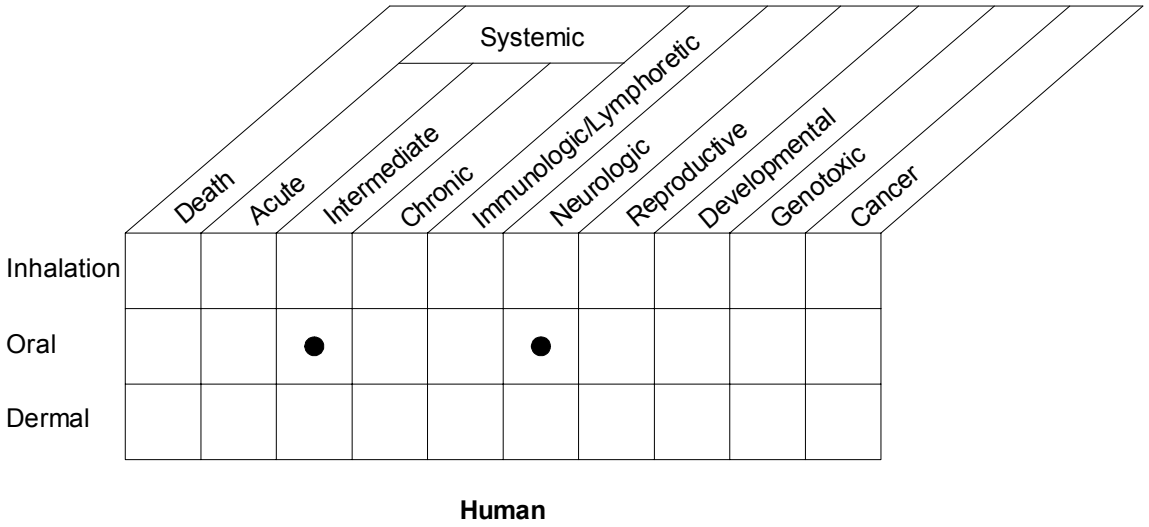
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cesium is available. Where adequate information is not available, 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 cesium.

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.

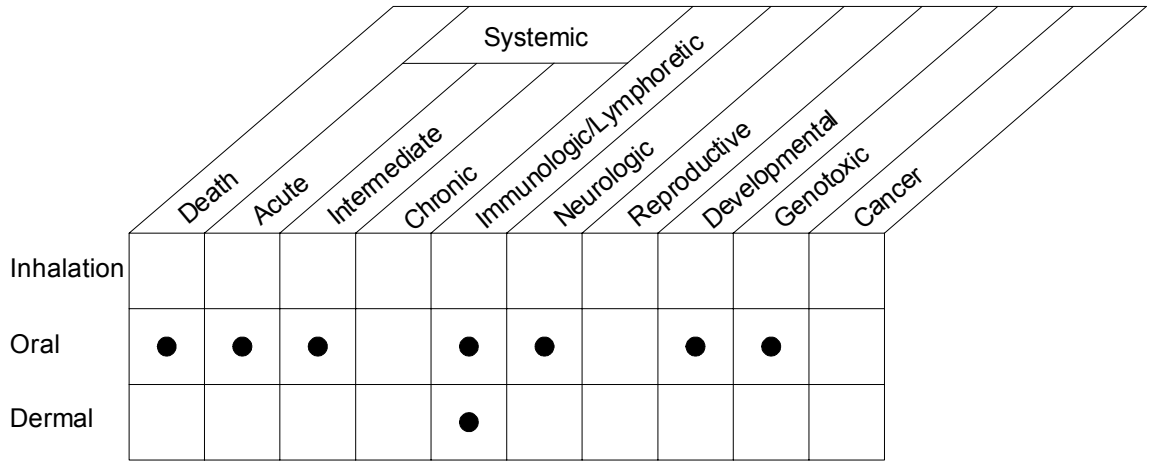
3.13.1 Existing Information on Health Effects of Cesium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to stable and radioactive cesium are summarized in Figure 3-8 and 3-9, respectively. The purpose of these figures is to illustrate the existing information concerning the health effects of cesium. 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

Figure 3-8. Existing Information on Health Effects of Stable Cesium



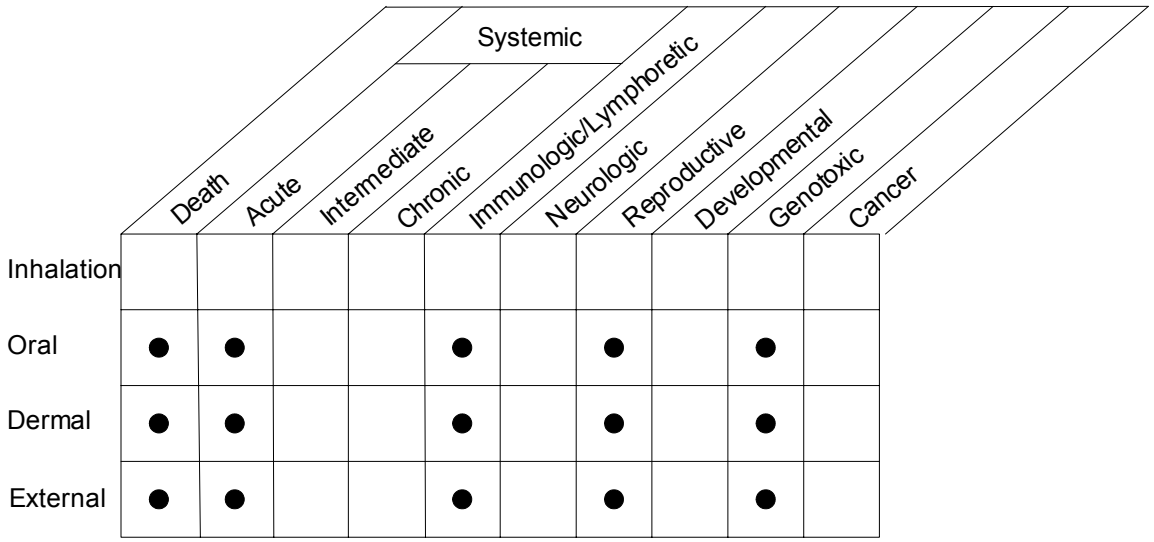
Human



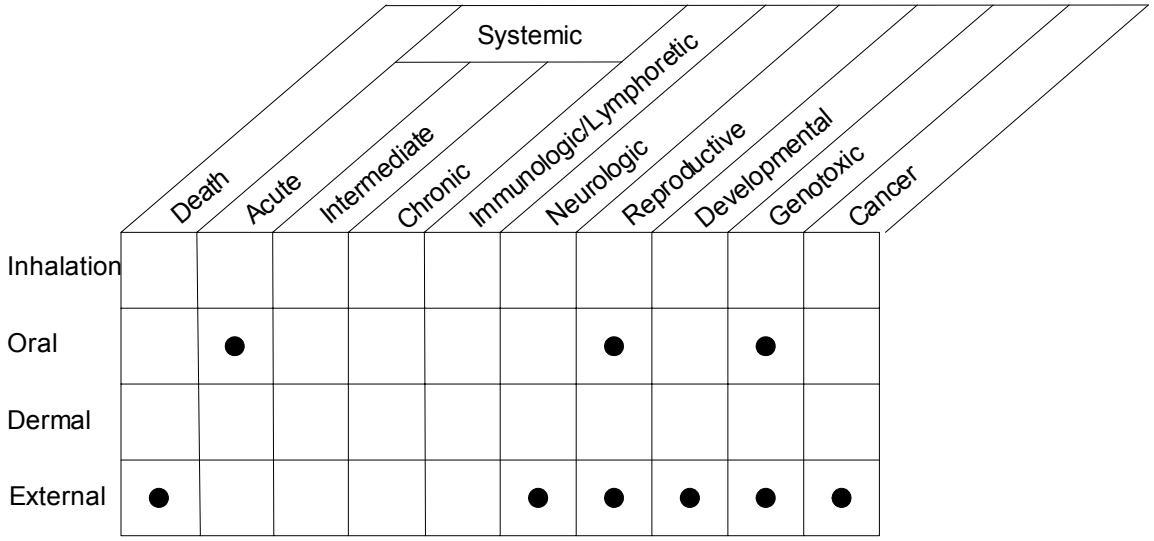
Animal

● Existing Studies

Figure 3-9. Existing Information on Health Effects of Radioactive Cesium



Human



Animal

● Existing Studies

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.

As shown in Figure 3-8, limited information is available regarding health effects in humans following intermediate-duration oral exposure to stable cesium. No information is available regarding health effects in humans following inhalation or dermal exposure to stable cesium. Information is available on the health effects in animals exposed to stable cesium. However, the available information is mostly from acute oral LD_{50} studies, a single intermediate-duration oral study, and a study of male reproductive toxicity.

As shown in Figure 3-9, limited information is available regarding oral and dermal exposure to radioactive cesium. An accidental exposure of a number of individuals in Goiânia, Brazil resulted in adverse health effects that could be attributed to external and internal (oral and dermal) exposure to radiation from a radioactive cesium source. Information is also available for humans externally exposed to a radiocesium source that resulted in adverse dermal effects. Numerous reports are available regarding other cases of external and internal environmental exposure to radioactive isotopes of cesium in humans, especially from areas with significant amounts of radioactive fallout. However, at present, associations between exposure to environmental levels of radioactive cesium and adverse health effects have not been confirmed. Present environmental levels of radiocesium, therefore, might not represent overexposure to radiation.

Reduced sperm counts in mice were found following oral administration of radioactive cesium. Studies of dogs, intravenously administered ^{137}CsCl, resulted in hematologic dyscrasia as early effects and tumors of various organs as late effects. Given by this route, the tissue distribution of ^{137}Cs is similar to that resulting from oral or inhalation exposure.

3.13.2 Identification of Data Needs

Acute-Duration Exposure. Results from human and animal studies indicate that stable cesium is of little acute oral toxicity concern. Toxicokinetic data regarding the widespread distribution of cesium absorbed following oral exposure indicate that dermal and inhalation exposure to stable cesium would not present a greater health concern than that posed by oral exposure. Acute-duration inhalation and oral MRLs were not derived for stable cesium due to a lack of human or animal data. To generate appropriate

data for deriving acute-duration inhalation and oral MRLs for stable cesium, at least one comprehensive acute inhalation and one acute oral toxicity study would be needed of at least one animal species exposed to several dose levels.

Reports of adverse effects in humans that can be specifically attributed to acute exposure to radioactive cesium are restricted to the accounts of accidental external exposure (Gottlöber et al. 2000) and both external and internal (dermal and oral) exposure (Brandão-Mello et al. 1991) to an opened ^{137}CsCl source. Observed health effects were representative of those resulting from overexposure to other beta- and gamma-emitting sources of ionizing radiation. Animal data regarding acute oral exposure to radioactive cesium are limited to reports of dominant lethal mutations and reduced fertility in mice (Ramaiya et al. 1994). Acute-duration inhalation and oral MRLs were not derived for radioactive cesium due to a lack of human or animal data. To generate appropriate data for deriving acute-duration inhalation and oral MRLs for radioactive cesium, at least one comprehensive acute inhalation study and one acute oral toxicity study of at least one animal species exposed to several dose levels would be needed. Such studies could be designed to also generate data regarding potential age-related differences in toxicity. However, great danger would be posed to investigators considering the exposure of laboratory animals to radioactive cesium at levels great enough to cause significant adverse health effects. Distribution patterns of ^{137}Cs are similar in animals exposed to relatively nontoxic levels of ^{137}CsCl by parenteral injection, inhalation exposure, or oral administration (Boecker et al. 1969a; Stara 1965). Therefore, the results of the intravenous injection studies in dogs (Nikula et al. 1995, 1996) provide the most reasonable indication of health effects that would be expected in animals exposed by inhalation or oral administration. An acute-duration MRL that was derived by Agency for Toxic Substances and Disease Registry (1999) for acute external exposure to ionizing radiation was considered to be appropriate as an acute-duration MRL for external exposure to ionizing radiation from a radioactive cesium source.

Intermediate-Duration Exposure. Limited information regarding intermediate-duration oral exposure in humans indicates that the nervous and cardiovascular systems are the most likely targets of toxicity for high-dose stable cesium (Bangh et al. 2001; Harik et al. 2002; Neulieb 1984; Saliba et al. 2001). Limited data indicate that intermediate-duration oral exposure of pregnant mice to stable cesium may adversely affect developing fetuses (Messiha 1988b, 1989b). Orally administered stable cesium has also been shown to be genotoxic to female mice (Ghosh et al. 1990, 1991). Intermediate-duration inhalation and oral MRLs were not derived for stable cesium due to the paucity of human or animal data. To generate appropriate data for deriving intermediate-duration inhalation and oral MRLs for stable cesium, at least one comprehensive intermediate-duration inhalation and one intermediate-duration oral

toxicity study of at least one animal species exposed to several dose levels would be needed. Such studies could be designed to also generate data regarding potential age-related differences in toxicity.

No human or animal data are available in which intermediate-duration inhalation or oral exposure to radioactive cesium can be associated with adverse human health effects. When humans are exposed to high levels of radioactivity from a radiocesium source, as were the cases of acute exposure in Goiânia, Brazil (Brandão-Mello et al. 1991) and Russia (Gottlöber et al. 2000), such exposures should be of value in assessing potential health hazards. Animal studies could be designed to assess the health effects associated with intermediate-duration exposure to radioactive cesium. Such studies could be designed to also generate data regarding potential age-related differences in toxicity.

Chronic-Duration Exposure and Cancer. Since there are no studies pertaining to noncancer or cancer health effects in humans or animals following chronic-duration inhalation or oral exposure to stable cesium, no chronic-duration inhalation or oral MRLs were derived for stable cesium. Additional data from acute- and intermediate-duration animal studies might be helpful in determining the need for longer-term studies.

There are no data regarding noncancer or cancer health effects in humans following chronic-duration inhalation or dermal exposure to radioactive cesium. Low levels of radioactive cesium are found in the diets of individuals living in areas that have been contaminated with radioactive fallout; however, there is a lack of information regarding dose-response following chronic-duration oral exposure. No chronic-duration inhalation or oral MRLs were derived for radioactive cesium. A chronic-duration MRL that was derived by Agency for Toxic Substances and Disease Registry (1999) for chronic external exposure to ionizing radiation was appropriate as a chronic-duration MRL for external exposure to ionizing radiation from a radioactive cesium source. Long-term research into health effects associated with chronic exposure to radioactive cesium following incidents such as the Chernobyl nuclear accident may help to elucidate long-term noncancer and cancer health risks from chronic exposure to radionuclides of cesium.

Genotoxicity. No genotoxicity studies of *in vivo* exposure of humans to stable cesium compounds were located. Stable cesium (as cesium chloride) induced chromosomal aberrations in human lymphocytes *in vitro* (Ghosh et al. 1993) and chromosomal aberrations and micronuclei in mouse bone marrow *in vivo* (Ghosh et al. 1990, 1991; Santos-Mello et al. 2001). Cesium sulfate was not mutagenic in *E. coli* either with or without metabolic activation (Olivier and Marzin 1987). Studies in mammalian

systems would be useful. Studies of workers exposed to known levels of stable cesium would be useful in establishing whether or not cesium is of genotoxicity concern in humans.

In vivo human data are limited to the findings of increased point mutations in T-lymphocytes and chromosomal aberrations among individuals who had been exposed to beta and gamma radiation from an opened ^{137}CsCl source (Natarajan et al. 1998; Skandalis et al. 1997) and apparently increased frequencies of chromosomal aberrations in lymphocytes of children living in areas contaminated by ^{137}Cs fallout following the Chernobyl nuclear accident (Padovani et al. 1993). *In vitro* exposure of human lymphocytes to a sealed ^{137}Cs gamma source resulted in an increased frequency of micronuclei (Balasem and Ali 1991). *In vivo* oral and external exposure of male mice to a ^{137}Cs gamma source resulted in increases in dominant lethal mutations (Ramaiya et al. 1994). Increases in the frequency of reciprocal translocations in spermatogonia were observed following oral exposure to ^{137}Cs in mice (Ramaiya et al. 1994) and external exposure to a ^{137}Cs source in crab-eating monkeys (Tobari et al. 1988). A number of *in vitro* genotoxicity assays have indicated chromosomal aberrations and breaks, sister chromatid exchanges, and micronuclei in animal cells (Arslan et al. 1986; Biedermann et al. 1991; Doggett and McKenzie 1983; Hintenlang 1993; Iijima and Morimoto 1991; Kamiguchi et al. 1991; Mikamo et al. 1990, 1991).

Human and animal studies show that external and internal exposure to radioactive cesium is a genotoxicity concern. External exposure to any gamma source would be expected to result in genotoxic effects similar to those observed following external exposure to radioisotopes of cesium (see Agency for Toxic Substances and Disease Registry 1999 for more information on ionizing radiation). Whenever possible, additional human studies should focus on exposure levels to establish dose-response relationships.

Reproductive Toxicity. There are no reports of reproductive effects in humans or animals exposed to stable cesium. Although stable cesium appears to be of relatively low toxicity concern, animal studies could be designed to assess the potential for adverse health effects (including reproductive effects) associated with repeated exposure. Human data could be collected from individuals occupationally exposed to significant levels of stable cesium.

Reports of human reproductive effects following exposure to radioactive cesium are limited to the findings of reduced sperm counts following external and internal exposure to an opened ^{137}CsCl source (Brandão-Mello et al. 1991). Mice, exposed to ^{137}Cs either orally or externally, exhibited reduced fertility

(including complete sterility) (Ramaiya et al. 1994). Persistent germinal epithelium damage and azoospermia were observed in all long-term surviving dogs that had been administered intravenous injections of ^{137}Cs (Nikula et al. 1995, 1996). In cases of known human exposure to radioactive cesium, exposure-response relationships should be established when possible. Although reduced fertility has been shown in males, additional animal studies could be designed to assess the potential for reproductive toxicity in females.

Developmental Toxicity. There are no reports of developmental effects in humans exposed to stable cesium. One investigator reported reduced body weight and certain organ weights among offspring, as well as indications of altered activity of some hepatic enzymes among offspring of pregnant mouse dams repeatedly exposed (orally) to stable cesium (Messiha 1988b). The same investigator reported similar results in pups exposed (via their nursing mothers) only during lactation (Messiha 1989b). These studies did not include gross and histopathologic examination of the offspring. Well-designed animal studies could more completely assess the potential for developmental toxicity of stable cesium.

Although there are no reports of developmental effects in humans exposed specifically to radioisotopes of cesium, impaired cognitive function was observed in atomic bomb survivors of Hiroshima and Nagasaki prenatally exposed to high levels of ionizing radiation during critical stages of neural development (Schull and Otake 1999; Schull et al. 1988). External exposure to sufficiently high doses of radiation from a radioactive cesium source would be expected to result in similar effects. *In utero* exposure of rat and mouse fetuses via whole body exposure of dams resulted in developmental effects such as reduced postnatal body weight, impaired motor activity, morphological changes in the brain, increased aggressive behavior, reduced brain and head size, and retarded odontogenesis and palatal closure (Minamisawa et al. 1990, 1992; Norton and Kimler 1987, 1988; Saad et al. 1991, 1994). Continued monitoring of populations known to have been exposed to ionizing radiation (including radioactive cesium sources) should help to refine estimates of dose-response and the relationship to adverse health effects, including developmental toxicity.

Immunotoxicity. There are no reports regarding the immunotoxicity of stable cesium in humans or animals. Animal studies could be designed to assess these parameters, but such studies do not presently seem necessary.

Severe bone marrow depression was observed in individuals exposed externally and internally to a ^{137}Cs source. This effect is typical of individuals exposed to ionizing radiation (see Agency for Toxic

Substances and Disease Registry 1999 for additional information on the effects of ionizing radiation). A similar effect was observed in dogs given an intravenous injection of ^{137}CsCl (Nikula et al. 1995). Data should be collected from individuals known to have been exposed to ionizing radiation (including that from radioactive cesium sources). Additional animal studies could be designed to establish dose-response relationships.

Neurotoxicity. Data regarding neurological effects of stable cesium in humans are restricted to a single case of an investigator reporting feelings of euphoria, heightened sense perception, and tingling sensations within 15 minutes of ingesting oral doses of cesium chloride during a 36-day exposure period. No apparent adverse effects on mental or motor skills were observed (Neulieb 1984). Administration of cesium chloride to animals has triggered stimulant (Johnson 1972; Messiha 1978) and depressant (Bose and Pinsky 1981, 1983b, 1984; Bose et al. 1981; Pinsky et al. 1980) central nervous system responses. Additional animal studies could be designed to elucidate mechanisms responsible for the observed neurological effects.

Although there are no reports of neurotoxicity in humans exposed specifically to radioisotopes of cesium, impaired cognitive function was observed in atomic bomb survivors of Hiroshima and Nagasaki prenatally exposed to high levels of external ionizing radiation during critical stages of neural development (Schull and Otake 1999; Schull et al. 1988). External exposure to sufficiently high doses of radiation from a sealed radioactive cesium gamma source would result in similar effects. *In utero* exposure of rat and mouse fetuses via whole-body exposure of dams resulted in impaired motor activity, morphological changes in the brain, increased aggressive behavior, and reduced brain and head size (Minamisawa et al. 1990, 1992; Norton and Kimler 1987, 1988; Saad et al. 1991, 1994), effects that have been shown to be related to critical developmental stages. Neurotoxic effects, noted in humans suffering from acute radiation syndrome due to ionizing radiation exposure, are well-characterized (see Agency for Toxic Substances and Disease Registry 1999 for more detailed information on the effects of ionizing radiation). Such effects would be expected in humans exposed to sufficiently high doses of radiation from a radioactive cesium source. Additional well-designed animal studies might elucidate mechanisms of neurotoxicity, but do not presently appear to be needed.

Epidemiological and Human Dosimetry Studies. Stable cesium is ubiquitous in the earth's crust, but is found at such low environmental levels that the probability of human intake of toxic amounts of stable cesium is negligible. Although there is no apparent need for specifically designed epidemiological or human dosimetry studies regarding stable cesium, such data, collected from

individuals occupationally exposed to significant amounts of cesium or persons living near toxic waste sites with significant levels of cesium, might be useful.

Due to accidental or intentional releases during nuclear fission, ^{134}Cs and ^{137}Cs can be found in air, soil, water, and food. There is concern for the health of humans living in close proximity to release or storage sites or in areas receiving significant amounts of radioactive fallout. Epidemiological studies of radiation doses typically involve estimates of exposure that are based on whole-body measurements of internally-deposited ^{134}Cs or ^{137}Cs or genotoxic effects such as chromosomal aberrations in peripheral blood lymphocytes. A need remains for epidemiological data that can provide quantitative human dose-response information while supplying additional information on the health effects of exposure to ionizing radiation and radioisotopes of cesium; in particular, for cases of known internal exposure.

Biomarkers of Exposure and Effect.

Exposure. Both stable and radioactive isotopes of cesium may be detected in samples of urine, blood, feces, or body tissues. Due to the relatively long biological half-time of cesium (several months in humans), short-term exposures cannot be readily distinguished from longer-term ones. No new biomarkers of exposure are needed at this time.

Effect. No known biomarkers of effect exist for exposure to stable cesium. Although high radiation doses from internally deposited radioactive cesium can cause bone marrow aplasia, altered blood values, and increased chromosomal aberrations in lymphocytes (Brandão-Mello et al. 1991; Natarajan et al. 1998), these effects are not specific to radioactive cesium.

Absorption, Distribution, Metabolism, and Excretion. Human and animal data show that inhaled or ingested cesium (in soluble compounds) is rapidly absorbed into the blood (Boecker 1969a, 1969b; Henrichs et al. 1989; Lie 1964; Miller 1964; Stara 1965; Stara and Thomas 1963), whereas relatively insoluble forms of cesium are not readily absorbed into blood following inhalation or oral exposure (Boecker et al. 1974, 1977; Leroy et al. 1966; Talbot et al. 1993). Dermal absorption has been qualitatively (but not quantitatively) demonstrated in rats (Pendic and Milivojevic 1966). Additional studies could measure relative absorption rates for a variety of soluble and insoluble cesium compounds. Furthermore, studies could be designed to measure dermal absorption rates. Other studies could further assess the fate of relatively insoluble inhaled particles containing radioisotopes of cesium that may be retained in lung tissue for long periods of time.

Cesium absorbed via inhalation or ingestion has been shown to be rapidly distributed throughout the body in humans and animals (Boecker 1969a, 1969b; Furchner et al. 1964; Lie 1964; Miller 1964; Rosoff et al. 1963; Stara 1965; Stara and Thomas 1963). Once absorbed by pregnant women, cesium can pass the placental barrier and be absorbed by the conceptus. Absorbed cesium can also be found in the milk of lactating women (Thornberg and Mattsson 2000). Once cesium is absorbed into body fluids, distribution patterns in soft tissue are expected to be similar for any route of exposure since cesium is distributed throughout the body as the cation (Cs^+), much like potassium (K^+). Available studies appear to adequately describe the distribution of absorbed cesium. Additional studies could be designed to elucidate mechanisms whereby cesium ions may influence central nervous system activity.

Human and animal studies adequately describe elimination of absorbed cesium, primarily via the urine (Boecker 1969b; Hölgye and Malý 2002; Iinuma et al. 1965; Rosoff et al. 1963; Stara 1965; Stara and Thomas 1963). Age-related differences in elimination rates have been described in humans (Boni 1969b; Melo et al. 1994) and dogs (Melo et al. 1996). In cases of known human exposure to cesium, additional information may help to further assess age-related differences in the toxicokinetics of cesium.

Comparative Toxicokinetics. Available cesium toxicokinetic data in humans and various animal species indicate similar patterns of absorption, distribution, and elimination. The central nervous system appears to be a target for effects in humans (Neulieb 1984) and animals (Bose and Pinsky 1981, 1983b, 1984; Bose et al. 1981; Johnson 1972; Messiha 1978; Pinsky et al. 1980). Additional studies could be designed to elucidate and compare mechanisms responsible for central nervous system effects.

Methods for Reducing Toxic Effects. Oral administration of Prussian blue that exchanges potassium for cesium, cathartics that shorten the transit time of ingested cesium within the gastrointestinal tract, and gastric lavage may aid in reducing peak absorption of ingested cesium, but due to the rapid absorption of cesium from soluble cesium compounds, these measures would only be of potential benefit within a short time following initial exposure. Most countermeasures focus on reducing the body burden of absorbed cesium. The intestinal reabsorption of cesium that is excreted into the small intestine via the bile can be blocked by oral administration of Prussian blue, forming an insoluble cesium complex that is excreted in the feces. Animal studies also indicate that increased plasma concentrations of potassium may increase the mobilization of cesium from tissues, increasing its excretion (Richmond and Furchner 1961). There are no prescribed methods for interfering with mechanisms of action for toxic effects of cesium, since such mechanisms have not been elucidated.

Children's Susceptibility. Available information on age-related differences in health effects comes from *in utero* exposure to radiation from external ionizing radiation sources (including radioisotopes of cesium). Studies have shown neurological effects in humans and animals exposed during critical periods of central nervous system development (Koshimoto et al. 1994; Minamisawa et al. 1990; Norton and Kimler 1987, 1988; Schull and Otake 1999). Comparative studies of neurological effects in animals first irradiated as juveniles or adults are lacking. No information was located regarding age-related health effects in humans or animals exposed to stable cesium.

PBPK models account for potential age-related differences in deposition of inhaled cesium, as well as differences in elimination rates for absorbed cesium (see Section 3.5.5 for more information on PBPK models). Potential differences in absorption rates of inhaled cesium compounds could be due to age-related differences in physical properties of the respiratory system and/or ventilation patterns. PBPK models also could adjust for potential age-related differences in gastrointestinal absorption. If such differences exist, they would likely be the result of differences in diffusion rates and active transport mechanisms. Young children exhibit biological half-times for absorbed cesium that are shorter than those of older children and adults (Boni 1969b; Melo et al. 1994); these age-related differences are associated with body mass and could be the result of age-related differences in tissue retention and excretory rates.

Cesium is found in the breast milk of mothers with an internal cesium burden (Johansson et al. 1998; Thornberg and Mattsson 2000), and can be transferred to nursing infants (Johansson et al. 1998). Cesium has been shown to cross the placental barrier of animals, but concentrations of cesium in the fetal tissues are less than those in corresponding tissues of the mother (Mahlum and Sikov 1969; Vandecasteele et al. 1989). Data collected from areas containing elevated concentrations of radioactive cesium fallout might be of value in further assessing age-related transfer rates.

Biomarkers of exposure or effect are the same in adults and children (see Section 3.9 for detailed information on biomarkers of exposure and effect). There are no data on interactions of cesium with other chemicals in children. No pediatric-specific methods have been found to reduce peak absorption, or body burden, of cesium following exposure, although methods employed to reduce the body burden of cesium in adults are also effective in children.

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

3.13.3 Ongoing Studies

A single relevant ongoing study was identified in the Federal Research In Progress database (FEDRIP 2002). Dr. R. Albertini, from the University of Vermont, Burlington, Vermont, is quantitatively examining radiation-induced mutation at the hprt gene in human T-lymphocytes. Gamma radiation sources used in the study include ^{137}Cs.