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 americium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

The potential for adverse health effects to humans exposed to americium is dependent on the amount of americium isotopes (^{241}Am and ^{243}Am) present in the body as well as the radiation dose and dose rate that each produce. Both ^{241}Am and ^{243}Am can be formed when either ^{238}U (the major uranium isotope used in nuclear power reactor fuel) or ^{238,239}Pu (primarily used in nuclear weapons) are exposed to neutrons, as occurs in a nuclear reactor or nuclear explosion. Neutron activation of ^{238}U to ^{239}U, followed by combinations of decay to ^{239}Np and ^{239}Pu and neutron activation to higher masses of each, produces a range of isotopes of these elements. Similarly, neutron activation of ^{238,239}Pu yields higher mass isotopes. Any ^{241}Pu or ^{243}Pu formed by these processes will decay to ^{241}Am and ^{243}Am, respectively. These can also be neutron activated, producing other americium isotopes (e.g., ^{242,244,245}Am). The isotopes, ^{242}Am and ^{243}Am, are produced in lower abundance than ^{241}Am (see Chapter 4 for decay schemes and other more detailed information). These americium radionuclides may be released into the atmosphere in sites that surround nuclear production facilities, store nuclear waste, or leak americium into the soil or groundwater. 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 americium radionuclides may be attributed to the gamma radiation. Alpha particle decay emits alpha radiation, which cannot penetrate the outer layers of the skin, and a variety of low energy gamma rays, which do penetrate the skin, although rarely in sufficient quantity to exceed a regulatory limit. At very high doses of americium, there is increased risk for gamma radiation to cause dermal and subdermal effects such as erythema, ulceration, or even tissue necrosis.

Once radioactive americium is internalized, it is distributed and excreted at a rate of transfer that is dependent on age. The internal radiation dose from americium is actually a measure of the amount of energy that the alpha and gamma emissions deposit in tissue. The short-range alpha radiation produces a localized dose, while the low energy gamma radiation contributes to a larger distribution of dose. Molecular damage results from the direct ionization of atoms that are encountered by alpha 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* refers to 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 (H) refers to the biologically significant dose, which is determined by multiplying the absorbed dose (D) by a quality factor (Q) for the type and energy of the radiations involved. Dose equivalent (H) is expressed as H=DxQ in units of rem or sievert (Sv). The quality factor (Q) for alpha radiation emitted from ^{241}Am is rated 20 because of the high stopping power for charged particles. The dose equivalent (H) from internalized americium radionuclides is estimated using the quantity of material entering the body (via ingestion or inhalation), the biokinetic parameters for americium (retention, distribution, and excretion), the energies and intensities of the alpha and gamma radiation emitted, and the parameters describing the profile of absorbed radiation energy within the body. If, for example, a person ingests a given activity of ^{241}Am (measured in curies [Ci] or becquerels [Bq]), the tissues of the body will absorb some of the energy of the emitted alpha and gamma radiation in a pattern reflecting the kinetics of distribution and elimination of the ingested ^{241}Am, 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 americium as well as the potential length of time over which the tissues can be exposed to the radiation). Each tissue, therefore, can receive a different dose equivalent. The total effective 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.

The EPA has published a set of internal dose conversion factors for reference 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 ^{241}Am is 2.1×10^{-7} 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 americium by the general public can be found in ICRP publications 67 (ICRP 1993), 71 (ICRP 1995), and 72 (ICRP 1996). Dose coefficients for inhalation, ingestion, and submersion in a cloud of americium

radionuclides can be found in U.S. EPA Federal Guidance Report No. 11 (EPA 1988). Dose coefficients for external exposure to radioisotopes of americium in air, surface water, or soil contaminated to various depths can be found in U.S. EPA Federal Guidance Report No. 12 (EPA 1993).

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure

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

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

Americium is a human-made element that has no stable form; all isotopes of americium are radioactive (see Section 4.1). Americium isotopes vary with respect to decay rates, decay chain isotopes produced, and specific activity (see Section 4.2). Of particular interest is ^{241}Am, a decay product of ^{241}Pu. Americium is produced in small quantities (see Section 5.1), and information regarding human exposure is limited. Although this Toxicological Profile is not limited to health and pharmacokinetics data for any particular radioisotope of americium, available studies primarily involve the isotope ^{241}Am and, to a much lesser extent, ^{243}Am. Accidental occupational or environmental exposures to ^{241}Am in humans are usually associated with co-exposures to ^{241}Pu (typically in a mixture with a range of plutonium isotopes of mass from 238 up to 244) and other radioactive isotopes comprising the major sources of radiation associated with nuclear fallout from nuclear explosions and releases from processing and fuel reprocessing plants (see Chapter 6). Isolated accidental exposures to household products containing ^{241}Am (e.g., ingestion of ^{241}Am-containing parts of smoke detectors) have been reported, but did not result in observed adverse health effects. Available information on the health effects of americium is based entirely on effects observed in humans and animals from radioactivity attributable, at least in part, to americium exposures. The animal studies discussed below involve exposures to high doses of ionizing radiation from uptake of ^{241}Am. As with other substances, uptake and disposition of americium in the body (and, hence, the potential for specific health effects from internalized americium) depend upon the chemical properties of the particular americium compound to which one may be exposed, as well as the route of exposure (see Section 3.4 for more information regarding uptake and disposition of americium). Based on available toxicokinetic information and the emissions of americium, the major health concern is radiation damage from internalized americium. Health effects may be deterministic in nature or stochastic with a lengthy latency period, similar to those reported for other radionuclides with comparable half-lives and distribution schemes. Inhalation, ingestion, or dermal absorption of americium compounds (or compounds that generate americium via radioactive decay) in amounts large enough to pose a chemical health risk would be expected to result in much more significant radiation toxicity.

3.2.1 Inhalation Exposure

Available information from human exposures indicates that airborne americium-containing particles are deposited in the respiratory tract, cleared to some extent via mucociliary action, and swallowed or expelled (Edvardsson and Lindgren 1976; Fry 1976; Newton et al. 1983; Sanders 1974; Toohey and Essling 1980). Descriptions of human respiratory tract models that can be used for radiation protection also include relevant information regarding biokinetics of inhaled particles (ICRP 1994b, 1995; NCRP 1997). Quantitative data for uptake fractions of americium compounds resulting in fast, medium, and slow systemic absorption are summarized by ICRP (1996). Supporting animal studies include inhalation exposure to aerosols of americium (Buldakov et al. 1972; DOE 1978; Gillett et al. 1985; Sanders and Mahaffey 1983; Talbot et al. 1989; Thomas et al. 1972) or intratracheal instillation of americium compounds (Moushatova et al. 1996). Estimates of tissue or organ body burden of americium are provided in some study reports to demonstrate the target areas of internal deposition of americium.

3.2.1.1 Death

No reports were located regarding death in humans resulting from acute-, intermediate-, or chronic-duration inhalation exposure to americium.

Death was noted within 6 months in an unspecified number of dogs following acute exposure to ^{241}Am aerosols (as americium nitrate) resulting in inhaled activity of 1.5 μCi/kg (55.5 kBq/kg) (Buldakov et al. 1972). Significant early mortality, attributed to radiation pneumonitis, was noted in rats following acute inhalation of $^{241}AmO_2$ particles (activity median aerodynamic diameter [AMAD] 0.75–1.39 μm) resulting in an approximate initial lung burden of 1.3 μCi (48 kBq) and radiation dose to the lungs of 1,500 rad (1.5 Gy) (Sanders and Mahaffey 1983).

3.2.1.2 Systemic Effects

No data were located regarding gastrointestinal, dermal, or ocular effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation exposure to americium.

Respiratory Effects. No reports were located regarding respiratory effects in humans following acute-, intermediate-, or chronic-duration inhalation exposure to americium. External measurements of internally deposited ^{241}Am in the lungs of a man exposed to americium in an occupational accident determined an initial lung burden of 960 kBq (26 μCi) measured 3 days after the exposure that decreased to 55 kBq (1.5 μCi) after 2 years (Breitenstein and Palmer 1989; Robinson et al. 1983). However, no pathological changes to the lung attributed to radiation exposure were identified in the autopsy of this man 11 years later (Filipy et al. 1995). Exposure was predominantly dermal via facial lacerations, but included inhalation. Toohey and Kathren (1995) estimated that the man received a total lung dose of 1.7 Gy (170 rem) based on the Breitenstein and Palmer (1989) estimate of 1.3 Gy (130 rem) for the first 5.7 years plus a dose of 0.4 Gy (40 rem) for the remaining 5.7 years, based on estimated lung burden at autopsy. See Section 3.2.3.2 for additional information regarding this case of accidental mixed exposure to americium.

No reports were located regarding respiratory effects in animals following intermediate- or chronic-duration inhalation exposure to americium. Respiratory insufficiency and pulmonary pneumonia were reported in a group of five dogs following acute exposure to ^{241}Am aerosols (as americium nitrate) resulting in an inhaled activity of 1.5 μCi/kg (55.5 kBq/kg) (Buldakov et al. 1972). In another study, gross and microscopic lung lesions, including pleural thickening, fibrosis, mineralization, and cell proliferation, were noted in dogs sacrificed from 127 to 1,022 days following a 10-minute inhalation exposure to aerosols of ^{241}Am dioxide (relatively insoluble) that was generated by heating ^{241}Am oxide to 600 ºC). Exposures resulted in estimated initial ^{241}Am body burdens between 38 and 51 μCi (1.4 and 1.9 MBq). Increased respiratory frequency and decreased tidal volume were observed in two of the early sacrifices (Thomas et al. 1972). Radiation pneumonitis was observed in rats exposed once (nose-only) to $^{241}AmO_2$ aerosols resulting in a lung tissue activity level of approximately 650 nCi (24 kBq), but not at lung tissue activity level of 31 nCi (1.15 kBq) (DOE 1978).

Cardiovascular Effects. No reports were located regarding cardiovascular effects in humans following acute-, intermediate-, or chronic-duration inhalation exposure to americium.

No reports were located regarding cardiovascular effects in animals following intermediate- or chronic-duration inhalation exposure to americium. Various effects on the cardiovascular system, including shifts in hemodynamics (blood pressure and flow), electrocardiographic changes, and myocardial ischemia were reported in a group of five dogs following acute exposure to ^{241}Am aerosols (as americium nitrate) resulting in inhaled activity of 1.5 μCi/kg (55.5 kBq/kg) (Buldakov et al. 1972).

Hematological Effects. Persistent clinical lymphopenia and thrombocytopenia were observed in a 64-year-old man exposed to ^{241}Am when an ion-exchange column containing about 100 g of ^{241}Am exploded in his face (Filipy et al. 1995). The explosion resulted in contact exposure predominantly via lacerated skin and chemical burns on the face and neck areas as well as presumed inhalation exposure introducing ^{241}Am into the surrounding tissues and blood circulatory system (Ragan et al. 1983; Robinson et al. 1983). The administration of chelating agents would have affected the blood concentration and deposition, and may have reduced the potential duration and severity of symptoms.

No reports were located regarding hematological effects in animals following intermediate- or chronic-duration inhalation exposure to americium. Leukopenia and elevated hematopoietic activity were reported in a group of five dogs following acute exposure to ^{241}Am aerosols (as americium nitrate) resulting in inhaled activity of 1.5 µCi/kg (55.5 kBq/kg) (Buldakov et al. 1972). Hematocrit, total white blood cell counts, neutrophils, lymphocytes, and platelets were decreased from pre-exposure values in dogs following a 10-minute inhalation exposure to aerosols of ^{241}Am (presumed to be relatively insoluble, having been generated by heating ^{241}Am oxide to 600 ºC), resulting in estimated initial ^{241}Am lung burdens between 38 and 51 µCi (1.4 and 1.9 MBq) (Thomas et al. 1972). These values remained lower than pre-exposure values in the dogs individually sacrificed 127, 256, and 512 days postexposure; the only apparent recovery occurred in the platelet count of the dog sacrificed 1,022 days postexposure, reaching near pre-exposure values approximately 900 days postexposure.

Musculoskeletal Effects. Information regarding musculoskeletal effects in humans is limited to the findings of bone marrow peritrabecular fibrosis and decreased cellularity in bone samples taken from the corpse of a 64-year-old man who had been exposed to ^{241}Am when an ion-exchange column containing about 100 g of ^{241}Am exploded in his face (Priest et al. 1995). See Section 3.2.3.2 for additional information regarding this accident.

No reports were located regarding musculoskeletal effects in animals following intermediate- or chronic-duration inhalation exposure to americium. Pathologic findings in the bone, including fibrosis with focal osteoid thickening, focal resorption, and cartilage degeneration, were observed in dogs (initial body weights between 8.4 and 10.6 kg) sacrificed between 127 and 1,022 days following a 10-minute inhalation exposure to aerosols of ^{241}Am dioxide (presumed to be relatively insoluble, having been generated by heating ^{241}Am oxide to 600 ºC). Exposures resulted in estimated initial ^{241}Am body burdens between 38 and 51 µCi (1.4 and 1.9 MBq) (Thomas et al. 1972).

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

No reports were located regarding hepatic effects in animals following intermediate- or chronic-duration inhalation exposure to americium. Changes were observed in the livers of male rats 30 days after a single intratracheal instillation (0.2 mL) of ^{241}Am (as americium nitrate), resulting in an internal activity of 0.05 µCi (1.8 kBq); the effects were predominantly hepatic parenchyma degeneration and focal necrosis with the effect observed in areas where blood entered the organ (Moushatova et al. 1996). Liver lesions (fatty changes in the centri-lobular region) were also observed in two beagle dogs 512 or 1,022 days following a 10-minute inhalation exposure to aerosols of ^{241}Am dioxide (presumed to be relatively insoluble, having been generated by heating ^{241}Am oxide to 600 ºC). Exposures resulted in estimated initial ^{241}Am body burdens between 38 and 51 µCi (1.4 and 1.9 MBq) (Thomas et al. 1972).

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

No reports were located regarding renal effects in animals following intermediate- or chronic-duration inhalation exposure to americium. Kidney lesions (generalized glomerular mesangial thickening with obliteration) were observed in two beagle dogs 512 or 1,022 days following a 10-minute inhalation exposure to aerosols of ^{241}Am dioxide (presumed to be relatively insoluble, having been generated by heating ^{241}Am oxide to 600 ºC). Exposures resulted in estimated initial ^{241}Am body burdens between 38 and 51 µCi (1.4 and 1.9 MBq) (Thomas et al. 1972).

Endocrine Effects. No reports were located regarding endocrine effects in humans following acute-, intermediate-, or chronic-duration inhalation exposure to americium.

No reports were located regarding endocrine effects in animals following intermediate- or chronic-duration inhalation exposure to americium. Thyroid gland lesions (gross atrophy, with fibrosis) were observed in two beagle dogs 512 or 1,022 days following a 10-minute inhalation exposure to aerosols of ^{241}Am dioxide (presumed to be relatively insoluble, having been generated by heating ^{241}Am oxide to 600 EC). Exposures resulted in estimated initial ^{241}Am body burdens between 38 and 51 µCi (1.4 and 1.9 MBq). Estimated radiation doses to the dogs' thyroids increased from 30 to 900 rad (0.3–9 Gy)

measured from day 127 through 1,022 days after exposure to ^{241}Am dioxide aerosols (Thomas et al. 1972).

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

No reports were located regarding body weight effects in animals following intermediate- or chronic-duration inhalation exposure to americium. One of four dogs lost approximately 15% of its body weight during the time period of 365 days to sacrifice at 512 days following a 10-minute inhalation exposure to aerosols of ^{241}Am dioxide (presumed to be relatively insoluble, having been generated by heating ^{241}Am oxide to 600 EC). Exposure resulted in an estimated initial body burden of 38 µCi (1.4 MBq) (Thomas et al. 1972).

Metabolic Effects. No reports were located regarding metabolic effects in humans following acute-, intermediate-, or chronic-duration inhalation exposure to americium.

No reports were located regarding metabolic effects in animals following intermediate- or chronic-duration inhalation exposure to americium. Increased B-glucuronidase activity was reported in mice receiving a single 30-minute nose-only exposure to aerosols of ^{241}Am (as americium nitrate) that resulted in a lung-averaged cumulative radiation dose of 2,000 rad (20 Gy) (Talbot et al. 1989).

3.2.1.3 Immunological and Lymphoreticular Effects

Lymphopenia was noted in a 64-year-old man exposed to ^{241}Am when an ion-exchange column containing about 100 g of ^{241}Am exploded in his face (Filipy et al. 1995), but information regarding the immunological consequences of this finding was not available (see Section 3.2.3.2 for additional information regarding this accident).

Leukopenia was reported in a group of five dogs following acute exposure to ^{241}Am aerosols (as americium nitrate) resulting in inhaled activity of 1.5 µCi/kg (55.5 kBq/kg) (Buldakov et al. 1972). Total white blood cell counts, neutrophils, and lymphocytes were decreased from pre-exposure values in dogs following a 10-minute inhalation exposure to aerosols of ^{241}Am dioxide (presumed to be relatively insoluble, having been generated by heating ^{241}Am oxide to 600 EC). Exposures resulted in estimated

initial ^{241}Am body burdens between 38 and 51 μCi (1.4 and 1.9 MBq) (Thomas et al. 1972). These values decreased in the dogs individually sacrificed 127, 256, and 512 days postexposure. However, no reports were located regarding immunological consequences of reduced leukocyte counts in animals exposed to americium.

No reports were located regarding the following health effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation exposure to americium:

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

No reports were located regarding cancer in humans following acute-, intermediate-, or chronic-duration inhalation exposure to americium, and no signs of cancer were found during the autopsy of a heavily exposed worker who died 11 years later of unrelated causes (see Section 3.2.3.2). However, EPA considers all radionuclides to be known human carcinogens and has calculated cancer risk factors for inhaled ^{241}Am and ^{243}Am (see Table 8-1 in Chapter 8 for additional information).

No reports were located regarding cancer in animals following intermediate- or chronic-duration inhalation exposure to americium. Osteosarcomas developed in 4 of 15 dogs surviving more than 1,000 days following a single inhalation exposure to aerosols of $^{241}AmO_2$ that resulted in initial lung burdens of approximately 2–6 μCi (74–222 kBq) (Gillett et al. 1985). Among the four dogs that developed osteosarcomas, the radiation doses to the skeleton, calculated to 1,000 days postexposure, were 96–410 rad (0.96–4.1 Gy).

3.2.2 Oral Exposure

No reports were located regarding the following health effects in humans or animals following acute-, intermediate-, or chronic-duration oral exposure to americium:

3.2.2.1 Death

3.2.2.2 Systemic Effects

3.2.2.3 Immunological and Lymphoreticular Effects

3.2.2.4 Neurological Effects

3.2.2.5 Reproductive Effects

3.2.2.6 Developmental Effects

3.2.2.7 Cancer

No reports were located regarding cancer in humans following acute-, intermediate-, or chronic-duration oral exposure to americium, and no signs of cancer were found during the autopsy of a heavily exposed worker who died 11 years later of unrelated causes (see Section 3.2.3.2). EPA considers all radionuclides to be known human carcinogens and has calculated cancer risk factors for ingested ^{241}Am and ^{243}Am (see Table 8-1 in Chapter 8 for additional information).

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 americium.

3.2.3.2 Systemic Effects

No data were located regarding respiratory effects, cardiovascular effects, gastrointestinal effects, hepatic effects, renal effects, endocrine effects, dermal effects, ocular effects, body weight effects, or metabolic effects in humans or animals following acute-, intermediate-, or chronic-duration dermal exposure to americium.

Information regarding systemic effects in humans following dermal exposure to americium derives mainly from a single case in which a 64-year-old male (USTUR Case 0246) was exposed when an ion-exchange column containing about 100 g of ^{241}Am exploded in his face. Numerous studies relate various aspects of this accident as well as subsequent treatment and follow-up (Breitenstein and Palmer 1989; Filipy et al. 1995; Jech et al. 1983; McMurray 1983; Palmer et al. 1983; Robinson et al. 1983; Thompson 1983; Toohey and Kathren 1995). The explosion resulted in contact exposure through the intact and lacerated skin and in presumed inhalation exposure, evident from external chest measurements of radioactivity. The amount of activity initially deposited on the man and his clothing was estimated to be 1–5 Ci (37–185 GBq). Immediate treatment reduced contamination to approximately 6 mCi (222 MBq). By the end of the first day after the accident, the activity had been reduced to 1 mCi (37 MBq). Intense, long-term chelation therapy was employed to reduce body burden. Levels of ^{241}Am in the victim's blood collected the day of the exposure was estimated initially at 6.4 μCi and decreased 10-fold 6 days later to 0.64 μCi following chelation therapy (Robinson et al. 1983).

Hematological Effects. Significant, but transient effects on erythropoiesis were indicated by a decrease in erythrocyte concentration, hemoglobin concentration, and packed red cell volumes. Clinical lymphopenia and thrombocytopenia persisted for 5 years post-exposure. The lymphopenia had rapid onset and a slow recovery, although pre-exposure values were not attained by 11 years postexposure, at which time, the man died of unrelated causes (Filipy et al. 1995). Histopathologic examination of bone at autopsy revealed pathologic changes including peritrabecular fibrosis, bone cell depletion, and bone marrow atrophy (Priest et al. 1995), but these changes could not be directly related to estimated radiation dose or bone turnover rates as a result of dermal exposure.

3.2.3.3 Immunological and Lymphoreticular Effects

Leukopenia was observed in a 64-year-old man following ^{241}Am exposure (Filipy et al. 1995), but information regarding the immunological consequences of this finding was not available.

No reports were located regarding the following health effects in humans or animals following acute-, intermediate-, or chronic-duration dermal exposure to americium:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No reports were located regarding cancer in humans following acute-, intermediate-, or chronic-duration dermal exposure to americium, however, no signs of cancer were found during the autopsy of a heavily exposed worker who died 11 years later of unrelated causes (see Section 3.2.3.2). EPA considers all radionuclides to be known human carcinogens and has calculated cancer risk factors for external exposure to ^{241}Am and ^{243}Am (see Table 8-1 in Chapter 8 for additional information).

3.2.4 Other Routes of Exposure

3.2.4.1 Death

No reports were located regarding death in humans resulting from acute-, intermediate-, or chronic-duration exposure to americium by routes other than inhalation, oral, dermal, or external exposure.

Dose-related decreased long-term survival was observed in beagle dogs following single intravenous injections of ^{241}Am at average activity levels of 1.9–2,900 nCi/kg (0.07–107 kBq/kg) (Taylor et al. 1991, 1993a).

3.2.4.2 Systemic Effects

No data were located regarding systemic effects in humans following acute-, intermediate-, or chronic-duration exposure to americium by routes other than inhalation, oral, dermal, or external exposure. No data were located regarding respiratory effects, cardiovascular effects, gastrointestinal effects, renal effects, dermal effects, ocular effects, or metabolic effects animals following exposure to americium by routes other than inhalation, oral, dermal, or external exposure.

Hematological Effects. A limited study reported dose-related depressions in white blood cell counts in dogs that were administered single intravenous injections of ^{241}Am at activity levels of 0.1–2.8 μCi/kg (3.7–103.6 kBq/kg) (Dougherty 1970). Maximum depression in granular leukocytes and monocytes was reached approximately 1 month post injection. Depression of lymphocytes occurred more slowly; minimal values were reached 1 year or more post injection, with little indication for recovery in the dogs receiving the two highest doses of 0.9 or 2.8 μCi/kg (33.3 or 103.6 kBq/kg). Depression of red blood cells was observed only in groups of dogs injected with ^{241}Am at activity levels of ≥0.9 μCi/kg (33.3 kBq/kg).

Hepatic Effects. Degenerative liver changes, severe reduction in liver weight, and early death (typically attributed to bone cancer) were observed in dogs following single intravenous injections of ^{241}Am citrate at activity levels of approximately 2.9 μCi/kg (107 kBq/kg) (Taylor et al. 1991). The average radiation dose to the liver in these dogs was 590 rad (5.9 Gy). Degenerative liver changes and early death were also reported in dogs administered single intravenous injections of ^{241}Am at a similar activity level (2.8 μCi/kg or 104 kBq/kg) (Lloyd et al. 1970; Taylor et al. 1993a).

Endocrine Effects. Thyroid weights were significantly lower in adult beagle dogs administered single intravenous injections of ^{241}Am citrate at activity levels ranging from approximately 0.3 to 2.75 μCi/kg (11–102 kBq/kg) than those of controls (Taylor et al. 1993a), resulting in thyroid doses of 8–2,976 rad (0.08–29.76 Gy). Histologic examination revealed follicular hyperplasia and degenerative cellular changes. Lower serum thyroxine levels were noted in the peripheral blood of dogs in the two highest exposure groups.

3.2.4.3 Immunological and Lymphoreticular Effects

A limited study reported dose-related depressions in white blood cell counts in dogs that were administered single intravenous injections of ^{241}Am citrate at activity levels of 0.1–2.8 μCi/kg (3.7–103.6 kBq/kg) (Dougherty 1970). Maximum depression in granular leukocytes and monocytes was reached approximately 1 month post injection. Depression of lymphocytes occurred more slowly; minimal values were reached 1 year or more post injection.

3.2.4.4 Neurological Effects

No reports were located regarding neurological effects in humans or animals following acute-, intermediate-, or chronic-duration exposure to americium by routes other than inhalation, oral, dermal, or external exposure.

3.2.4.5 Reproductive Effects

No reports were located regarding reproductive effects in humans following acute-, intermediate-, or chronic-duration exposure to americium by routes other than inhalation, oral, dermal, or external exposure.

Dose-related increased incidences of death were reported among 14- and 17-day-old fetuses of rats that had been administered single intravenous injections of ^{241}Am between 1 and 10 days prior to mating (Moskalev et al. 1969). In this study, ^{241}Am was administered at activity levels of 0.2–96 μCi/kg (7.4–3,552 kBq/kg) that produced antenatal fetal tissue doses up to 200 rad (2 Gy). During gestation, concentrations of ^{241}Am were 9–15 times higher in placental tissues than in fetuses. The investigators indicated that death may have been the result of placental changes.

3.2.4.6 Developmental Effects

No reports were located regarding developmental effects in humans following acute-, intermediate-, or chronic-duration exposure to americium by routes other than inhalation, oral, dermal, or external exposure.

Decreased fetal weight and increased fetal death were reported following single intravenous injection of pregnant rats with ^{241}Am (activity level 90 μCi/kg or 3,330 kBq/kg) on gestation day 9 (Rommereim and Sikov 1986; Rommereim et al. 1985). The investigators indicated a tendency toward increased incidences of fetuses with anomalous ribs, which they attributed to americium exposure at an early critical stage of fetal development.

3.2.4.7 Cancer

No reports were located regarding carcinogenic effects in humans following acute-, intermediate-, or chronic-duration exposure to americium by routes other than inhalation, oral, dermal, or external exposure.

Increases in bone cancers occurred in animals administered a single intraperitoneal or intravenous injection of ^{241}Am and observed over their life span. Schoeters et al. (1991) reported bone tumor induction in mice receiving injections of 22,000 or 58,000 Bq ^{241}Am/kg (0.59 μCi or 1.57 μCi/kg) and early mortality from non-neoplastic diseases in mice receiving larger activities of 190, 373, or 1,197 kBq ^{241}Am/kg (5.14, 10.1, or 32.4 μCi/kg). Mice administered 45,000, 90,000, or 213,000 Bq ^{241}Am/kg (1.22, 2.43, or 5.76 μCi) (Van Den Heuvel et al. 1995) via intravenous injection, which produced respective radiation doses to the femur of 2.3, 3.6, and 8.4 Gy (230, 360, and 840 rad), showed increased incidence for osteosarcomas at 45,000 Bq/kg (0.8 kBq/mouse). Rats administered 0.03 μCi ^{241}Am/g via injection into the tail developed osteosarcomas (Carter et al. 1951). Young adult beagle dogs were administered a single injection of graded activities of 0.016-3.0 μCi/kg ^{241}Am (592–111,000 Bq/kg) that resulted in bone sarcomas at low doses not expected to cause adverse effects. A 100% incidence of sarcomas was observed in the dogs receiving higher activities (Jee et al. 1985). Companion experiments using bone-seeking radionuclides in beagle dogs were conducted over 35 years (1952–1987) by Lloyd et al. (1994a, 1994b, 1995); several biological effects were observed during the lifespan of the animals. The initial report, a comparative toxicity study for ^{241}Am to ^{226}Ra, both bone-seeking internal emitters, showed similar ratios for relative effectiveness for bone cancer induction in dogs (Lloyd et al. 1994a) and mice (Taylor et al. 1983) administered ^{241}Am via intravenous injection. Lloyd et al. (1994b) reported skeletal malignancies among beagles receiving graded activities of 0.07–104 kBq ^{241}Am/kg (0.002–2.8 μCi/kg) via a single intravenous injection as the first of the companion experiments. In the second part of the experiment, Lloyd et al. (1995) conducted an analysis of all soft tissue tumors in the dogs treated by intravenous injection. The authors reported both positive and negative associations between exposure and tumor incidence, apparent in a variety of soft tissues, but the development of these tumors appeared to be influenced by the competing risk of death from bone cancer or other severe radiation effects (Lloyd et al. 1995). Incidence of tumors in mice administered activities of 6, 17, or 29 kBq ^{241}Am/kg (0.2, 0.5, or 0.8 μCi/kg) were higher for liver (adenomas and carcinomas) than for bone sarcomas (Ellender et al. 2000), supporting similar findings in earlier investigations. In a study of dogs administered single intravenous injections of ^{241}Am that ranged from 0.07 to 107 kBq Am/kg (from 0.002 to 2.9 μCi/kg), the incidence of death was dose-related and was predominantly due to bone cancer (Taylor et al. 1991).

However, the incidence of liver tumors was higher than that of bone tumors in dogs exposed to lower levels of ^{241}Am. Moskalev et al. (1989) reported that injecting pregnant Wistar rats with 92.5 kBq ^{241}Am/kg (3.4 μCi/kg) as nitrate on gestation day 16 produced 4 osteosarcomas in 78 female and 52 male offspring, compared with no cancers in the controls. In a communication by Lloyd et al. (2001), the authors concluded that longevity of irradiated mammals exposed to low-level exposures of bone-seeking radionuclides was independent of dose, except for radiation-induced malignancies or other radiation effects.

3.3 GENOTOXICITY

No reports were located regarding genotoxic effects in humans following acute- or intermediate-duration inhalation exposure to americium. Chromosomal aberrations (symmetrical translocations and dicentrics and ring chromosomes) in lymphocyte preparations were elevated for an entire group of seven nuclear fuel production workers who were exposed for 11–22 years to external gamma radiation, with an additional internal exposure for six of these workers to alpha-emitting ^{241}Am 5 years prior to the analysis (Bauchinger et al. 1997). The total effective dose equivalent for the workers from exposure to external gamma radiation and internal contamination with ^{241}Am were: 393, 39, 207, 304, 202, 237, and 349 mSv (whole body) (39.3, 3.9, 20.7, 30.4, 20.2, 23.7, and 34.9 rem). In five of the six cases that included internal contamination, the committed effective dose equivalent from ^{241}Am represented 5–25% of the total dose, the main contribution coming from external exposure to gamma radiation. In the other worker, internalized ^{241}Am represented 66% of the total effective dose equivalent of 39 mSv (3.9 rem). Another case involved a radiation worker and his wife, college-age daughter, and 10-year-old son who were exposed for several years in their house to elevated levels of ^{241}Am that resulted in body burdens of 6.5–89 nCi (0.24–3.3 kBq) from a source used by the father for private experiments. Chromosomal aberrations in isolated leukocytes were noted to be similar to those observed in other cases of accidental or therapeutic exposure to external radiation sources (Kelly and Dagle 1974). The cytogenetic damage observed was low and only grossly comparable to historical control values available to the authors. The limited human data do not indicate a significant genotoxic response to inhaled americium.

No reports were located regarding genotoxic effects in animals following intermediate- or chronic-duration inhalation exposure to americium. A single report regarding genotoxic effects following acute inhalation exposure to americium indicated decreased numbers of pulmonary alveolar macrophages (PAMs) (maximum decrease at day 21), increased numbers of micronuclei, and multinucleated cells in

mice receiving a single 30-minute nose-only exposure to ^{241}Am (as americium nitrate) producing a cumulative radiation dose of 2,000 rad (20 Gy) to lungs (Talbot et al. 1989). The initial alveolar deposition was 32.4 nCi (1.2 kBq), but rapidly declined to about 8.1 nCi (300 Bq) by 21 days and to approximately 2.7 nCi (100 Bq) by the end of the study (day 98). Following exposure to ^{241}Am, essentially all PAMs contained ^{241}Am; significant amounts of ^{241}Am were still observed at each sacrifice time period between postexposure days 3 and 98.

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

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Evidence for absorption of inhaled americium to blood of humans is provided by several cases of workers who were accidentally exposed to airborne ^{241}Am (Edvardsson and Lindgren 1976; Fry 1976; ICRP 1996; Kathren et al. 2003; Newton et al. 1983; Sanders 1974; Toohey and Essling 1980). Although these cases do not provide a complete quantitative description of the absorption of inhaled americium in humans, they clearly demonstrate that inhaled americium oxides (e.g., AmO_2) can be absorbed, as indicated by the detection of ^{241}Am radioactivity in regions of the body such as liver and bone, and excretion in urine.

In one case, an adult worker inhaled aerosols of plutonium and americium dioxides ($^{239}PuO_2$ and $^{241}AmO_2$) (Newton et al. 1983). Thoracic counts of radioactivity that were determined by an external radiation detector starting 7 days after the exposure showed that ^{241}Am was removed from the chest area with biological half-times of 11 (80%) and 920 (20%)days. These estimates were assumed to reflect clearance from the lung to systemic compartments. However, fecal excretion was estimated to be approximately 50% of the estimated initial deposit of ^{241}Am in the lung, suggesting that extensive mechanical transport to the gastrointestinal tract, typical of inhaled large particles, may have occurred. External counting also detected ^{241}Am in the skull on day 913 post accident, suggesting that ^{241}Am was transferred to the skeleton.

In a second case, an adult worker inhaled mixed oxides of curium and americium dioxides ($^{244}CmO_2$ and $^{241}AmO_2$) (^{244}Cm:^{241}Am airborne ratio, 3:1), which resulted in the deposition of approximately 450 nCi (16.6 kBq) of radioactivity in the lungs, or approximately 112 nCi (4.1 kBq) of ^{241}Am (Sanders 1974). Chest counts of the subject indicated that total radioactivity was retained in the lungs with a half-time (i.e., decay-corrected) of 28 days; however, data on the elimination of each isotope from the lung were not reported. Most of the elimination from the chest area was accounted for by recovery of radioactivity in the feces, consistent with mechanical clearance of the deposited activity to the gastrointestinal tract. Evidence for systemic absorption in this case was the detection of ^{241}Am in urine; approximately 1.1 nCi (41 Bq, 1% of the deposited activity) of ^{241}Am was excreted in urine in 365 days, with a half-time of 35 days.

In a third case, two adults accidentally inhaled $^{241}AmO_2$ (particle size not specified), which resulted in the deposition of approximately 15 nCi (555 Bq) of activity in the lungs (Fry 1976). Chest activity measured over a period of 200–1,500 days after the accident indicated that the retention half-time for ^{241}Am in the lungs was between 900 and 1,400 days. Activity measured over the chest, liver, and extremities (knees and ankles, reflecting primarily bone activity) indicated that by 324 days after the accident, approximately 41% of the whole-body activity was in the lung, 47% was in the liver, and 12% was in bone. After 1,392 days, lung activity had decreased to 18%, liver activity was unchanged (47%), and bone activity had increased to 35%.

In a more recent case, an adult male accidentally inhaled ^{241}Am (believed to be in oxide form), which resulted in an intake of approximately 6.3 kBq (170 nCi) of activity (Kathren et al. 2003). Results of radioactivity measurements in the chest area between days 48 and 2,135 following the accident indicated that ^{241}Am was cleared from the lungs with half-times of 110 and 10,000 days.

Additional evidence for absorption of inhaled americium, and more quantitative estimates of the extent of and rates of absorption, are provided by animal experiments. The lung deposition and absorption of inhaled aerosols of americium nitrates and oxides have been studied in experimental animals; the results of representative studies are provided in Table 3-1. In general, exposures were nose-only (although this was not always specified in the reports) to relatively well-characterized aerosols of ^{241}Am compounds. In most studies, the actual exposure concentration of americium was not reported. Estimates of lung retention half-times reflect the rate of loss of radioactivity from the lung following any initial (3–8 days) loss of americium that may have been transferred to the gastrointestinal tract and excreted without absorption. In some studies, absorption half-times to the blood were estimated. In either case, the

Table 3-1. Retention and Absorption Estimates in Animals Exposed to Americium Compounds by Inhalation

Animal model	Am species	Exposure	Exposure concentration[a]	Aerosol AMAD (µm±GSD)	Lung deposition (percent of intake)	Lung retention or absorption half-life[b]
Stanley et al. 1982						
Monkey, adult	$^{241}AmO_2$ (dust)[c]	Aerosol	No data	1.5±1.6	67 nCi 21 ng	47 days (89%) 550 days (11%) (retention)
Mewhinney and Muggenburg 1985						
Monkey, 3–5 years	$^{241}AmO_2$	Aerosol, nose-only	No data	1.4	75 µCi/kg 23 µg/kg	0.1 days (32%) 160 days (68%) (retention)
Mewhinney et al. 1982						
Dog, adult	$^{241}AmO_2$	Aerosol, nose-only, 20 minutes	No data	0.75±1.2	41% 60–250 nCi/kg 18–77 ng/kg	9 days (89%) 283 days (11%) (retention)
			No data	1.5±1.07	39% 39–240 nCi/kg 12–74 ng/kg	13 days (76%) 171 days (24%) (retention)
			No data	3.0±1.06	30% 30–190 nCi/kg 12–59 ng/kg	13 days (69%) 167 days (31%) (retention)
Stanley et al. 1982						
Dog, adult	$^{241}AmO_2$ (dust)[c]	Aerosol	No data	2.2±1.8	190 nCi 59 ng	39 days (67%) 5,000 days (33%) (retention)
Thomas et al. 1972						
Dog, adult	$^{241}AmO_2$	Aerosol, nose only 10 minutes	2.18 Ci/m^3 673 mg/m^3	0.8–1.0±1.5	50% 2.1–3.1 µCi/kg 0.7–1.0 µg/kg	20–30 days (retention)
Craig et al. 1975						
Dog, adult	$^{241}AmO_2$	Aerosol, nose-only	42–336 Ci/m^3 13–104 mg/m^3	1.40±1.69	No data	~60 days (retention)

Table 3-1. Retention and Absorption Estimates in Animals Exposed to Americium Compounds by Inhalation

Animal model	Am species	Exposure	Exposure concentration[a]	Aerosol AMAD (μm±GSD)	Lung deposition (percent of intake)	Lung retention or absorption half-life[b]
Craig et al. 1979						
Dog, adult	$^{241}AmO_2$	Aerosol, nose-only	0.66 mCi/m^3 0.20 mg/m^3	0.63±2.64	13% 1,2 nCi 0.38 ng	20–30 days 120 days 400 days (retention)
			42 mCi/m^3 13 mg/m^3	1.25±1.77	30% 120 nCi 37 ng	
			340 mCi/m^3 105 mg/m^3	1.35±1.74	35% 1,150 nCi 355 ng	
Stather et al. 1979						
Hamster, adult	$^{241}AmO_2$	Aerosol	No data	1.9±2.0	45 nCi/kg 14 ng/kg	11 days 200 days (retention)
Stanley et al. 1982						
Rat, adult	$^{241}AmO_2$ (dust)[c]	Aerosol	No data	2.3±1.7	7.8 nCi 2.4 ng/kg	95 days (89%) 2,800 days (11%) (retention)
Stradling et al. 1992, 1994						
Rat, adult	$^{241}AmO_2$ (dust)[d]	Aerosol, nose-only, 1-hour	No data	2.1±1.78	0.14 nCi/kg 0.042 ng/kg	2,000 days >10,000 days (absorption)
Stradling and Stather 1989						
Rat, adult	^{241}Am nitrate	Aerosol, nose-only 1–2 hour	No data	0.3±2.5	75 nCi/kg 23 ng/kg	49 days 315 days (absorption)
	$^{241}AmO_2$ (dust)[e]		No data	1.4±2.0	26 nCi/kg 8.1 ng/kg	7,000 days 7,000 days (absorption)
	^{241}Am nitrate (dust)[f]		No data	3.8±1.6	0.51 nCi/kg 0.16 ng/kg	170 days 1,200 days (absorption)
	^{241}Am chloride (dust)[g]		No data	1.8±2.4	0.11 nCi/kg 0.035 ng/kg	47 days 1,700 days (absorption)

Table 3-1. Retention and Absorption Estimates in Animals Exposed to Americium Compounds by Inhalation

Animal model	Am species	Exposure	Exposure concentration[a]	Aerosol AMAD (µm±GSD)	Lung deposition (percent of intake)	Lung retention or absorption half-life[b]
Moody et al. 1991						
Rat, adult	^{241}Am (dust)[h]	Aerosol, nose-only	No data	1.26±1.29	11 nCi/kg 3.6 ng/kg	14,000 days >17,000 days (absorption)
				0.21±1.61	89 nCi/kg 27.6 ng/kg	5,800 days 8,600 days (absorption)
				1.74±1.94	47 nCi/kg 14 ng/kg	4,600 days >14,000 days (absorption)
	^{241}Am (dust)[i]			1.63±1.76	2.3 nCi/kg 0.7 ng/kg	170 days 290 days 380 days (absorption)

[a]Where only activity was reported, mass concentration of Am was calculated assuming a specific activity of 3.24 Ci/g.
[b]Retention reflects total elimination from lung; absorption reflects transfer to blood
[c]Powder collected from plutonium oxide milling operation
[d]Dust from a weapons test site
[e]Dust from ambient oxidation of Pu metal
[f]Dust from corrosion of industrial process line equipment, mainly aged Pu/Am nitrate intimately mixed with corrosion products
[g]Dust from green salt formed in the electrorefining of Pu metal
[h]Dust derived from ignition of Pu (900–1,000 EC)
[i]Dust derived from air oxidation of molten Pu

Note: Footnotes d-i apply to americium in a Pu-bearing matrix where Am absorption kinetics may have been determined by Pu dissolution.

AMAD = activity median aerodynamic diameter; GSD = geometric standard deviation

estimates were based on curve-fitting of the data on lung radioactivity-time profiles and other assumptions. Thus, some of the differences in estimates undoubtedly reflect differences in particle size (known to significantly affect deposition pattern within and mucociliary clearance from the respiratory tract), solubility in biological fluids, curve-fitting method, duration of observations, and intra-study variability; nevertheless, general trends are evident. Retention and systemic absorption can be described with two or three rate functions that represent fast and slower processes for transfer of americium from the lung (albeit with considerable differences in the rates reported in various studies, probably reflecting differences in particle size distribution, animal species, and exposure scenarios). For example, in monkeys exposed to aerosols of $^{241}AmO_2$ (AMAD, 1.4 μm), retention half-times of ^{241}Am were 0.1 days (32% of the initial deposited) and 160 days (68%) (Mewhinney and Muggenburg 1985). Stanley et al. (1982) also observed both fast and slower phases of lung retention in monkeys exposed to $^{241}AmO_2$. Mewhinney et al. (1982) found that in dogs exposed to aerosols of americium dioxide (AMAD 0.8–3.5 μm), approximately 30–50% of the inhaled activity was deposited in the lung; for an AMAD of 0.8 μm, the estimated retention half-times were 9 and 290 days for 89% and 11% of the lung burden, respectively. Within 8 days of exposure, 32% of the initial lung burden was detected in extra-respiratory tissues, mainly the liver (21%) and skeleton (11%). The observations of rapid and slow phases of retention of americium initially deposited in the respiratory tract are consistent with the results of other studies of dogs exposed to $^{241}AmO_2$ aerosols (Craig et al. 1975; Thomas et al. 1972). Studies in rodents indicate that inhaled americium nitrates and chlorides are absorbed more rapidly than americium oxides (Stather et al. 1979b; Stradling and Stather 1989; Stradling et al. 1994). Americium oxides in dusts from weapon sites and industrial facilities were absorbed particularly slowly, with absorption half-times of 5–25 years, although this may also vary depending on the process that leads to the production of the dust. For example, americium oxides in dust formed during the ignition of plutonium were absorbed from the lung with a half-time of 0.5–1 year, whereas americium oxides produced from the air oxidation of molten Pu had absorption half-times exceeding 12 years (Moody et al. 1991). This may reflect differences in the compounds produced (e.g., Pu-Am particles that are surface but not volume oxidized) or oxide species formed under different conditions (e.g., temperature, etc.).

Information on the absorption of americium from the lung also can be derived from studies in which americium compounds were instilled directly into the trachea. Although intratracheal instillation does not precisely mimic inhalation exposure, rates of absorption of the deposited americium have been shown to be comparable for both routes of exposure. For example, Stradling et al. (1992) estimated nearly identical half-times for absorption of ^{241}Am in rats that received either intratracheal instillations of ^{241}Am oxide-containing dust or inhalation exposure to aerosols of the same dust (fast phase approximately 2,000 days,

slower phase >10,000 days). Estimates of absorption half-times in rats that received intratracheal instillations of $^{241}AmO_2$ in various types of dusts from weapons or fuel facilities indicate a slow and fast component to absorption, with the fast component ranging from 1 to 5 years, and rates of absorption following intratracheal instillation of americium nitrate, citrate, or hydroxide are higher than after instillation of americium oxides (Crawley et al. 1976; Müller et al. 1989; Stradling et al. 1989, 1992, 1994).

3.4.1.2 Oral Exposure

Human studies indicate that <0.1% of the ingested activity is absorbed into blood, which is consistent with numerous observations that have been made in experimental animals. Infant uptake may be closer to 0.5% (ICRP, 1996). Absorption of americium contained in shellfish (molluscs) has been studied in humans. Eight adult subjects (six males and two females) ingested molluscs (winkles), collected from marine waters near the British Nuclear Fuels facility at Sellafield, Cumbria, that contained ^{241}Am (Hunt et al. 1986a, 1986b). The range in the ingested activity of ^{241}Am was 18–76 Bq (0.49–2.1 nCi, 0.15–0.63 ng). Serial 24-hour urine samples were collected from each subject for up to 10 days after they ingested the molluscs. The fraction of the activity absorbed was estimated as the ratio of the observed cumulative urinary excretion of ^{241}Am to that of the excretion predicted to occur if absorption had been complete. The latter was predicted using a kinetic model of excretion of absorbed americium described by Takada et al. (1984). The reported geometric mean absorption for the eight subjects was $0.6x10^{-4}$ (geometric standard deviation [GSD], 0.1; range, $0.4x10^{-4}$–$2.1x10^{-4}$), or 0.006% of the ingested activity. Seven of the initial eight subjects and one new subject participated in a subsequent study (six males and two females) in which the same protocol was implemented and the ^{241}Am activity range was 10–25 Bq (0.27–0.68 nCi, 0.083–0.21 ng) (Hunt et al. 1990). The arithmetic mean absorption fraction was $0.8x10^{-4}$ (range, $0.4x10^{-4}$–$1.5x10^{-4}$) or 0.008% of the ingested activity. When the results of the two studies were combined, the arithmetic mean absorption fraction was $0.9x10^{-4}$ (range, $0.3x10^{-4}$–$2.5x10^{-4}$) or 0.009% of the ingested activity; absorption fractions for males and females were similar. Three of the initial eight subjects and three new subjects participated in a third study (five males and one female) in which the same protocol was implemented; however, the subjects ingested cockles collected from Ravenglass, Cumbria for a range of ingested activity of 15–17 Bq (0.41–0.46 nCi, 0.13–0.14 ng) (Hunt 1998). The arithmetic mean absorption fraction was $1.2x10^{-4}$ (range, $0.3x10^{-4}$–$2.6x10^{-4}$) or 0.012% of the ingested activity.

Information on the absorption of ingested AmO_2 is provided from accidental oral exposures. In one case, a worker ingested a ceramic particle containing approximately 2.85 μCi (105 kBq, 0.88 μg Am) of $^{241}AmO_2$. During the first 8 days after the particle was ingested, approximately 4 pCi (0.15 Bq) or 0.00014% of the estimated activity was excreted in the urine (Smith et al. 1983). In a second case, a worker swallowed two 2-mm (diameter) silver disks used in the manufacture of smoke detectors, which contained approximately 4.22 μCi (156 kBq, 1.3 μg) of ^{241}Am. The subject excreted the disks in feces on days 16 and 24 post ingestion. Urinary ^{241}Am excretion during this time was approximately 3 pCi (0.11 Bq, 0.7 ng Am) or 0.0007% of the ingested activity (Rundo et al. 1977). The time lapse between ingestion and fecal excretion of the disks was related to suspected delay in esophageal transit and infrequent bowel movements by the subject.

Studies in nonhuman primates provide additional evidence that <0.1% of an ingested amount of americium is absorbed. Ham et al. (1994) estimated the gastrointestinal absorption of americium in marmosets by comparing the retention of ^{241}Am in the liver and carcass after intraperitoneal injection of a citrate solution containing ^{241}Am (1.6 Bq, 43 pCi, 0.012 ng Am) or after gastric intubation with ^{241}Am mixed with potato powder (250 Bq, 6.7 nCi, 2.0 ng Am). The absorption fraction of ^{241}Am mixed with potato powder was estimated to be approximately $6x10^{-4}$ or 0.06% of the administered activity.

Gastrointestinal absorption of americium has also been estimated in pigs, guinea pigs, mice, and rats. The results of representative studies are provided in Table 3-2. Whilst these studies differ in the methodology used to estimate absorption, they reveal certain important trends. In general, the animal studies reveal a relatively low absorption of ingested americium across species (<1% in adult animals). In the pig, guinea pig, hamster, and rat, absorption is higher by a factor of 30–200 in neonatal animals compared with adults and/or progressively decreases in magnitude with age after birth (to a factor of 4 at 30 days for the guinea pig) (Bomford and Harrison 1986; David and Harrison 1984; Sullivan et al. 1985). Americium appears to be absorbed to a similar extent when it is ingested as an aqueous solution of water soluble nitrates or citrates or when it is incorporated into foods, such as molluscs, potato, or liver tissue (Bulman et al. 1993; Ham et al. 1994; Harrison et al. 1988; Hisamatsu and Takizawa 1987; Stather et al. 1979a). Absorption of relatively water insoluble oxides of americium is lower by a factor of 4–10 compared with the absorption of americium citrate, whose absorption factor is a factor of 3–6 lower than that of americium nitrate (Stather et al. 1979a; Sullivan 1980a, 1980b). Similarly, in rats, the absorption of americium from surface dust from a weapons site was lower by a factor of 10–50 compared to americium oxide or nitrate (Harrison et al. 1994; Sullivan 1980b). A species difference was noted; guinea pigs absorbed 5 times more americium than rats. Other factors that appear to increase absorption in rats include fasting

Table 3-2. Absorption Estimates in Animals Exposed to Americium Compounds by Ingestion

Animal model	Dose and media[a]	Absorption (percent of dose)	Basis for estimate of absorption	Reference
Marmoset, adult	^{241}Am in potato powder, single gavage dose, 2.0 ng	0.06	Absorption estimate based on comparisons with liver and carcass ^{241}Am after an intraperitoneal dose	Ham et al. 1994
Pig, adult	^{241}Am citrate aqueous solution, single gavage dose, 190 µg/kg	0.16	Absorption estimate based on maximum whole-body ^{241}Am (8 days), without adjustment for excretion	Eisele et al. 1987
Pig, miniature	^{241}Am citrate aqueous solution, single gavage dose, 75 µg/kg	0.06		
Pig, neonate	^{241}Am nitrate aqueous solution, single gavage dose	~3	Absorption estimate based on carcass ^{241}Am (5 days), without adjustment for excretion	Sullivan and Gorham 1983
Guinea pig, neonate–adult	^{241}Am citrate aqueous solution, single dose applied to tongue, 0.6–0.9 µg/kg	% / Age 1.1 / 0.5 d 0.55 / 1 d 0.19 / 5 d 0.17 / 10 d 0.06 / 15 d 0.03 / 20 d 0.02 / 30 d 0.005 / adult	Absorption estimate based on comparisons with liver and carcass ^{241}Am after an intraperitoneal dose (neonates) or intravenous dose (adults), with adjustment for excretion	Bomford and Harrison 1986
Guinea pig and rat, adult	^{241}Am in three surface dust samples, single dose applied to tongue (GP, 5–15 ng/kg) or fed (rat, 12–49 ng/kg)	GP / Rat 0.002 / 0.0003 0.005 / 0.001 — / 0.001	Absorption estimate based on comparisons with liver and carcass ^{241}Am after an intraperitoneal dose, with adjustment for excretion	Harrison et al. 1994
Guinea pig, adult	^{241}Am nitrate, aqueous solution, single gavage dose, 2–4.4 µg	0.017–0.031	Absorption estimate based on sum of liver, skeletal, and urine ^{241}Am	Sullivan 1980a
Hamster, neonate–weaning	^{241}Am nitrate, aqueous solution, single dose applied to tongue, 1.6–2.5 ng	% / Age 4.5 / 1 d 1.70 / 4 d 0.50 / 7 d 0.006 / 22 d 0.02 / 30 d	Absorption estimate based on comparisons with liver and carcass ^{241}Am after an intraperitoneal dose, with adjustment for excretion	David and Harrison 1984

Table 3-2. Absorption Estimates in Animals Exposed to Americium Compounds by Ingestion

Animal model	Dose and media[a]	Absorption (percent of dose)	Basis for estimate of absorption	Reference
Hamster, adult	^{241}Am nitrate, aqueous solution, single gavage dose, 2.8 ng/kg	0.054	Absorption estimate based on comparisons with liver and carcass ^{241}Am after an intravenous dose, with adjustment for excretion	Stather et al. 1979
	^{241}Am citrate aqueous solution, single gavage dose, 2.6 ng/kg	0.012		
	^{241}Am dioxide, aged aqueous suspension, single gavage dose, 19 ng/kg	0.0058		
	^{241}Am in liver from exposed hamsters, single dose, 2.9 ng/kg	0.0034		
Mouse, adult	^{241}Am nitrate, aqueous solution, single gavage dose, 32 µg/kg	0.0028	Absorption estimate based on sum of ^{241}Am in carcass (excluding the gastrointestinal tract) and liver	Hisamatsu and Takizawa 1987
	^{241}Am citrate, aqueous solution, single gavage dose, 43 µg/kg	0.015		
	^{241}Am in liver from exposed mice, single gavage dose	0.0024–0.0026		
Rat, adult	^{241}Am in wild molluscs or ^{241}Am nitrate injected into mollusc tissue, twice weekly for 8 weeks	0.026–0.12 (wild mussels) 0.016–0.040 (injected mussel)	Absorption estimate based on comparisons with liver and carcass ^{241}Am after an intravenous dose, with adjustment for excretion, twice weekly for 8 weeks	Harrison et al. 1988
Rat, adult	^{241}Am in potatoes exposed to ^{241}Am, or injected into potatoes, single dose or daily for 23 days	0.12–0.16	Absorption estimate based on comparisons with liver and carcass ^{241}Am after an intravenous or intraperitoneal dose, with adjustment for excretion	Bulman et al. 1993
Rat, adult	^{241}Am nitrate, aqueous solution, single gavage dose, 5 µg/kg	0.063	Absorption estimate based on sum of liver, skeletal, and urine ^{241}Am	Sullivan 1980a
Rat, adult	^{241}Am oxide, aqueous suspension, single gavage dose, 33 µg/kg	0.015		

Table 3-2. Absorption Estimates in Animals Exposed to Americium Compounds by Ingestion

Animal model	Dose and media[a]	Absorption (percent of dose)	Basis for estimate of absorption	Reference
Rat, adult	^{241}Am nitrate, aqueous solution, single gavage dose, 12 µg/kg; fed or fasted, with or without Fe^{3+}	0.017 (fed) 0.124 (fast) 1.19 (fast w/Fe^{3+})	Absorption estimate based on sum of ^{241}Am in carcass (excluding the gastrointestinal tract) and urine, Fe^{3+} gavage dose before ^{241}Am dose	Sullivan et al. 1986
Rat, neonate	^{241}Am nitrate, aqueous solution, single gavage dose, 0.44 µg	4.6	Absorption estimate based on ^{241}Am in carcass, excluding the gastrointestinal tract	Sullivan 1980b
	^{241}Am oxide, aqueous solution, single gavage dose, 0.59 µg	0.32	Absorption estimate based on ^{241}Am in carcass, excluding the gastrointestinal tract	
Rat, neonate or adult	^{241}Am nitrate, gavage single dose, 285 µg/kg (adult), 1,380 µg/kg (neonate)	% Age 5.7 2 d 0.0062 adult	Absorption estimate based on ^{241}Am in carcass, excluding the gastrointestinal tract	Sullivan et al. 1985
	^{241}Am citrate, aqueous solution, single gavage dose, 285 µg/kg (adult), 1,480 µg/kg (neonate)	% Age 5.9 2 d 0.047 adult		
Rat, weanling	^{241}Am nitrate, aqueous solution, single gavage dose, Fe deficient or replete, 7–9 µg/kg	4.8 (Fe deficient) 1.8 (Fe replete)	Absorption estimate based on sum of ^{241}Am in carcass, excluding the gastrointestinal tract and urine	Sullivan and Ruemmler 1988

[a]Where the chemical form and/or dose are not presented, these were not provided in the referenced report. Where only activity was reported, mass concentration of americium was calculated assuming a specific activity of 3.24 Ci/g.

d = days; Fe = iron; GP = guinea pig

compared to the fed state and iron deficiency compared with the iron-replete state (Sullivan and Ruemmler 1988; Sullivan et al. 1986). Concurrent oral exposure to Fe^{3+} and americium also appears to increase the absorption of ingested americium; the latter effect may result from redox reactions in the gastrointestinal tract catalyzed by Fe^{3+} (Sullivan et al. 1986). While the exact site and chemical species of americium that is absorbed from the gastrointestinal tract is not known, chemical speciation models applied to saliva and gastric fluid predict that the major species in saliva will be citrate and phosphate complexes, whereas in gastric fluid, the major species will be Am^{3+} (Webb et al. 1998). Speciation models for americium in the small intestine have not been reported; however, complexes with citrate, lactate, and phosphate would be expected based on equilibrium constants for these weak acid complexes and their abundance in intestinal fluid (Webb et al. 1998).

3.4.1.3 Dermal Exposure

Information on the dermal absorption of americium in humans or animals is extremely limited. Some qualitative information is available from accidental exposures that included other routes of exposure. One of the most well studied was an accident in which a worker received facial wounds from projectile glass (and other debris) and nitric acid during an explosion of a vessel containing ^{241}Am (Filipy et al. 1995; McMurray 1983; Toohey and Kathren 1995). The subject also inhaled ^{241}Am released to the air as dust and nitric acid aerosols, which was evident from external chest measurements of radioactivity (Palmer et al. 1983). Accurate estimates of dermal absorption of americium cannot be made from this case because of the complex exposure scenario and because of the occurrence of acid and projectile wounds to the skin that might have greatly affected the penetration of any americium that was deposited on the surface of the skin. Nevertheless, it is possible to conclude from measurements of the dermal ^{241}Am activity soon after the accident and measurements of long-term excretion of ^{241}Am that a substantial fraction of the initial radioactivity deposited in the area of the wounds was absorbed. Quantitative measurements of internally deposited ^{241}Am in target organs were recorded from the third day following exposure to monitor rates of radionuclide excretion and accretion by these organs that continued up to time of death 11 years later. Based on measurements at day 3 postexposure, the organs that received the highest doses included the skin, liver, lung, and bone with estimated organ burdens of 26,000, 1,400, 960, and 480 kBq, respectively (Breitenstein and Palmer 1989; Robinson et al. 1983). The organ burdens of ^{241}Am decreased under DTPA chelation therapy until conclusion after 5 years where monitoring data show that the activity decreased in the skin, entered systemic circulation, and deposited into the bone and liver. Dosimetric evaluation for years 6–10 following exposure showed a decrease in the skin by 93 kBq (2.5 μCi) ^{241}Am,

increased activities in the bone by about 67 kBq (1.8 μCi) and in the liver by about 7.4 kBq (0.2 μCi), and 30 kBq (0.8 μCi) excreted via urine and feces. Over the first 60 days after the accident, dermal ^{241}Am activity decreased from >5 mCi (185 MBq, 1.5 mg) to approximately 0.15 mCi, (5.5 MBq, 0.046 mg), largely as a result of skin decontamination procedures, although normal epidermal sloughing would be an expected contributor as well (Robinson et al. 1983). Cumulative urinary and fecal excretion of ^{241}Am over an observation period of 5 years was estimated to be 1 mCi (37 MBq, 20% of the initial deposited activity), and peak body burden, excluding the skin, was estimated to have been approximately 0.08 mCi (3 MBq, 1.6% of the estimated initial deposited activity). Thus, the combination of transdermal injection and dermal absorption, under these extreme conditions of mechanical and chemical skin wounds, may have been as high as 20%.

3.4.1.4 Other Routes of Exposure

Several cases of accidental exposure to americium as a result of wound penetrations have been reported (Thompson 1983). These exposures have resulted in ^{241}Am burdens in the liver and skeleton, indicating absorption and distribution from the wound site (McInroy et al. 1989).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

The liver is the primary soft tissue site of initial accumulation of absorbed americium in humans. Americium deposited in bone and skeletal muscle has longer retention half-times than americium in the liver. Therefore, at long times after exposure (years), bone and skeletal muscle will contain a larger fraction of the systemic americium burden than the liver (Filipy and Kathren 1996; Kathren 1994; McInroy et al. 1995; Toohey and Kathren 1995). Information on the distribution of americium within the human liver is not available; however, studies in dogs and rats have shown that within a few days after an intravenous injection, hepatic ^{241}Am is associated with lysosomes (Gruner et al. 1981; Lindenbaum and Rosenthal 1972; Seidel et al. 1986; Sütterlin et al. 1984). Americium in the hepatic cytosol is bound to ferritin and other unidentified proteins (DOE 1984; Stover et al. 1970). It is not known whether americium reacts with metallothionein; however, since americium forms stable complexes with polycarboxylate compounds such as DTPA (Lloyd et al. 1975a, 1975b), stable complexes with sulfhydryl

groups in proteins such as metallothionein would not be expected. However, binding of ^{241}Am to an unidentified low molecular weight protein fraction in a rat liver has been reported (DOE 1984).

The United States Transuranium and Uranium Registries (USTUR) collect data on the americium content of human tissues obtained from autopsies. Recent data summaries reported from the USTUR show that after occupational inhalation exposures, ^{241}Am activity resides primarily in the respiratory tract, skeleton, liver, and muscle (see Table 3-3). In three cases in which occupational exposures were believed to have been primarily, if not exclusively by inhalation, the following average tissue distribution was observed at autopsy 30 or more years after exposure: skeleton, 48%; respiratory tract, 35%; muscle, 10%; liver, 3%; and other issues, 4% (McInroy et al. 1989). Analyses of larger sets of USTUR cases have shown that, excluding the respiratory tract and other site of entry tissues (e.g., wound, gastrointestinal tract), approximately 80–90% of the americium in the body is associated with the skeleton, liver, and muscle, the skeletal:soft tissue burden ratio is approximately 3, and the highest soft-tissue concentrations are observed in the liver (Filipy and Kathren 1996; Filipy et al. 1994; Kathren et al. 1988). Whole-body counting of workers who were chronically exposed to plutonium and americium aerosols yielded a similar distribution of ^{241}Am between the skeleton and soft tissue. In a separate study of 20 former workers, the geometric mean skeletal:liver burden ratio was 4.4 (GSD, 2.4; range, 1.2–17) (Badjin and Molokanov 1998). Further evidence that the skeleton and liver are the primary sites of accumulation of absorbed americium is provided by inhalation studies conducted in monkeys (Stanley et al. 1982), dogs (Craig et al. 1975, 1979; Mewhinney et al. 1982; Thomas et al. 1972), and rats (Stradling et al. 1992, 1994). Americium is also taken up by teeth. In rats, americium accumulates in the dental pulp of developing teeth and eventually is incorporated into the mineralized dentin (Hammerström and Nilsson 1970b).

Information on the distribution of americium in blood after exposures to americium is available from an accident victim who was exposed by inhalation, dermal deposition, and wound penetration as a result of an explosion of a vessel containing ^{241}Am, followed by aggressive chelation therapy (McMurray 1983). The internal ^{241}Am activity was sufficiently high in this case to provide reliable estimates of blood and serum ^{241}Am concentrations. Essentially all of the ^{241}Am in blood was in the serum (Robinson et al. 1983). Studies in animals provide further evidence that americium is confined largely to the plasma portion of blood. In baboons, dogs, and rats, >95% of americium in blood is associated with plasma. A variety of human and animal studies (*in vivo* and *in vitro*) have shown that americium in plasma binds extensively to proteins (80–90%), including albumin and transferrin (Boocock and Popplewell 1966; Bruenger et al. 1969; Cohen and Wrenn 1973; Cooper and Gowing 1981; Durbin 1973; Popplewell and Boocock 1967; Turner and Taylor 1968). When americium was incubated with human serum *in vitro*,

Table 3-3. Tissue Americium Levels from Human Autopsies

Tissue	Mean percent of body burden	Mean percent of systemic burden (excluding respiratory tract)
	Based on three inhalation cases[a]	
Respiratory tract	34.8[b]	—
Liver	3.3	6.3
Skeleton	47.6	70.3
Muscle	10.0	16.1
Other	4.3	7.2
Tissue	Soft tissue:liver concentration ratio[c] (number of mixed exposures)	
Brain	0.08 (8)[d]	
Heart	0.123 (6)	
Kidneys	0.06 (38)	
Muscle	0.056 (8)	
Pancreas	0.03 (4)[d]	
Spleen	0.06 (38)	
Testes	0.029 (23)	
Thyroid	0.03 (21)	

[a]McInroy et al. 1989
[b]Estimates of the contribution of the respiratory region to the total body burden in the three individuals from whom the mean value was calculated were 60.7, 23.7, and 14.7%. See McInroy et al. (1989) for additional statistical information.
[c]Filipy et al. 1994
[d]Calculated from Filipy and Kathren 1996

<1% of the americium was ultrafilterable; however, essentially all of the americium could be rendered ultrafilterable by the inclusion of 50 mM citrate in the serum incubate, suggesting reversible binding of americium to serum proteins (Chipperfield and Taylor 1972). As noted above, bone is a primary site of long-term accumulation of americium in the skeleton. One human case of inhaled americium oxide resulted in an estimated deposition of 78 kBq (2,100 nCi) and a reported body burden of 34 kBq (900 nCi) after 12 years; 79% was located in the bone (Fasiska et al. 1971). In another human case, approximately 55% of an estimated lung deposition of 6.3 kBq (170 nCi) of ^{241}Am was deposited in bone (Kathren et al. 2003). In human autopsy samples of bone, ^{241}Am is found primarily at the cortical and trabecular bone surfaces (Priest et al. 1995; Schlenker et al. 1989).

Americium that is observed in the deeper regions of human bones is thought to result from burial of historic surface deposits by newly accreted bone. Supporting evidence for accretion being a mode of redistribution of americium in bone comes from studies of monkeys, rats, and dogs that received single injections of ^{241}Am (Durbin 1973; Herring et al. 1962; Lloyd et al. 1972; Nenot et al. 1972; Polig 1976; Priest et al. 1983). In these studies, the initial deposition of ^{241}Am occurred at bone surfaces, including the periosteal and endosteal surfaces of trabecular bone and along the vascular channels of cortical bone, with more pronounced deposition at surfaces that were undergoing resorption, and with subsequent overlay of new bone (Priest et al. 1983). Because most americium in bone is associated primarily with the bone surface, the americium concentration in bone (per g bone ash) tends to vary with the bone ash content, as reflected by the variability in bone surface-to-volume ratio in a human who was occupationally exposed to americium (Kathren et al. 1987, 1990; Stevens et al. 1977).

When residence times (time between exposure and autopsy) for the americium measured in autopsy cases are taken into consideration, the measured skeletal burdens are consistent with elimination half-times of approximately 50 years (McInroy et al. 1989, 1995). This value represents an average; however, in an individual, exchanges between bone and soft tissue stores of americium may be more rapid during periods of active bone metabolism such as infancy and childhood, pregnancy, and menopause (Lloyd et al. 1999). Studies in animals provide evidence for this concept (Durbin 1973). After an intravenous injection of americium citrate, skeletal tissue accumulated approximately 76% of the injected activity in neonatal dogs and 29% in adult dogs (Stevens et al. 1977). Higher skeletal uptakes of injected americium have also been observed in neonatal rats and mice, relative to adult animals (Hollins et al. 1973; Schoeters et al. 1990) and in young rats (3 months of age) compared to old rats (13 months of age) (Sontag 1983). On the other hand, americium uptake into maternal bone of lactating rats was similar to that of non-lactating rats, while concurrent calcium uptake into bone was lower in lactating rats (Hollins and Durakovic 1972).

Thus, active mobilization of bone mineral, *per se*, may not always promote release of americium from bone.

Information on the placental transfer of inhaled americium in humans is not available. Studies in animals that received parenteral injections of americium show that absorbed americium is transferred to the fetus. To some extent, therefore, this distribution pathway would be expected after inhalation exposure (Sikov 1987; Sikov and Kelman 1989; Stather et al. 1992). In baboons that received a single intravenous injection of americium citrate during the 5th month of pregnancy, approximately 0.4% of the activity was transferred to the fetus within 7 days post administration (Paquet et al. 1998). The fetal:maternal whole-body ^{241}Am concentration ratio was approximately 0.1 and the tissue distribution in the fetus was similar to that observed in adult animals, with the skeleton and liver accounting for most of the ^{241}Am activity in the body. Transfer of injected americium to the fetus has also been quantified in mice and rats that received intravenous injections of americium citrate during pregnancy (Sikov 1987). In both rats and mice, the fetal skeleton and liver were the major sites of accumulation of americium (DOE 1986; Hisamatsu and Takizawa 1983; Sasser et al. 1986; Schoeters et al. 1990; Van Den Heuvel et al. 1992; Weiss et al. 1980). In rats that received an injection of ^{241}Am citrate on days 18 or 19 of pregnancy, fetal transfer was approximately 0.01% of the amount of americium administered to the dams. The fetal:maternal ^{241}Am concentration ratio in rats was approximately 0.02 (Hisamatsu and Takizawa 1983). In mice that received an injection of ^{243}Am citrate (0.01 μCi/mouse) on day 16 of pregnancy, fetal transfer was approximately 0.04% of the administered maternal amount per gram of fetus; the ratio of ^{243}Am activity (μCi/g) in fetal tissue:maternal tissue exclusive of fetuses at the time of dissection was 0.029 (Weiss et al. 1980)

Information on the distribution of absorbed americium to mammary milk in humans is not available. Numerous studies in animals have shown that transfer to milk occurs and that neonates can be exposed to americium during lactation. These studies include experiments in which the animals were exposed by intravenous injection or oral administration of americium; however, the implications are relevant to any route of exposure, including inhalation. In rats that received an intravenous injection of americium citrate during lactation, approximately 0.1% of the injected activity was transferred to the nursing pups (Sasser et al. 1986). Oral and intravenous exposure to americium has resulted in the transfer of americium to mammary milk of cows, goats, and sheep (McClellan et al. 1962; Sutton et al. 1979). In a study of sheep that received americium chloride intravenously, the concentration of americium in mammary milk was 2–3 times that of maternal plasma (McClellan et al. 1962).

3.4.2.2 Oral Exposure

Although it has been demonstrated that americium can be absorbed through the gastrointestinal tract (see Section 3.4.1.2), the systemic distribution by the oral exposure route has been moderately characterized (ICRP, 1986, 1994a). However, it is reasonable to suggest that the distribution of americium absorbed into the systemic circulation from the gastrointestinal tract would be similar to that absorbed after inhalation (see Section 3.4.2.1). Studies in experimental animals support this; the major sites of americium accumulation after ingestion of americium are the skeleton and liver. In pigs ingesting americium citrate once, the distribution of the americium body burden 8 hours post ingestion, when the highest total body burdens were observed, was as follows: bone, 56%; liver, 29%, and muscle, 5% (Eisele et al. 1987). The skeleton and liver accounted for 40% (range, 8–67%) and 29% (range, 7–30%) of the body burden of ^{241}Am, respectively, 7 days following a single gavage administration of americium citrate or nitrate to rats (Sullivan et al. 1985, 1986). Although it is possible that americium absorbed from the gastrointestinal tract might be taken up preferentially by the liver because of the hepatic portal blood flow, there is no evidence that a first pass effect substantially alters the overall tissue distribution of absorbed americium. For example, in marmosets that received an intravenous injection of americium citrate, the liver accounted for 27% of the total body burden of americium (excluding the gastrointestinal tract); whereas after a single gavage administration of americium in potato powder, the liver accounted for 31% of the body burden (oral:intravenous ratio of 1.14) (Ham et al. 1994). A similar comparison made in hamsters resulted in an oral:intravenous ratio for the fractional liver burden of 0.9 (Stather et al. 1979a), and comparisons made in guinea pigs and rats resulted in ratios <1 (Bomford and Harrison 1986; David and Harrison 1984; Harrison et al. 1994).

3.4.2.3 Dermal Exposure

The tissue distribution of americium that is absorbed across the skin would be expected to be similar to that from other routes. Evidence for this is provided from an accident in which a worker received facial wounds from projectile debris and nitric acid during an explosion of a vessel containing ^{241}Am (McMurray 1983; Toohey and Kathren 1995). The subject also inhaled ^{241}Am released to the air as dust and nitric acid aerosols, which was evident from external chest measurements of radioactivity (Palmer et al. 1983). However, since the peak tissue burdens (lung, liver, and bone) of ^{241}Am, measured 3 days after the accident, were collectively only 0.08 mCi, whereas the 5-year cumulative excretion of ^{241}Am was approximately 1 mCi, it is almost certain that the source of most of the absorbed ^{241}Am was the skin

and/or skin wounds. The bone:liver ratio of ^{241}Am 3 days after the exposure was approximately 3, and was 17–23 at autopsy 11 years after the accident. This suggests that bone and liver would be the major sites of accumulation of americium absorbed from the skin, as is the case for americium that is absorbed by other routes. The bone:liver ratio at 3 days was probably strongly affected by the aggressive DTPA therapy being employed at that time, since americium can be more easily removed from soft tissue deposition sites than from bone. Autopsy results (Toohey and Kathren 1995) were used to refine the estimates of organ burdens and doses and to facilitate a comparison with various models. Terminal burdens and tissue doses were estimated for the skeleton (490±40 kBq [13±1 μCi as average of six separate methods], 18 Gy [1,800 rad]), bone surface (490±40 kBq [13±1 μCi], 510 Gy [51,000 rad]), liver (28 kBq [0.8 μCi], 8.1 Gy [810 rad]), lung (1.9 kBq [0.05 μCi], 1.6 Gy [160 rad]), and muscle (13.5 kBq [0.36 μCi], 28 Gy [2,800 rad]). These USTUR measurements indicate that the long-term ^{241}Am skeletal burden was 95% of the total in skeleton plus liver. This compared favorably with estimates using newer models (ICRP 1993; Leggett 1992), but less so when based on earlier models (ICRP 1979; ICRP 1986). Another finding was that muscle was a major repository, based on the total radiation dose it received being larger than that of the liver, whose terminal burden was actually twice as large.

3.4.2.4 Other Routes of Exposure

Various cases have been reported of internal exposure to americium resulting from skin punctures with materials also containing plutonium. Information on the distribution of americium in these cases has been derived from the analysis of autopsy tissues. In most cases, the largest fraction of the ^{241}Am activity measured in the body was associated with tissues near the puncture wound. In one case, 18 years after a puncture wound to the left hand resulting in the deposition of a splinter of plutonium metal, 80% of the measured ^{241}Am activity (a product of ^{241}Pu decay) was associated with the left arm axillary lymph nodes and left hand, 12% was measured in the skeleton, and 1% was measured in the liver (Popplewell and Ham 1989). The large amount of activity associated with the left arm lymph nodes and left hand reflects the local accumulation of americium near the wound site. However, if such local accumulations are subtracted from the total body activity, then most of the systemic americium measured after puncture wound exposures has been associated with the skeleton (80–90%) while liver, muscle, and spleen account for the remainder (5–10%), with skeletal:liver ratios of approximately 9:1 (Lagerquist et al. 1972b; McInroy et al. 1989; Popplewell and Ham 1989). These observations are consistent with those made from autopsy analyses after inhalation exposures (McInroy et al. 1989).

A large degree of variation is apparent in retention rates for americium in the liver among various animal species (Durbin 1973), as indicated by measured or estimated liver clearance half-times of approximately 5–16 days in rats, 152 days in baboons, 1–10 years in dogs, and 10 years in Chinese hamsters. A liver clearance half-time of 2 years has been estimated for humans (Griffith et al. 1983). Refer to Section 3.5.1 for information regarding toxicokinetic mechanisms that may play a role in interspecies differences in liver retention of americium.

3.4.3 Metabolism

The metabolism of americium involves binding interactions with proteins and probably complex formation with various inorganic anions, such as carbonate and phosphate, and carboxylic acids, such as citrate and lactate (Durbin 1973; Taylor 1973; Webb et al. 1998). These types of interactions would be expected for all routes of exposure.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Americium deposited in the nasopharyngeal or tracheal-bronchial regions of the respiratory tract will undergo extensive mucociliary transport to the esophagus with subsequent ingestion and fecal excretion. Evidence for this in humans is provided by cases of accidental inhalation exposure of americium oxides in which a substantial fraction (>50%) of the estimated initially deposited activity was found to be excreted in feces during the first days to weeks after the exposure (Edvardsson and Lindgren 1976; Newton et al. 1983; Sanders 1974). Once absorbed from the lung, americium is excreted in feces and urine. The relative contribution of each in humans is difficult to assess from existing data because most data are derived from accidental exposures, after which the victims were subjected to chelation therapy, which would have increased the urinary excretion of americium. Following an accidental inhalation exposure in which approximately 1.22 μCi (45.1 kBq) of ^{244}Cm and ^{241}Am (in the form of mixed oxides) were deposited in the respiratory tract, the cumulative 1-year excretion of radioactivity was approximately 1,174 nCi (43.4 kBq, 96% of the deposited activity) in feces and 5.4 nCi (200 Bq, 0.4% of the deposited activity) in urine (Sanders 1974). The equivalent fractions of ^{241}Am, based on measurements of the ^{244}Cm:^{241}Am ratios in feces and urine, were similar, 96% in feces and 0.4% urine. The subject received

14 treatments with the chelating agent, DTPA, which may have effectively increased rates of excretion of americium.

Studies of excretion in animals after inhalation exposures also indicate a relatively large contribution of fecal excretion to the total elimination of americium that deposits in the respiratory tract. In dogs that inhaled an aerosol of AmO_2, fecal and urinary excretion of americium during the first 10 days after exposure were 30 and 0.7% of the initial body burden, respectively, and were 50 and 6% of the initial burden, respectively, by 810 days postexposure (Craig et al. 1979). Mechanical clearance from the upper respiratory tract to the gastrointestinal tract would be expected to make a substantial contribution to fecal excretion during the first few weeks after exposure and may continue for longer periods. The observation that fecal excretion continued to be the main route of excretion months after the exposure suggests two possibilities: (1) mechanical clearance from the lower respiratory tract (e.g., lung) continues to contribute to fecal excretion for longer periods of time (ICRP 1994b), and (2) absorbed americium is excreted in feces, suggesting a role for biliary excretion (Durbin 1973).

Lung deposition patterns and the relative contributions of the fecal and urinary pathways vary with the aerosol particle size. Evidence for this is provided by a study in which dogs inhaled AmO_2 aerosols having different size distributions. As the particle size AMAD increased from 0.8 μm (±1.2 GSD) to 3.5 μm (±1.06 GSD), the urine:fecal ratios of cumulative excretion (from days 8 to 730 after the exposure) decreased from 4 to 0.3 (Mewhinney et al. 1982). These observations are consistent with an effect of particle size on deposition patterns in the respiratory tract. Larger particles will be deposited in the tracheo-bronchial airways and will be subjected to mucociliary transport to the esophagus where they can enter the gastrointestinal tract. Therefore, the fraction of the deposited activity transferred to the gastrointestinal tract and excreted in the feces would be expected to increase with increasing mean particle size of the inhaled aerosol. The general trend of increased fecal excretion with increasing particle size would be expected to occur in humans, although the exact relationship between particle size and deposition patterns will vary across species because of species differences in airway geometry, breathing patterns, and air flow rates in the respiratory tract (see Section 3.4.5).

Once absorbed into the general circulation, regardless of the route of exposure, americium is excreted in both feces and urine. Evidence for this derives from a human accident case study and from experiments in animals that received an intravenous or intramuscular injection of americium (see Section 3.4.4.4).

3.4.4.2 Oral Exposure

Urinary excretion of ingested americium has been measured in humans who ingested shellfish (molluscs) that had assimilated americium from their aquatic environment. In eight adult subjects (six males and two females) who ingested molluscs (winkles) containing ^{241}Am (activity range 10–25 Bq, 0.27–0.68 nCi, 0.083–0.21 ng), the mean cumulative urinary excretion during the 7 days after ingestion was approximately 0.0005% and the estimated fraction of the absorbed activity excreted in the urine was 0.07% (Hunt et al. 1990). In a similar study of six subjects (five males and one female) who ingested cockles collected from Ravenglass, Cumbria (activity range of 15–17 Bq, 0.41–0.46 nCi, 0.13–0.14 ng), the mean cumulative urinary excretion during the 7 days post ingestion was approximately 0.0009% of the ingested americium and the estimated portion of the absorbed activity excreted in the urine was 0.08% (Hunt 1998). Three of these subjects had participated in the earlier study with winkles (Hunt et al. 1990); urinary excretion during 3 days prior to ingestion of the cockles was used to correct for internalized americium from prior exposures. Measured ^{241}Am activity in the cockles was indistinguishable from the cumulative activity measured in fecal samples collected from the subjects during the 7 days post ingestion.

Additional information on the excretion of ingested americium derives from an accident in which a worker ingested a ceramic particle containing $^{241}AmO_2$ (Smith et al. 1983). Five days after the accident, the particle, containing approximately 2.85 μCi (105 kBq) of ^{241}Am (0.88 μg Am), was excreted in the feces. Previous fecal samples and one subsequent fecal sample collected the day after the particle was excreted had essentially no ^{241}Am activity. During the first 8 days after the particle was ingested, approximately 4 pCi (0.15 Bq, 0.00007% of the estimated activity) was excreted in the urine.

Studies in rats and guinea pigs have shown that urinary excretion is the major route of excretion of americium absorbed from the gastrointestinal tract during the first week after exposure in these species. In rats that were administered americium nitrate or citrate by gavage, 30–80% of the estimated absorbed activity was excreted in urine during the first 7 days post administration (Sullivan 1980a; Sullivan et al. 1985). The wide range may reflect the uncertainty in the estimates of the relatively low fraction absorption of the americium. The fraction of the absorbed activity that was excreted in urine was lower in iron-deficient rats (35%) than in iron-replete rats (78%) (Sullivan et al. 1985). In guinea pigs, 35–50% of the absorbed activity was excreted in urine during the first 7 days after a single gavage dose of americium nitrate (Sullivan 1980a).

Once absorbed into the general circulation, regardless of the route of exposure, americium is excreted in both feces and urine. Evidence for this derives from human accident case study and from experiments in animals that received an intravenous or intramuscular injection of americium (see Section 3.4.4.4).

3.4.4.3 Dermal Exposure

Information on the excretion of americium after dermal exposure in humans or animals is extremely limited. Some qualitative information is available from an accidental exposure in which a worker received facial wounds from projectile debris and nitric acid during an explosion of a vessel containing ^{241}Am (McMurray 1983). The subject also inhaled ^{241}Am released to the air as dust and nitric acid aerosols, which was evident from external chest measurements of internal radioactivity; thus, excretion estimates reflect combined inhalation, dermal, and wound penetration exposures (Palmer et al. 1983). Measurements of cumulative fecal and urinary excretion of ^{241}Am during the first years after the accident, and periodic measurements made from day 10 to 11 years post accident, indicated a fecal:urine excretion ratio of approximately 0.2–0.3, although the ratio was approximately 1 on day 3 post accident (Breitenstein and Palmer 1989; Robinson et al. 1983). The ratio was almost certainly affected, however, by initial chelation with Ca-DTPA, followed by daily intravenous therapy with the chelating agent, Zn-DTPA; these treatments would have increased the urinary excretion of americium (Breitenstein and Palmer 1989). The above not withstanding, the observations made on this subject demonstrate that fecal excretion was an important pathway of excretion in this subject long after mechanical clearance of americium from the respiratory tract would have been complete. This is consistent with observations made in nonhuman primates that show that americium is excreted into bile (see Section 3.4.4.4). However, the extent to which the biliary excretion pathway in humans might resemble that of nonhuman primates is not known.

Once absorbed into the general circulation, regardless of the route of exposure, americium is excreted in both feces and urine. Evidence for this derives from experiments in animals that received an intravenous or intramuscular injection of americium (see Section 3.4.4.4).

3.4.4.4 Other Routes of Exposure

Measurements of fecal and urinary excretion of americium after an inhaled or ingested dose do not provide all of the information needed to assess the relative importance of either route in the excretion of

absorbed americium. This is because inhaled americium is subject to mucociliary transport and ingestion, and only a small fraction of ingested americium is absorbed. Studies in which animals were parenterally administered americium have provided quantitative information on the routes of excretion of absorbed americium. The relative contribution of the fecal and urinary pathways appears to vary with species and time post administration; however, in general, the fecal pathway predominates. In monkeys, urinary excretion of radioactivity following intravenously administered americium citrate was the major route of excretion only during the first few weeks post administration, at which time, cumulative urinary and fecal excretion accounted for 10 and 3% of the administered activity, respectively (Durbin 1973). Long-term cumulative excretion (months to years), however, was primarily in feces, with 37% of the administered activity excreted in feces and 20% excreted in urine. A similar pattern of urinary and fecal excretion over time was evident in baboons (Cohen and Wrenn 1973; Durbin 1973; Guilmette et al. 1980). Similarly, in rats, dogs, and hamsters, urinary excretion of radioactivity following intramuscularly or intravenously injected americium citrate or chloride was the major route of excretion only during the first few days to weeks, with a fecal:urine excretion ratio of approximately 0.11–0.15; however, over a 1–2-year period, the fecal:urine ratio was approximately 5–9 (Durbin 1973; Stather et al. 1979a).

The large contribution of the fecal route to excretion of absorbed americium appears to be the result of excretion of americium into the bile. In monkeys that received an intravenous injection of americium citrate, ^{241}Am was detected in gall bladder bile and its concentration increased as the relative rate of fecal excretion increased over time post injection (Durbin 1973). Durbin (1973) estimated that at bile production rates similar to humans, biliary excretion could have accounted for most, if not all, of the fecal excretion of americium observed in the monkeys.

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

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

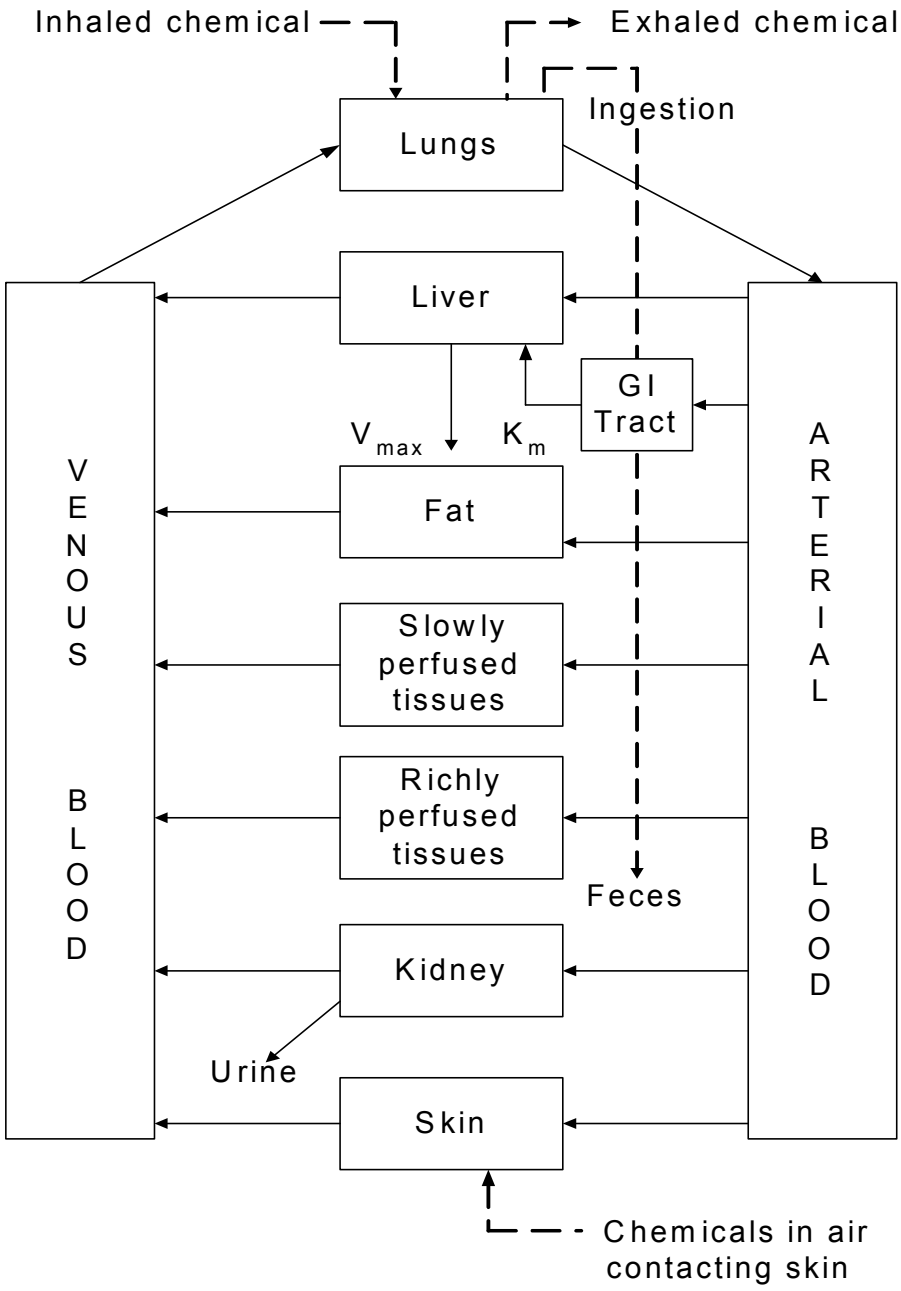
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al.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

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

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). Similar models have been developed for radionuclides. These models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-1 shows a conceptualized representation

Figure 3-1. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



of a PBPK model. Figures 3-2 through 3-8 show models for radionuclides in general or specifically for americium.

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

The ICRP (1994b, 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 americium compounds. The ICRP (1986, 1989) has a biokinetic model for human oral exposure that applies to americium. The National Council on Radiation Protection and Measurements (NCRP) has also developed a respiratory tract model for inhaled radionuclides (NCRP 1997). At this time, the NCRP recommends the use of the ICRP model for calculating exposures for radiation workers and the general public. Readers interested in this topic are referred to NCRP Report No. 125; Deposition, Retention and Dosimetry of Inhaled Radioactive Substances (NCRP 1997). In the appendix to the report, NCRP provides the animal testing clearance data and equations fitting the data that supported the development of the human mode for americium.

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

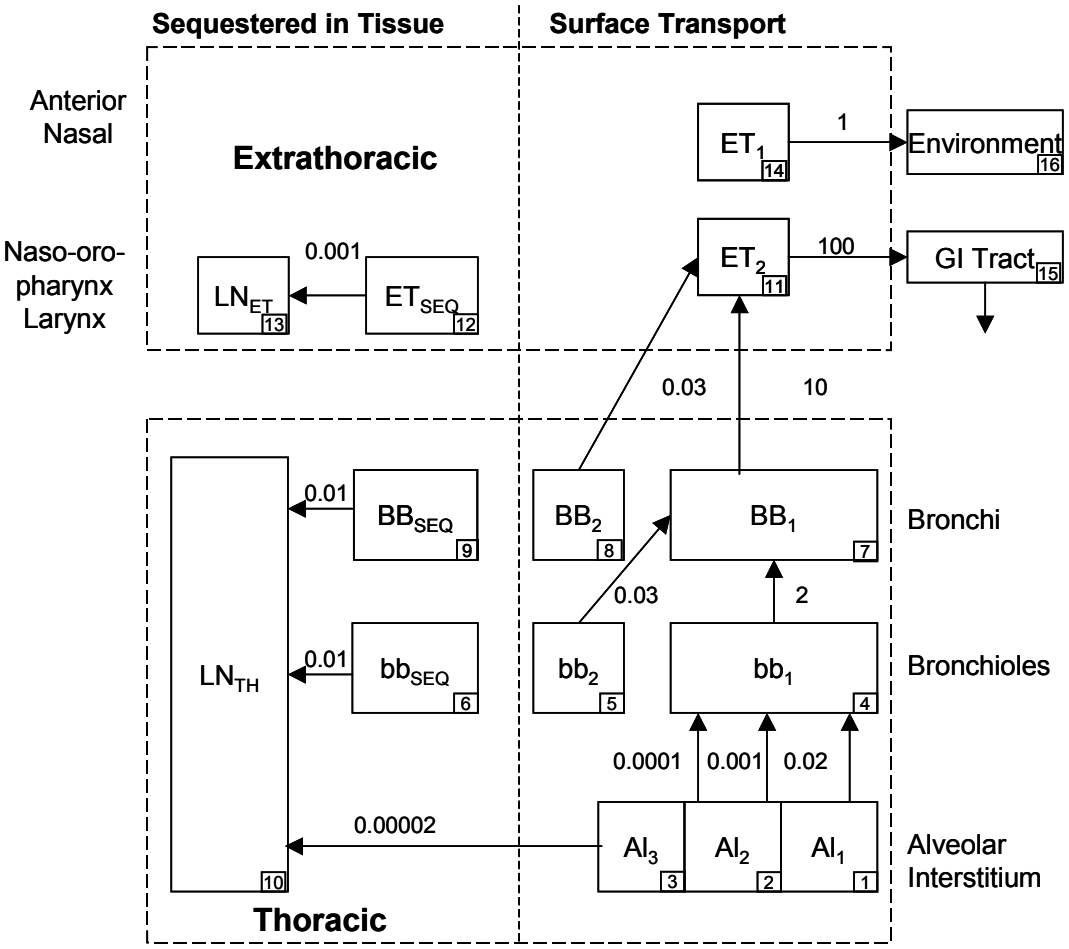
Deposition. The ICRP (1994b) has developed a deposition model for behavior of aerosols and vapors in the respiratory tract. It was developed to estimate the fractions of substances in breathing air that are deposited in each anatomical region of the respiratory tract. ICRP (1994b) provides inhalation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

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

For extrathoracic deposition of particles, the model uses measured airway diameters and experimental data, where deposition is related to particle size and airflow parameters, and scales deposition for women and children from adult male data. Similar to the extrathoracic region, experimental data served as the basis for lung (bronchi, bronchioles, and alveoli) aerosol transport and deposition. A theoretical model of gas transport and particle deposition was used to interpret data and to predict deposition for compartments and subpopulations other than adult males. Table 3-4 provides reference respiratory values for the general Caucasian population during various intensities of physical exertion.

Respiratory Tract Clearance. This portion of the model identifies the principal clearance pathways within the respiratory tract. The model was developed to predict the retention of various radioactive materials. The compartmental model represents particle deposition and time-dependent particle transport in the respiratory tract (see Figure 3-2) with reference values presented in Table 3-5. This table provides clearance rates, which are expressed as a fraction per day and also as half-time (Part A), and deposition

Figure 3-2. 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 3-5.

Source: ICRP 1994b

Table 3-4. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity[a]

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

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

B = ventilation rate; f_R = respiration frequency; h = hour; L = liter; m = meter; min = minute; N/A = not applicable; V_T = tidal volume

Table 3-5. 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	$1x10^{-4}$	7,000 days
$m_{3,10}$	AI_3	LN_{TH}	$2x10^{-5}$	No data
$m_{4,7}$	bb_1	BB_1	2	8 hours
$m_{5,7}$	bb_2	BB_1	0.03	23 days
$m_{6,10}$	bb_{seq}	LN_{TH}	0.01	70 days
$m_{7,11}$	BB_1	ET_2	10	100 minutes
$m_{8,11}$	BB_2	ET_2	0.03	23 days
$m_{9,10}$	BB_{seq}	LN_{TH}	0.01	70 days
$m_{11,15}$	ET_2	GI tract	100	10 minutes
$m_{12,13}$	ET_{seq}	LN_{ET}	0.001	700 days
$m_{14,16}$	ET_1	Environment	1	17 hours

See next page for Part B

Table 3-5. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract (*continued*)

Part B

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

[a]The half-times are approximate since the reference values are specified for the particle transport rates and are rounded in units of $days^{-1}$. 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.
[b]See paragraph 181, Chapter 5 (ICRP 1994b) for default values used for relating f_s to d_{ae}.
[c]It is assumed that f_s is size-dependent. For modeling purposes, f_s is taken to be:

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

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

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

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

Source: ICRP 1994b

fractions (Part B) for each compartment for insoluble particles. ICRP (1994b) also developed modifying factors for some of the parameters, such as age, smoking, and disease status. Parameters of the clearance model are based on human evidence for the most part, although particle retention in airway walls is based on experimental data from animal experiments.

The clearance of particles from the respiratory tract is a dynamic process. The rate of clearance generally changes with time from each region and by each route. Following deposition of large numbers of particles (acute exposure), the mass flow of material between compartments decreases as particles are cleared from the various regions. Physical and chemical properties of deposited material determine the rate of dissolution, and as particles dissolve, absorption rates of material between the compartments tend to change. By creating a model with compartments of different clearance rates within each region (e.g., BB1, BB2, BBseq), the ICRP model overcomes problems associated with time-dependent functions. Each compartment clears to other compartments by constant rates for each pathway.

Particle transport from all regions is toward both the lymph nodes and the pharynx, and a majority of deposited particles, if sufficiently large, end up being swallowed. In the front part of the nasal passages (ET1), nose blowing, sneezing, and wiping remove most of the deposited particles. Particles remain here for about a day. For particles with AMADs a few micrometers or greater, the ET1 compartment is probably the largest deposition site. A majority of particles deposited at the back of the nasal passages and in the larynx (ET2) are removed quickly by the fluids that cover the airways. In this region, particle clearance is completed within 15 minutes.

Ciliary action removes deposited particles from both the bronchi and the bronchioles. Though it is generally thought that mucociliary action rapidly transports most particles deposited here toward the pharynx, a fraction of these particles is cleared more slowly. Evidence for this is found in human studies. For humans, retention of particles deposited in the lungs (BB and bb) is apparently biphasic. The “slow” action of the cilia may remove as much as half of the bronchi- and bronchiole-deposited particles. In human bronchi and bronchiole regions, mucus moves more slowly when it is closer to the alveoli. For the faster compartment, it has been estimated that it takes about 2 days for particles to travel from the bronchioles to the bronchi and 10 days from the bronchi to the pharynx. The second (slower) compartment is assumed to have approximately equal fractions deposited between BB2 and bb2, with both fractions having clearance half-times estimated at 20 days. Particle size is a primary determinant of the fraction deposited in this slow thoracic compartment. A small fraction of particles deposited in the BB and bb regions is retained in the airway wall for even longer periods (BBseq and bbseq).

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

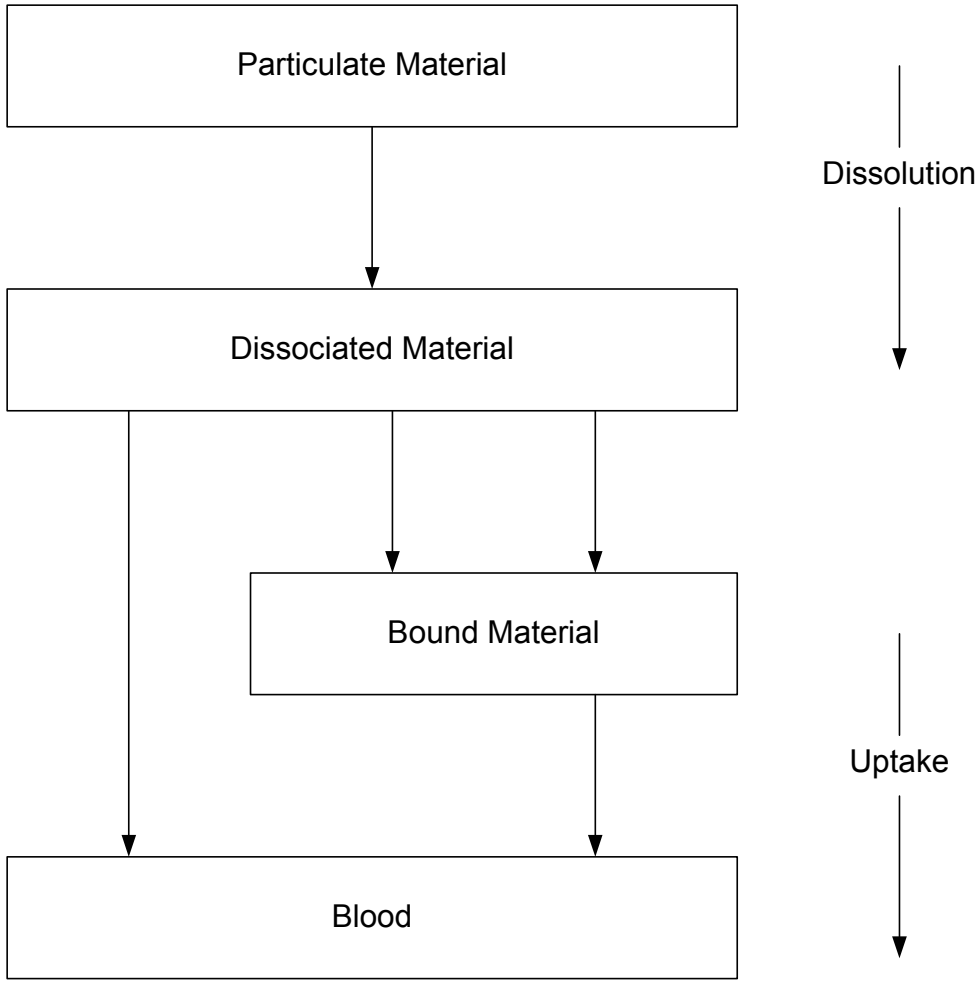
In the AI region, human lung clearance has been measured. The ICRP model uses three half-times to represent clearance: about 30, 60, and 10% of the particles have half times that approximate 30, 700, and 7,000 days, respectively. Over time, AI particle transport falls, and some compounds have been found in lungs 10–50 years after exposure.

Absorption into Blood. The ICRP model assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages (ET1), where no absorption occurs. It is essentially a 2-stage process, as shown in Figure 3-3. First, there is a dissociation (dissolution) of particles, and then the dissolved molecules or ions diffuse across capillary walls and are taken up by the blood. Immediately following dissolution, rapid absorption is observed. For some elements, rapid absorption does not occur because of binding to respiratory-tract components. In the absence of specific data for specific compounds, the model uses the following default absorption rate values for those specific compounds that are classified as Types F (fast), M (medium), S (slow), and V (instantaneous):

- For Type F, there is rapid 100% absorption within 10 minutes of the material deposited in the BB, bb, and AI regions and 50% absorption of material deposited in ET_2. Thus, for nose breathing, there is rapid absorption of approximately 25% of the deposit in ET; for mouth breathing, the value is 50%.
- For Type M, about 70% of the deposit in AI eventually reaches the blood. There is rapid absorption of about 10% of the deposit in BB and bb and 5% of material deposited in ET_2. Thus, there is rapid absorption of approximately 2.5% of the deposit in ET for nose breathing and 5% for mouth breathing.
- For Type S, 0.1% is absorbed within 10 minutes and 99.9% is absorbed within 7,000 days, so there is little absorption from ET, BB, or bb, and about 10% of the deposit in AI eventually reaches the blood.
- For Type V, complete absorption (100%) is considered to occur instantaneously (which is not relevant to americium compounds).

ICRP (1995) considers the experimental data on americium nitrate, chloride, citrate, and hydroxide to support classification of these compounds as either Type F or M. Americium oxides are classified as

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



Source: ICRP 1994b

Type M. ICRP (1995) recommends assigning all americium aerosols to Type M in the absence of specific information supporting an alternative classification. Substance specific values should be used where feasible to reduce uncertainties in results.

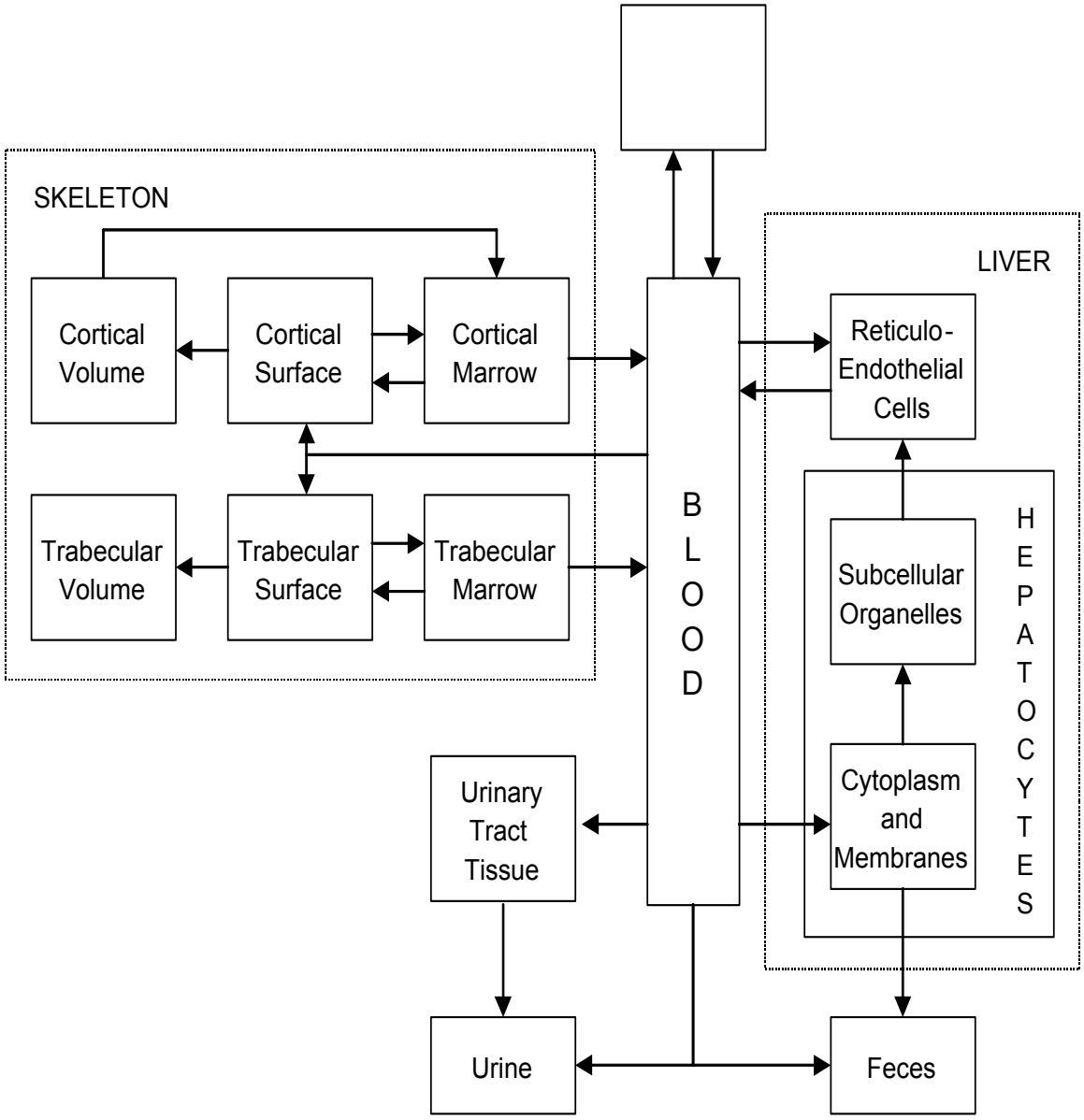
ICRP (1989) Americium Biokinetic Model

Description of the model.

ICRP (1989) developed a compartmental model of the kinetics of ingested americium in humans that is applicable to infants, children, adolescents, and adults. The model is a modification and expansion of a similar model for plutonium, described by Leggett et al. (1984, 1985). The fraction of ingested americium that is absorbed (uptake to blood) is assumed to vary with age and have values of 0.01 in infants up to 12 months of age and 0.001 from 12 months of age through adulthood (ICRP 1986). Absorbed americium enters the blood plasma where it distributes to the skeleton, liver, and other tissues (Figure 3-4). Excretion pathways included in the model are plasma to urine and liver to feces. Transfer rate coefficients between compartments are age-specific and, depending on the specific coefficient, values can change at ages 3 months, 1 year, 5 years, 10 years, 15 years, and adult (>15 years). The model assumes that, in adults, 50% of the americium that enters the body and is not excreted is transferred to the liver and 30% is transferred to the skeleton. In newborns, 70% is assumed to be transferred to the skeleton and 10% to the liver. Skeletal deposition is assumed to distribute into two pools: 50% goes to the trabecular bone surface and 50% goes to the cortical bone surface. A first-order rate coefficient for elimination of americium from liver to plasma is assumed to be 0.0019 day^{-1} (half-time, 365 days).

Bone is divided into trabecular and cortical components, with each further divided into surface bone, bone volume, and bone cavity (marrow compartment). Deposition of americium is assumed to occur from plasma directly to bone surfaces, whereas elimination from bone occurs by transfer from the bone surface or volume to the marrow cavity, and then from the marrow cavity to plasma (Figure 3-4). Transfers of americium within the cortical or trabecular bone compartments are modeled based on assumptions about rates of bone formation and resorption, which are assumed to be vary with age, but are equal within a given age group (Leggett et al. 1982). Movement of americium to the marrow compartment is determined by the bone resorption rate, whereas movement from the bone surface to the bone volume is assumed to occur by burial of surface deposits with new bone and is determined by the bone formation rate. During growth, bone formation and resorption are assumed to occur at different sites within bone; therefore, the rate of removal of americium from the bone surface is approximated by the sum of the bone resorption rate (represented in the model by the movement of americium to the marrow compartment) and

Figure 3-4. ICRP (1989) Model of Americium Biokinetics



the rate of bone formation, which results in burial of surface deposits (represented by movement of americium from the bone surface to bone volume). In adults, the possibility of resorption and formation of bone occurring at the same site is assumed; therefore, only a portion of the bone formation rate results in burial of surface deposits and movement of americium from the bone surface to the bone volume.

Validation of the model.

The extent to which the ICRP model has been validated is not described in ICRP (1989).

Risk assessment.

The model has been used to establish the radiation dose (Sv) per unit of ingested ^{241}Am activity (Bq) for ages 3 months to 70 years (ICRP 1989).

Target tissues.

The model is designed to calculate the ^{241}Am intake that would produce the maximum allowed occupational radiation dose to all major organs, including the bone surfaces, bone marrow, and liver, but the conversion factors for other tissues and organs are published in the same tables.

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

Interroute extrapolation.

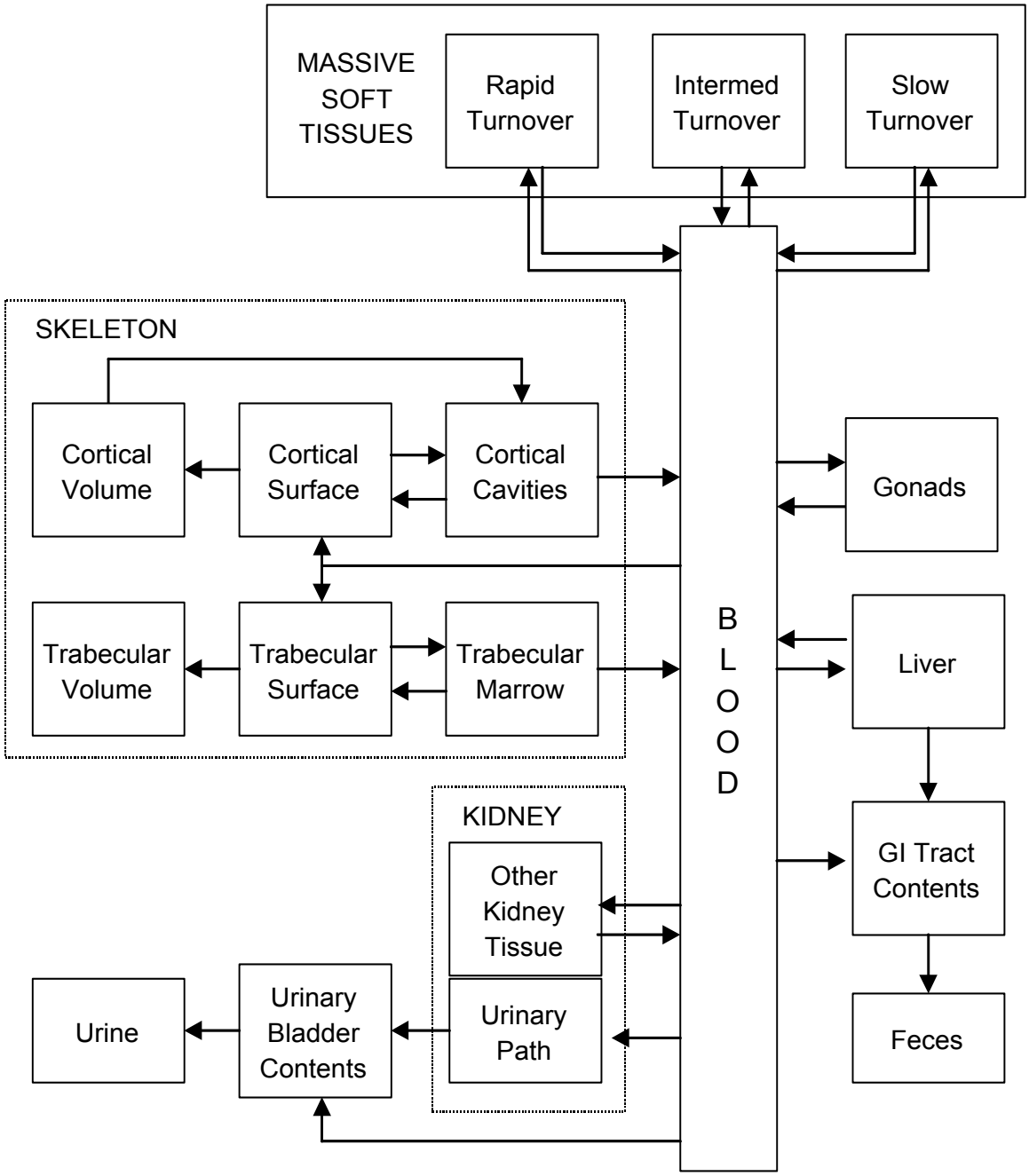
The model is designed to simulate oral exposures to americium. It can be applied to any other route of exposure for which the transfer rate to blood is available.

Leggett (1992) Americium Biokinetic Model

Description of the model.

Leggett (1992) proposed a model for the retention and excretion of americium in humans. The model is a modification of a similar model for plutonium (Leggett et al. 1984, 1985) with the following changes (Figure 3-5): (1) the liver is represented as a single pool rather than having distinct pools for hepatocytes

Figure 3-5. Leggett (1992) Model of Americium Biokinetics



and other cell types; (2) the gonads are represented by a separate compartment; (3) a kidney compartment is included in place of the compartment for urinary tract tissue; (4) a compartment representing the urinary bladder contents is included; and (5) other soft tissues are represented as having slow, intermediate, and fast turnover pools.

The fraction of ingested americium that is absorbed (uptake from the small intestine to blood) is represented by age-specific functions that yield the following values: decreasing from 0.05 to 0.0005 during the first 12 months, 0.0005 at 1–15 years of age, decreasing from 0.0005 to 0.0002 at 15–18 years of age, and 0.0002 from age 18 years through adulthood. The model assumes that, in adults, 62% of the americium that enters the body and is not excreted is transferred to liver and 38% is transferred to the skeleton (skeleton:liver deposition ratio, 3:5). In newborns, 88% is assumed to be transferred to the skeleton and 12% to the liver (skeleton:liver deposition ratio, 7:1). The half-time for elimination of americium from the liver is assumed to be 365 days, although the half-time for elimination measured externally would be longer and would increase with increasing time after intake, due to recycling of americium from tissues to blood to tissues.

Validation of the model.

Predictions based on the model have been compared to observed urinary or fecal excretion of americium in humans. Model predictions agreed reasonably well with the empirical observations (Leggett 1992).

Risk assessment.

The Leggett (1992) model was developed to predict tissue doses and whole-body dose to people who may be exposed to americium and for interpretation of bioassay data for americium. The model is considered an updated version of the ICRP (1989) model for americium, which has been used to establish risk-based limits of intake of ^{241}Am (ICRP 1989). The Leggett (1992) and ICRP (1989) models predict similar long-term average doses of americium to the liver and skeleton for an injection exposure and would be expected to predict similar radiation risks and risk-based intake limits (Leggett 1992). Descriptions of applications of the Leggett (1992) model in risk assessment have not been reported.

Target tissues.

The model is designed to calculate americium excretion and time courses for americium levels in the liver, skeleton, and gonads. This output could be used to predict radiation doses to these tissues.

Species extrapolation.

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

Interroute extrapolation.

The model is designed to simulate oral, inhalation, and parenteral (e.g., injection) exposures to americium and cannot be applied to other routes of exposure without modification.

ICRP (1993) Americium Biokinetic Model

Description of the model.

ICRP (1993) adopted the model of Leggett (1992) as its systemic biokinetic model for americium with the following modifications: (1) the Leggett (1992) model addresses changes throughout life in the rate of bone turnover, whereas the ICRP (1993) model assumes bone turnover rates to remain constant in adults, and (2) assumptions regarding uptake and retention by gonadal tissues of children are more cautious in the ICRP (1993) model compared to those used in the Leggett (1992) model.

Validation of the model.

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

Risk assessment.

The model has been used to establish the radiation dose (Sv) per unit of ingested ^{241}Am activity (Bq) for ages 3 months to 70 years (ICRP 1993).

Target tissues.

The model is designed to calculate the ^{241}Am intake that would produce the maximum allowed occupational radiation dose to all major organs, including the bone surfaces, bone marrow, and liver, but the conversion factors for other tissues and organs are published in the same tables.

Species extrapolation.

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

Interroute extrapolation.

The model is designed to simulate oral exposures to americium. It can be applied to any other route of exposure for which the transfer rate to blood is available.

USTUR (1994) Americium Biokinetics Model

Description of the model.

The USTUR proposed modifications to the ICRP americium model, based on post-mortem americium measurements in human exposure cases (Kathren 1994). The major modifications are: (1) the initial deposition fraction is assumed to be skeleton 45%, liver 25%, muscle 20%, and other tissues 10%; and (2) the half-times for elimination of americium were assumed to be 2.5 years in liver, 10 years in muscle, 50 years in skeleton, and 10 years in other tissues.

Validation of the model.

Predictions based on the model have been compared to observed post-mortem tissue americium levels in whole-body and tissue donations to the USTUR. Model predictions agreed reasonably well with the empirical observations (Kathren 1995; USTUR 1997). They, however, depend heavily on the accuracy of initial uptake and distribution data that, in certain cases, were difficult to reconstruct due to delays between times of exposure and initial analysis.

Risk assessment.

The USTUR (Kathren 1994) model was developed to predict tissue doses and whole-body dose to people who may be exposed to americium. The model has been used to verify annual limits on intake (ALIs) for ^{241}Am, and yielded similar, but lower limits than those estimated using the ICRP model (1989).

Target tissues.

The model is designed to calculate americium excretion and time courses for americium levels in the liver, skeleton, and gonads. This output could be used to predict radiation doses to these tissues.

Species extrapolation.

The model is designed for application to human dosimetry and does not apply to other species.

Interroute extrapolation.

The model is designed to simulate oral, inhalation, and parenteral (e.g., injection, wounds) exposures to americium and cannot be applied to other routes of exposure without modification.

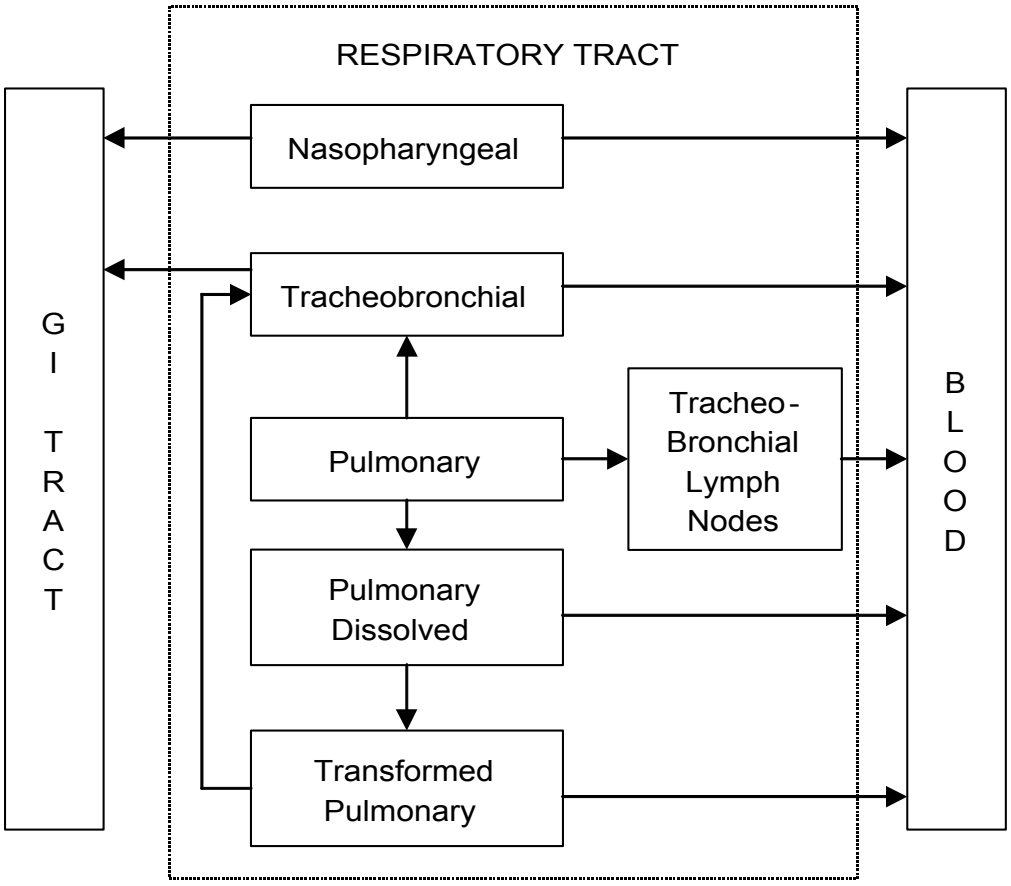
Mewhinney and Griffith (1983) Americium Biokinetics Model

Description of the model.

Mewhinney and Griffith (1983) proposed a model for the absorption and tissue distribution of inhaled americium dioxide in humans. The model is a modification of a model of the beagle dog (Mewhinney and Griffith (1982) and formed part of the basis for the Leggett (1992) model. The model is similar to other actinide models (ICRP 1989; Leggett 1992), but has several additional features in the respiratory tract portion of the model (Figure 3-6) including: (1) dissolution of particles in the respiratory tract is simulated with rate functions, rather than zero or first-order rate constants, that include various parameters of particle size and surface area that affect dissolution rate (Mercer 1967); (2) the pulmonary region includes three pools; a pool of deposited particulate; a pool of dissolved americium which can be rapidly absorbed into the blood; and a pool of locally bound americium (transformed) which can be absorbed into blood or mechanically cleared to the tracheobronchial region; and (3) absorption from the pulmonary region of the respiratory tract includes a pathway for transfer to tracheobroncheal lymph nodes.

Excretion is assumed to be in feces, from either the intestine or from the liver to the intestine, and from the blood to the urine (i.e., the kidney is represented as a distribution compartment). An absorption fraction of 0.0005 is assumed for americium in the small intestine.

Figure 3-6. Mewhinney and Griffith (1983) Model of Deposition and Retention of Americium in the Human Respiratory Tract



Validation of the model.

Predictions based on the model have been compared to observed time courses for lung, liver, and skeletal americium burden in dogs that inhaled americium oxide (Mewhinney and Griffith 1983). Data on lung retention for four humans who accidentally inhaled americium were also compared to model predictions. The empirical observations fell within predicted retention patterns for particle sizes (AMAD) 0.5 and 1.8 μm (Mewhinney and Griffith 1983).

Risk assessment.

The Mewhinney and Griffith (1983) model was developed to predict lung retention and tissue distributions of americium in people who may be exposed to americium. Descriptions of applications of the model in risk assessment have not been reported.

Target tissues.

The model calculates americium burdens in lung, liver, skeleton, kidney, and body. This output could be used to predict radiation doses to these tissues.

Species extrapolation.

The model is designed for applications to human dosimetry; however, it predicts reasonably well the retention of americium in beagle dogs as well (Mewhinney and Griffith 1982). The model cannot be applied to other species without modification.

Interroute extrapolation.

The model is designed to simulate inhalation exposures to americium; however, it could be applied to ingestion exposures since the model simulates the absorption of americium from the gastrointestinal tract. The model can be applied to other routes of exposure with modification.

Durbin and Schmidt (1985) Americium Biokinetics Model

Description of the model.

Durbin and Schmidt (1985) proposed a model for tissue distribution and excretion of absorbed americium in humans. A unique feature of this model is that transfers from plasma to tissues are assumed to be

instantaneous; therefore, a central plasma (and blood) compartment is not included in the model (see Figure 3-7). Tissue compartments included in the model are slow and fast turnover bone compartments, representing cortical and trabecular bone, respectively; liver; and slow and fast turnover for other soft tissue compartments. Excretion pathways include urine and feces. Urinary excretion is represented as a sum of the contributions from bone, liver, and other soft tissues. Fecal americium is assumed to be excreted from the liver.

Validation of the model.

Predicted skeletal americium concentrations were compared to values observed in a USTUR case and the predicted and observed values agreed reasonably well. However, the same USTUR case was used to derive values for model parameters and, therefore, agreement with the observations would be expected. No other validation results are described.

Risk assessment.

The model was developed to predict skeletal and soft tissue burdens of americium in people who may be exposed to americium. Comparisons of ALIs derived from the model and the ICRP (1979) model are presented. Descriptions of applications of the model in risk assessment have not been reported.

Target tissues.

The model calculates americium burdens in liver and skeleton. This output could be used to predict radiation doses to these tissues.

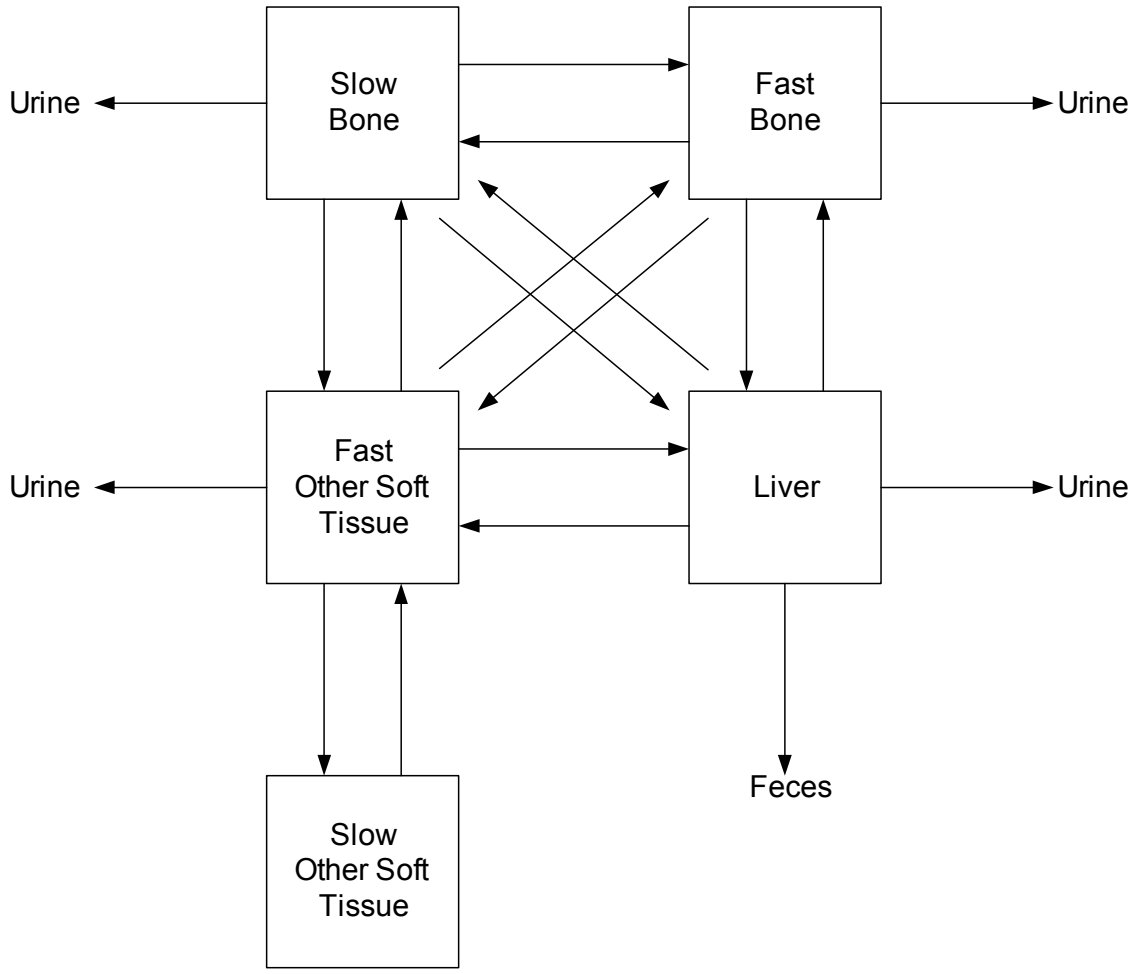
Species extrapolation.

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

Interroute extrapolation.

The model, as described in Durbin and Schmidt (1985), does not have an intake component, but it could be linked to an oral or inhalation intake model or a wound model to simulate the biokinetics of americium associated with such exposures.

Figure 3-7. Durbin and Schmidt (1985) Model of Distribution and Excretion of Absorbed Americium in the Human



Other Models

Leggett (1992) also proposed a respiratory tract model. Deposition of americium particles, depending on their size, are assumed to deposit in three compartments representing extrathoracic, fast-clearing thoracic, and slow-clearing thoracic regions of the respiratory tract (Figure 3-8).

An early model to calculate doses to workers exposed to radionuclides by ingestion or inhalation was developed by ICRP (1979). In 1996, ICRP recommended that a task group be set up to revise the model.

This task group developed a new model for the human alimentary tract (Métivier 2003) that has yet to be endorsed by the ICRP.

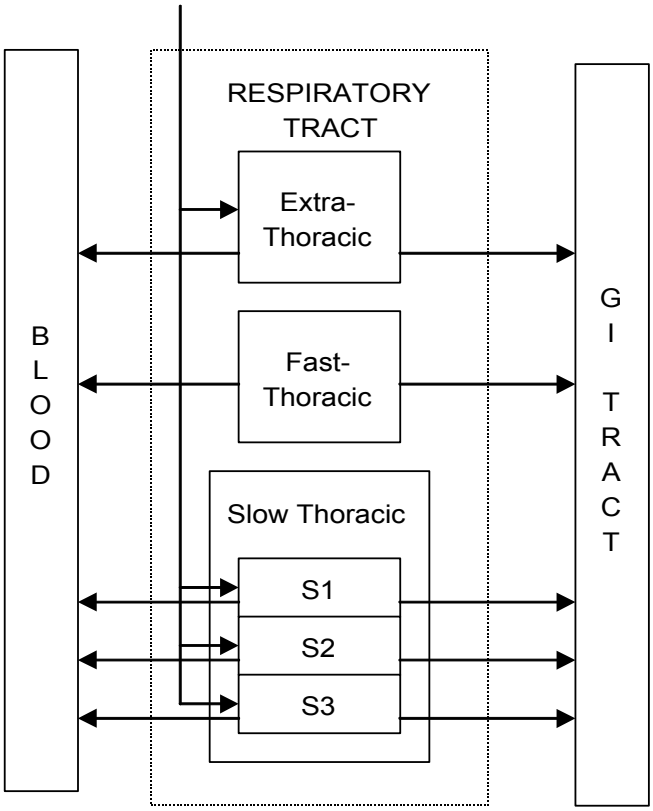
A biokinetic model for radionuclide-contaminated wounds is under development by a scientific committee established jointly by the U.S. National Council on Radiation Protection (USNCRP) and ICRP, a draft of which was recently published (Guilmette and Durbin 2003).

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Inhaled particulate aerosols of americium will be deposited in the respiratory tract. Amounts and patterns of deposition of particulates in the respiratory tract are affected by the size of the inhaled particles, age-related factors, breathing route (e.g., nose breathing versus mouth breathing), airway geometry, and airstream velocity within the respiratory tract (ICRP 1994b; James et al. 1994; Roy et al. 1994). In general, large particles (>2.5 μm) preferentially deposit in the nasopharyngeal region where high airstream velocities and airway geometry facilitate inertial impaction (Chan and Lippman 1980; James et al. 1994). In the tracheobronchial and alveolar regions, where airstream velocities are lower, processes such as sedimentation and interception become important for deposition of smaller particles (<2.4 μm). Airflow velocity and airway geometry change with age, giving rise to age-related differences in particle deposition (James 1978; James et al. 1994; Phalen et al. 1985). Anatomical features, as well as their use (nose versus mouth breathing), also affect the intake route (nose or mouth). Deposition in the various regions of the respiratory tract in children may be higher or lower than in adults depending on particle size; for submicron particles, fractional deposition in 2-year-old children has been estimated to be 1.5 times greater than in adults (Xu and Yu 1986). Absorption of deposited americium is

Figure 3-8. Leggett (1992) Model of Deposition and Retention of Americium in the Human Respiratory Tract



		AmO_2		Other americium	
Pool	To	Half-time	f	Half-time	f
Extra-thoracic	Blood	–	0.0	0.4 days	0.05
	Gastrointestinal tract	0.4 days	1.0	0.4 days	0.95
Fast thoracic	Blood	–	0.0	0.2 days	0.25
	Gastrointestinal tract	0.2 days	1.0	0.2 days	0.75
Slow thoracic					
S_1		(80%)		(45%)	
	Blood	11 days	0.90	15 hours	0.80
	Gastrointestinal tract	11 days	0.10	15 hours	0.20
S_2		(17%)		(45%)	
	Blood	0.5 years	0.0	25 days	0.80
	Gastrointestinal tract	0.5 years	1.0	25 days	0.20
S_3		(3%)		(10%)	
	Blood	3 years	0.20	500 days	0.20
	Gastrointestinal tract	3 years	0.80	500 days	0.80

GI = gastrointestinal tract

influenced by particle size and solubility as well as the pattern of regional deposition within the respiratory tract. Larger particles (>2.5 μm) that are primarily deposited in the ciliated airways (nasopharyngeal and tracheobronchial regions) can be transferred by mucociliary transport into the esophagus and swallowed. Particles deposited in the alveolar region can be absorbed after extracellular dissolution or ingestion by phagocytic cells. Americium-bearing pulmonary alveolar macrophages (PAMs) can either migrate to the airways where mucociliary transport to the esophagus can occur or to tracheobronchial lymph nodes (Taya and Mewhinney 1992; Taya et al. 1986, 1992). The relative contributions of these two pathways to americium absorption have not been quantified. Studies in dogs and monkeys have shown that americium is present in tracheobronchial lymph nodes within days after inhalation of americium dioxide (Mewhinney et al. 1982; Stanley et al. 1982; Thomas et al. 1972). PAMs isolated from dogs, monkeys, and rats demonstrated the presence of phagocytosed and dissolved americium dioxide particles (Taya et al. 1992).

The site and mechanism of absorption of ingested americium are not known. Based on studies of plutonium, it is likely that americium absorption occurs, at least to some extent, in the small intestine. Studies of the absorption of plutonium in preparations of *in situ* isolated segments of small intestine of immature miniature swine indicate that absorption of actinides can occur along the entire small intestine, with the highest rates of absorption occurring in the duodenum (Sullivan and Gorham 1982).

Distribution. Once americium is in systemic circulation, the route of exposure is not expected to affect its distribution. The mechanisms by which americium is taken up and retained in bone are only partially understood. The distribution of americium in bone initially is confined to bone surfaces, including endosteal and periosteal surfaces, and adjacent to vascular canals in cortical bone (Polig 1976; Priest et al. 1983, 1995; Schlenker et al. 1989). Deposition appears to be favored at sites of active bone resorption, and concentrations are highest in trabecular bone where there is a high surface to volume ratio (Kathren et al. 1987; Priest et al. 1983). Surface deposits can eventually appear in somewhat deeper regions of bone as a result of accretion of new bone and burial of older surface deposits (Polig 1976; Priest et al. 1983). The observation that americium does not distribute more uniformly in bone has been taken as evidence that it does not exchange readily with calcium or other minerals in the bone mineral matrix and that the initial interactions with bone may be with organic components of bone (Bruenger et al. 1973; Priest et al. 1983); however, experimental evidence for this is equivocal. While americium has been shown to bind to the glycoprotein fraction of bovine cortical bone, even in the presence of an excess mass of bone mineral (Chipperfield and Taylor 1972), it also binds to bone mineral and bone calcium hydroxyapatite (Guilmette et al. 1998).

The highest concentrations of americium in soft tissues occur in the liver (Filipy and Kathren 1996). The mechanisms of accumulation and retention of americium in liver have not been characterized. In rats and hamsters, americium appears to initially and extensively associate with lysosomes (Gruner et al. 1981; Seidel et al. 1986; Sütterlin et al. 1984). Agents that disrupt microtubules and lysosome formation and processing, such as colchicine and vinblastine, have been shown to decrease liver uptake of americium in rats (Seidel 1984, 1985). The effect is thought to involve disruption of hepatic microtubule formation, which is critical to the formation and intracellular processing of lysosomes, the initial site of accumulation of americium in the liver. The major bound form of americium in dog liver cytosol was shown to be a ferritin complex (Stover et al. 1970). Substantial species differences in liver retention of americium have been observed. Most notable is the Chinese hamster for which liver retention half-times of 3,400 days have been estimated, compared to 5–16 days in rat liver (Durbin 1973; McKay et al. 1972). Elimination of americium from liver is relatively slow in dogs (1–10 years) compared with rats and mice (Durbin 1973; Lindenbaum and Rosenthal 1972). Mechanisms involved in the species differences in retention of americium in the liver have not been elucidated, although it has been proposed that animals with shorter retention times might be capable of excreting lysosomes in the bile (Sütterlin et al. 1984). The relatively slow elimination of americium from the hamster liver does not appear to be related to the initial tissue distribution, as the degree of association of americium with the lysosomal fraction of livers from rats and hamsters is similar (Sütterlin et al. 1984).

The placental transfer of ^{241}Am to the fetus has been studied in several animal models and in the *in situ* perfused guinea pig placenta (Sikov 1987). After injections of ^{241}Am in mice and rats, a small fraction (<0.1%) of the maternal dose is transferred to the fetus (Hisamatsu and Takizawa 1983; Sikov 1987; Stather et al. 1992; Van Den Heuvel 1992; Weiss et al. 1980). Placental concentrations generally exceed those of the fetus, and concentrations in the embryo/fetal membranes are higher than in the fetus (Sikov 1987). Mechanisms of transport across the placenta have not been elucidated.

Metabolism. As noted in Section 3.4.3, the metabolism of americium consists of binding interactions with proteins and probably complex formation with various inorganic anions, such as carbonate and phosphate, and carboxylic acids, such as citrate and lactate (Durbin 1973; Taylor 1973; Webb et al. 1998). Experiments have not been conducted to determine whether americium binds to metallothionein, but such binding is not likely.

Excretion. Although fecal excretion appears to be a major route of excretion of absorbed americium, the mechanisms by which americium is transferred to feces have not been characterized in humans. Injection studies in animals suggest a contribution of biliary excretion to the fecal excretion of absorbed americium (Durbin 1973). Similarly, the mechanisms by which americium is excreted in urine have not been elucidated. Renal plasma clearance has been measured in rats, dogs, and monkeys; in all three species, the renal clearance was <10% of the glomerular filtration rate (Durbin 1973; Lloyd et al. 1970; Taylor et al. 1961; Turner and Taylor 1968). However, simultaneous measurements of the renal plasma clearance of ultrafilterable americium and glomerular filtration rate are not available; thus, the relative contributions of filtration, tubular secretion, and tubular reabsorption to urinary excretion of americium cannot be ascertained with the available information. Studies of human urine incubated with ^{241}Am or urine collected from rats that were exposed to americium indicate that the major form of americium in urine appears to be a low molecular weight complex (1,000–10,000 daltons) with citrate (Stradling et al. 1976). This would be consistent with citrate complexes occurring in plasma from which they could enter the urine by glomerular filtration.

3.5.2 Mechanisms of Toxicity

Americium toxicity results primarily from the damage done by the alpha particle emitted during radioactive decay. This alpha particle has very limited penetration in tissue, and hence, the cellular damage (including damage to genomic material) occurs only in the immediate vicinity of the sequestered americium. Alpha particles deposit all of their energy in a short distance of travel. The large charge and mass of the alpha particle account for the strong interaction with surrounding cells. The transferred energy ionizes localized cell matter in its path directly and via hydrolysis of water (approximately 70%) in human cells. Radiation interaction with water produces ionized and excited water molecules referred to as radiolysis products. These reactive water species have sufficiently long half-times that they can diffuse away from the interaction site and interact with biological molecules, which can increase the resulting cellular damage. Thus, cellular damage can result both directly from radiation itself and indirectly from the chemical reactions involving reactive species of radiolysis products.

3.5.3 Animal-to-Human Extrapolations

Significant interspecies differences are apparent regarding liver retention rates of absorbed americium (Durbin 1973; Griffith et al. 1983) (see Sections 3.4.2.4 and 3.5.1 for more detailed information).

Interspecies differences are also apparent in skeletal distribution of absorbed americium (Lynch et al. 1989). However, no data were located to indicate significant interspecies differences in health effects associated with exposure to americium.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by 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 1997a). 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 in humans or animals resulting from exposure to americium.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

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

Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

No studies were located in which comparisons were made between the sensitivity of children and adults to the toxicity of americium. Some studies indicate that radiation effects may be greater per unit dose in children than in adults. However, study of bone cancer induction from injected ^{239}Pu or ^{226}Ra in dogs suggests that, on a per Gy basis, dogs exposed at 3 months of age were less sensitive than dogs exposed at 1.5 years of age (Lloyd et al. 1999). Both plutonium and radium are alpha-emitters that accumulate in bone, as does americium. No direct evidence was located to indicate that the pharmacokinetics of americium in children may be different from that in adults. Based on dosimetric considerations related to differences in the parameters of available models, as well as studies in animals, it seems likely that children may be more susceptible to americium toxicity than adults by virtue of age-related differences in pharmacokinetics or radiosensitivity. Therefore, a potential for increased risk of effects to the bones of children is attributed to the uptake and long-term biological storage of ^{241}Am in the bone during critical periods of growth, which may result in genetic damage and an increased risk for cancer. Differences in airway geometry and airflow rates between children and adults would be expected to result in higher fractional deposition of inhaled submicron particles in children than in adults (Xu and Yu 1986) (see Section 3.5.1). Thus, children who are exposed to americium aerosols may receive a higher dose to the lung and greater absorption than would similarly exposed adults (ICRP 1995).

Studies of experimental animals indicate that absorption of ingested americium may be as much as 200 times greater in neonates than in adults (Bomford and Harrison 1986; David and Harrison 1984;

Sullivan et al. 1985) (see Section 3.4.1.2 and Table 3-2). Thus, infants exposed to levels of americium in food or water similar as adults, or who ingest similar amounts of americium subsequent to an inhalation exposure, may absorb more americium and acquire a higher internal burden of americium. The ICRP (1989, 1994b, 1995) assumes age-related differences in intestinal absorption of americium swallowed following clearance from the lungs. The fractional absorption value employed for a 3-month-old infant is a factor of 10 higher than for an adult.

Absorption of americium is greater in iron-deficient animals than in iron-replete adult animals (Sullivan and Ruemmler 1988; Sullivan et al. 1986) (see Section 3.4.1.2). Concurrent oral exposure to Fe^{3+} and americium also appears to increase the absorption of ingested americium; the latter effect may result from redox reactions in the gastrointestinal tract catalyzed by Fe^{3+} (Sullivan et al. 1986). These differences are accounted for in the discussions and dosimetric/metabolic models of the ICRP (1989, 1993) and the NEA (1988).

As inherent in these ICRP (1989, 1993) models, deposition of americium in bone occurs predominantly at bone surfaces that are actively undergoing resorption; therefore, exchanges between bone and soft tissue stores of americium would be expected to be more rapid during periods of active bone metabolism such as infancy and childhood, pregnancy, and menopause. Higher skeletal accumulation of americium has been observed in neonatal animals that received americium intravenously than in similarly exposed adult animals (Hollins et al. 1973; Schoeters et al. 1990; Stevens et al. 1977) and in young rats (3 months of age) compared to old rats (13 months of age) (Sontag 1983). This suggests the possibility that infants and children may accumulate higher concentrations of americium in bone than similarly exposed adults. On the other hand, americium uptake into maternal bone of lactating rats was similar to that of nonlactating rats, while concurrent calcium uptake into bone was lower in lactating rats (Hollins and Durakovic 1972). Thus, active mobilization of bone mineral, *per se*, may not always promote release of americium from bone (see Section 3.4.2.1). Studies of other bone-seeking radionuclides indicate that vulnerability may be higher in adolescence and early adulthood than during earlier development or later adulthood (Carnes et al. 1997; Lloyd et al. 1999).

Information on the transplacental transfer of americium in humans is not available directly, but the information from experiments with americium and other actinides has been used to derive biokinetic models and perform dosimetric models for the human (NCRP 1998; Sikov and Kelman 1989; USNRC 1996). Studies in animals that received parenteral injections of americium have shown that absorbed americium is partially transferred to the fetus (Hisamatsu and Takizawa 1983; Paquet et al. 1998; Sasser

et al. 1986; Schoeters et al. 1990; Weiss et al. 1980) (see Section 3.4.2.1). Limited reports indicate that relatively large doses of ^{241}Am may induce fetal death and teratogenic effects in rodents (Moskalev et al. 1969; Rommerein and Sikov 1986).

Information on the distribution of absorbed americium to mammary milk in humans is not available; however, maternal (oral or intravenous) exposures of animals, including cows and goats, have shown that transfer to milk occurs and that neonates can be exposed to americium during lactation (McClellan et al. 1962; Sasser et al. 1986; Sutton et al. 1979) (see Section 3.4.2.1). Thus, it is possible that children who breast feed from mothers who have been exposed to americium, or who ingest milk from cows or other livestock that have been exposed to americium, may also be exposed to americium.

Bone serves as a long-term reservoir of americium in the body. The kinetics of bone formation and remodeling appear to be important factors in the overall biokinetics of americium in experimental animals (ICRP 1989, 1993). Quantitative evidence for their effects in humans has not been characterized, but exchanges between bone and soft tissue stores of americium would be expected to be more rapid during periods of active bone metabolism such as infancy and childhood, pregnancy, and menopause (see Section 3.4.2.1). Thus, it is possible that, in humans, some of the maternal bone americium stores may be transferred to the fetus during gestation and may be incorporated into fetal bone during the development of the fetal skeleton. However, the finding of similar americium uptake in maternal bone of lactating and nonlactating rats (Hollins and Durakovic 1972) may be an indication that active bone metabolism is not necessarily a major source of americium release from bone at this maternal stage.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

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., biological 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 americium are discussed in Section 3.8.1.

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 americium are discussed in Section 3.8.2.

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 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Americium

Biomarkers or tests to identify or quantify exposure to americium are available only at a limited number of government or nuclear facilities, or through contractors engaged in this type work. Americium is a radioactive element. Internalized americium can be quantified through the use of *in vivo* radiation counters that measure the gamma emissions specific to each isotope of americium (Graham and Kirkman 1983; Palmer and Rhoads 1989; Palmer et al. 1983). Americium within the body can be inferred from radioassays of urine, feces, or tissue samples by gross alpha analysis, alpha spectroscopy, gamma-ray

spectroscopy, mass spectrometry, and liquid scintillation techniques (Alvarez and Navarro 1996; Dacheux and Aupiais 1997; DOE 1997b; Guilmette 1986; McInroy et al. 1985). Americium radioactivity can be measured in the teeth of rats, where it accumulates in the dental pulp of developing teeth and eventually is incorporated into the mineralized dentin (Hammerström and Nilsson 1970b), so it may be feasible to analyze human teeth for americium.

3.8.2 Biomarkers Used to Characterize Effects Caused by Americium

Although a sufficiently high dose of americium may produce chromosomal aberrations in lymphocytes (Bauchinger et al. 1997; Kelly and Dagle 1974), these effects are not specific to americium or to ionizing radiation in general.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Ethanol may enhance the fecal excretion of absorbed americium. In baboons that received repeated oral doses of ethanol (1 mL ethanol/kg body weight), 3–6 months after receiving americium citrate intravenously, fecal excretion was approximately 2.5 times that of baboons that received water in place of the ethanol dose (Cohen et al. 1978). Long-term ethanol consumption accelerated the elimination of americium from the livers of beagle dogs that had been administered single intravenous injections of ^{241}Am (Taylor et al. 1992). The risk of americium-induced liver tumors, however, was 2–3 times higher in the ethanol-treated dogs than in similarly ^{241}Am-injected dogs not consuming ethanol.

Colchicine (a drug used in treatment of gout) and vinblastine (a cancer chemotherapy agent) may decrease liver uptake of americium. In rats that received an intraperitoneal injection of either colchicine and vinblastine prior to an intravenous or intramuscular injection of americium citrate, liver uptake of americium was lower, relative to controls, and kidney and skeletal americium uptakes were higher (Seidel 1984, 1985). The effect is thought to involve disruption of hepatic microtubule formation, which is critical to the formation and intracellular processing of lysosomes, the initial site of accumulation of americium in the liver.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to americium than will most persons exposed to the same level of americium 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 ^{241}Am, or compromised function of organs affected by ^{241}Am. Populations who are at greater risk due to their unusually high exposure to ^{241}Am are discussed in Section 6.7, Populations With Potentially High Exposures.

As discussed in Section 3.7, theoretical pharmacokinetics consideration suggests that children may be at greater risk from the effects of exposure to americium. Furthermore, some studies indicate that children may be more susceptible than adults to radiation-induced adverse effects. A study of bone cancer induction from injected ^{239}Pu or ^{226}Ra in dogs suggests that, on a per Gy basis, dogs exposed as young adults (1.5 years of age) were more susceptible than either juveniles exposed at 3 months of age or older adults (5 years of age) (Lloyd et al. 1999). Both plutonium and radium are alpha-emitters that accumulate in bone, as does alpha-emitting americium.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Medical toxicology: Diagnosis and Treatment of Human Poisoning. 2nd Baltimore (Williams & Wilkins), 1682-1723.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical Management of Poisoning and Drug Overdose. 3rd edition. Philadelphia (W.B. Saunders), 413-425.

Viccellio P, ed. 1998. Emergency Toxicology. 2nd edition. Philadelphia (Lippincott-Raven), 991-996.

3.11.1 Reducing Peak Absorption Following Exposure

Topical applications of saline containing DTPA, tartaric acid, or citric acid (e.g., Schubert's solution) have been used to remove americium from the skin and wounds after accidental dermal exposures (Breitenstein 1983). These agents form stable, water-soluble complexes with americium. Based on experiments with laboratory animals, it appears that aerosols of DTPA may reduce the absorption of soluble forms of inhaled americium compounds (Stradling et al. 2000). Postexposure treatments that are effective in reducing toxic effects of radionuclides such as americium typically concentrate on decorporation (removal of americium from the body following absorption) and are discussed in Section 3.11.2.

3.11.2 Reducing Body Burden

Calcium or zinc complexes of polycarboxylate compounds such as DTPA or ethylenediaminetetratacetic acid (EDTA) have been used as chelating agents to accelerate the urinary excretion of americium in humans who were accidentally exposed to americium (Breitenstein 1983; Doerfel and Oliveira 1989; Durbin 1973; Fasiska et al. 1971). Extended chelation therapy was considered to have been a primary factor in the long-term survival of a man who had been accidentally exposed to a massive amount of ^{241}Am (Breitenstein and Palmer 1989; Filipy et al. 1995; Toohey and Kathren 1995). Immediate and continued DTPA treatment of rats that had been exposed to $^{241}AmO_2$ by inhalation resulted in the near-total blockage of ^{241}Am translocation to liver and bone (Guilmette et al. 1988). Continuous subcutaneous infusion of DTPA was more effective in blocking the uptake than were periodic intravenous injections. Dogs receiving DTPA treatments following single intravenous injections of ^{241}Am at activity levels of approximately 11 kBq/kg (297 nCi/kg) exhibited greater longevity and lower rates of bone cancer than ^{241}Am-treated dogs not given subsequent DTPA treatment (Lloyd et al. 1998). DTPA and EDTA form relatively stable complexes with americium in the extracellular fluid that can be excreted in the urine (Durbin 1973; Taylor 1973). The calcium and zinc complexes are used to decrease the risk of calcium and zinc depletion. Both DTPA and EDTA appear to affect primarily the americium in soft tissues, which exchanges more rapidly with americium in plasma than does americium in bone. As a result, treatments with DTPA or EDTA may have only a marginal effect on bone americium levels (Durbin 1973). In a study in rats, DTPA treatment, administered beginning 1.5 hours following intravenously administered ^{241}Am citrate, decreased bone ^{241}Am levels in trabecular bone at locations where bone resorption and remodeling occurred, but had little effect on americium levels in cortical bone (Polig

1976). This effect may have resulted from accelerated excretion and, therefore, diminished redeposition of americium released during bone resorption.

Hydroxypyridonate ligands such as octadentate 3,4,3-LI(1,2-HOPO) and hexadentate TREN-Me-3,2-HOPO) have been shown to be highly effective chelating agents in laboratory animals (Durbin et al. 1994; Stradling et al. 2000). Recent *in vitro* studies have indicated that octadentate 3,4,3-LI(1,2-HOPO) may be effective in decorporation of americium from bone tissues (Guilmette et al. 2003).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

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

3.12 ADEQUACY OF THE DATABASE

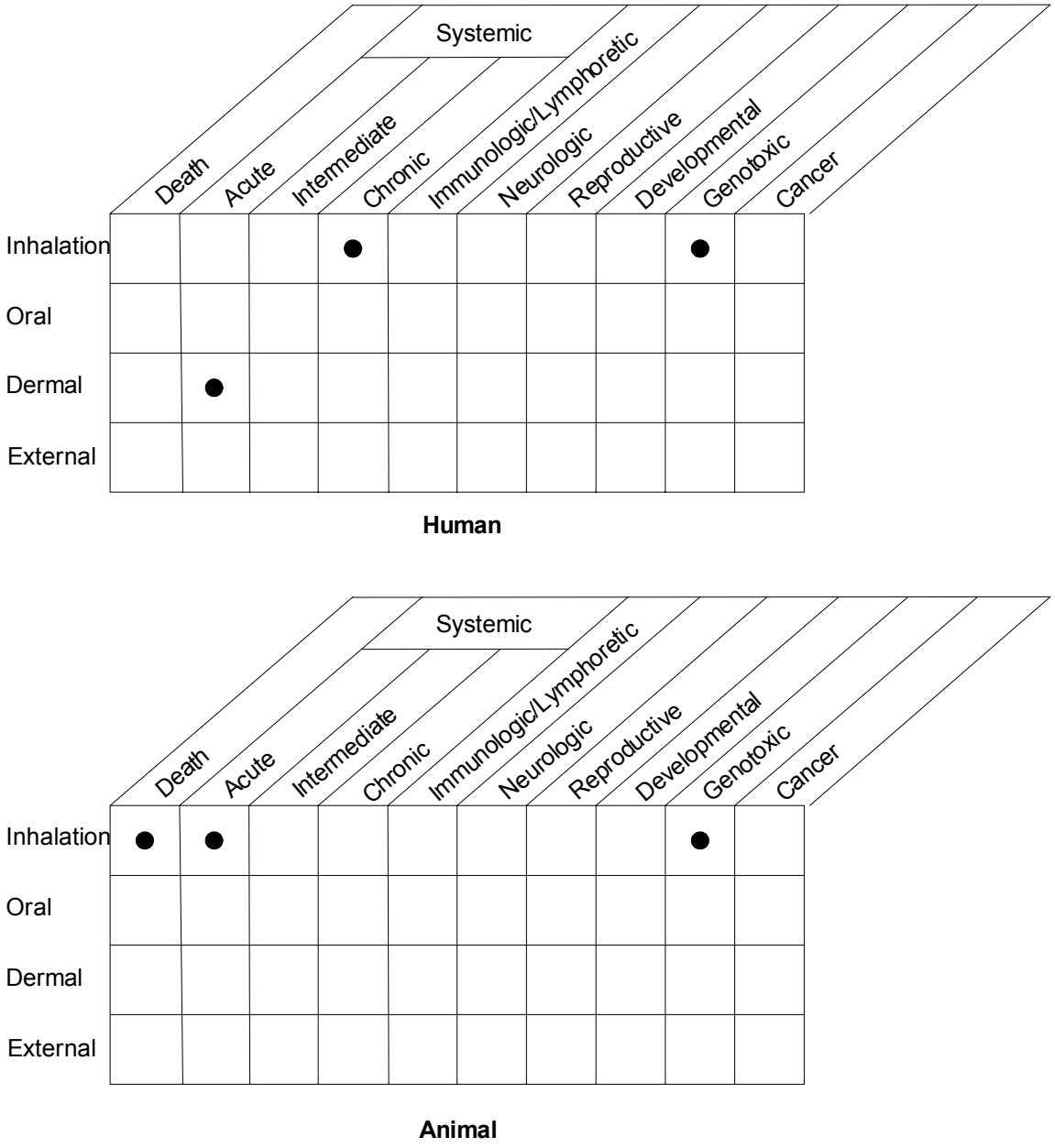
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of americium is available. Where adequate information is not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

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

3.12.1 Existing Information on Health Effects of Americium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to americium are summarized in Figure 3-9. The purpose of this figure is to illustrate the existing

Figure 3-9. Existing Information on Health Effects of Americium



● Existing Studies

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

Information regarding health effects following exposure to americium is mainly limited to reports of acute exposure. Accidental occupational overexposure of a 64-year-old man resulted in signs of hematological and bone marrow damage. Animal studies indicate that overexposure to americium can result in compromised hematological and immunological systems, as well as degenerative changes in the bone, liver, kidneys, and thyroid, and bone and liver cancer in long-term surviving animals. Although most studies employed parenteral injection as the route of exposure, available inhalation data indicate similarity in targets of toxicity. Data regarding health effects related to oral or dermal exposure are lacking for both humans and animals. Levels of radioactivity from americium employed in animal studies are much higher than those likely to be environmentally experienced by humans. Therefore, americium does not likely pose an immediate health concern to humans.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Human data regarding acute adverse health effects resulting from exposure to americium are limited to the accidental occupational overexposure (inhalation, dermal, subcutaneous) of a 64-year-old man in whom possible hematological and bone marrow changes may have been elicited (Filipy et al. 1995; Priest et al. 1995). Overexposure of animals to americium by the inhalation exposure route resulted in compromised respiratory function and radiation pneumonitis (Buldakov et al. 1972; DOE 1978; Thomas et al. 1972), persistent depressed blood values (Buldakov et al. 1972; Thomas et al. 1972), degenerative changes in bone, liver and kidney lesions, and gross atrophy and fibrosis of the thyroid gland (Thomas et al. 1972). Following acute inhalation exposure to americium, 4 of 15 dogs surviving more than 1,000 days developed osteosarcomas (Gillett et al. 1985). With the exception of the respiratory effects following inhalation exposure, the other targets of toxicity were likewise identified in animals administered single parenteral injections of americium at relatively

high levels of radioactivity (Carter et al. 1951; Dougherty 1970; Jee et al. 1985; Lloyd et al. 1970, 1994a, 1994b; Schoeters et al. 1991; Taylor et al. 1983, 1991, 1993a; Van Den Heuvel et al. 1995). Acute-duration inhalation and oral MRLs were not derived for radioactive americium due to a lack of human or animal data. To generate appropriate data for deriving acute-duration inhalation and oral MRLs for radioactive americium, 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, since americium is not found naturally, and is produced and used in small quantities, the risk of overexposure to americium in humans should be low. Thus, additional studies may not be presently needed.

Intermediate-Duration Exposure. A single report indicated the potential for cytogenetic damage in a radiation worker and his family members following exposure to an americium source used by the father for private experiments at home for several years. No additional human or animal data were located. Intermediate-duration inhalation and oral MRLs were not derived for americium due to the lack of human or animal data. To generate appropriate data for deriving intermediate-duration inhalation and oral MRLs for americium, 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. However, since americium is not found naturally, and is produced and used in small quantities, the risk of overexposure to americium in humans should be low. Thus, additional studies may not be presently needed.

Chronic-Duration Exposure and Cancer. No data were located regarding chronic-duration exposure of humans or animals to americium. Chronic-duration inhalation and oral MRLs were not derived for americium due to the lack of human or animal data. To generate appropriate data for deriving chronic-duration inhalation and oral MRLs for americium, at least one comprehensive chronic-duration inhalation and one chronic-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. However, since americium is not found naturally, and is produced and used in small quantities, the risk of overexposure to americium in humans should be low. Thus, additional studies may not be presently needed.

Genotoxicity. Chromosomal aberrations have been reported in lymphocytes following exposure to ^{241}Am (Bauchinger et al. 1997; Kelly and Dagle 1974). A single animal study reported increased

numbers of micronucleated and multinucleated pulmonary alveolar macrophages in lung lavage of mice that had been exposed to ^{241}Am by inhalation (Talbot et al. 1989). External and internal exposure to radioactivity is a genotoxicity concern. External exposure to gamma-emitting americium would be expected to result in genotoxic effects similar to those observed following external exposure to any other gamma-emitting radionuclide (see ATSDR 1999 for more information on ionizing radiation). Internalized americium could cause damage to nearby cellular components that might be encountered by high energy alpha particles emitted from americium. Additional genotoxicity studies could be designed to assess the potential for genotoxicity from internalized americium, with special emphasis on blood-forming cells.

Reproductive Toxicity. No reports were located regarding reproductive effects in humans or animals following inhalation, oral, or dermal exposure to americium. In a limited study, increased incidences of fetal death were observed following single intravenous injections of ^{241}Am, administered to female rats prior to mating (Moskalev et al. 1969). Concentrations of ^{241}Am were much higher in placental tissues than in fetuses, and the investigators indicated that death may have been the result of placental changes. Animal studies could be designed to assess the potential for the reproductive toxicity of americium.

Developmental Toxicity. Data concerning developmental effects related to exposure to americium are restricted to a single report of decreased fetal weight, increased fetal death, and a tendency toward increased incidences of fetuses with anomalous ribs following exposure of pregnant rats with single intravenous injections of ^{241}Am (Rommerein and Sikov 1986). Animal studies could be designed to further assess the potential for the developmental toxicity of americium.

Immunotoxicity. Information regarding the immunotoxicity of americium is limited to a report of lymphopenia in a man following accidental overexposure when a glass column containing ^{241}Am blew up in his face (Filipy et al. 1995) and reports of depressed white blood cell counts in dogs exposed to ^{241}Am by inhalation (Buldakov et al. 1972; Thomas et al. 1972) or intravenous injection (Dougherty 1970). Additional animal studies could be designed to assess dose-response relationships.

Neurotoxicity. No data were located regarding neurotoxicity in humans or animals following exposure to americium. Neurotoxic effects, noted in humans suffering from acute radiation syndrome due to ionizing radiation exposure, are well-characterized (see ATSDR 1999 for detailed information on the effects of ionizing radiation). External overexposure to any gamma-emitting source could result in

neurotoxic effects. However, it is extremely unlikely that an americium source capable of producing such an overexposure would be encountered. Studies concerning the potential of americium to induce neurotoxicity do not appear to be needed at present.

Epidemiological and Human Dosimetry Studies. Epidemiological studies of radiation dose typically involve estimates of exposure that are based on whole-body measurements of internally-deposited americium. 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 americium; in particular, for cases of known internal exposure.

Biomarkers of Exposure and Effect.

Exposure. Americium may be detected during *in vivo* counting as well as in samples of urine, blood, feces, or body tissues. Due to the relatively long biological half-time of americium in skeleton, short-term exposures cannot be readily distinguished from longer-term ones. An increased understanding of the biokinetics and health effects of internalized americium can be achieved through continued monitoring of individuals following known overexposure to americium.

Effect. Chromosomal aberrations have been reported in lymphocytes following exposure to ^{241}Am (Bauchinger et al. 1997; Kelly and Dagle 1974). Additionally, high radiation doses from internally deposited americium can cause bone marrow changes and altered blood values (Filipy et al. 1995; Priest et al. 1995). However, none of these effects are specific to americium.

Absorption, Distribution, Metabolism, and Excretion. Inhaled americium can be absorbed and transferred to the blood (Edvardsson and Lindgren 1976; Fry 1976; Newton et al. 1983; Sanders 1974; Toohey and Essling 1980). Limited information indicates that americium is rather poorly absorbed via the gastrointestinal tract (Hunt 1998; Hunt et al. 1986a, 1986b). Once americium reaches the blood, it is distributed throughout the body, accumulating mainly in the skeleton, liver, and muscle (Filipy and Kathren 1996; Filipy et al. 1994; Kathren et al. 1988; McInroy et al. 1989). Animal studies indicate that americium can pass through the placental barrier of a pregnant mother to a developing fetus (DOE 1986; Hisamatsu and Takizawa 1983; Paquet et al. 1998; Sasser et al. 1986; Schoeters et al. 1990; Sikov 1987; Van Den Heuvel et al. 1992; Weiss et al. 1980), and also can be distributed to the breast milk of lactating mothers (McClellan et al. 1962; Sasser et al. 1986; Sutton et al. 1979). The metabolism of americium consists of binding interactions with proteins and probably complex formation with various inorganic anions, such as carbonate and phosphate, and carboxylic acids, such as citrate and lactate (Durbin 1973;

Taylor 1973; Webb et al. 1998). Americium is slowly eliminated from soft tissues and bone, but may remain in the skeleton for much longer periods. Once absorbed into the general circulation, americium is excreted in both feces and urine (Cohen and Wrenn 1973; Durbin 1973; Guilmette et al. 1980; Stather et al. 1979a). Additional quantitative toxicokinetic studies could be designed to further assess absorption following inhalation, oral, and dermal exposure, as well as age-related differences in the toxicokinetics of americium. However, the predominant data need for americium, and other sources of internal radiation exposure, is the validation (through biokinetic studies) and refinement of the models that describe internal distribution from which the radiation dose derives.

Comparative Toxicokinetics. Toxicokinetic properties of americium are generally similar in humans and animals. Inhaled americium, in relatively soluble forms, is readily absorbed in the respiratory system of humans and animals. Ingested americium is not absorbed to any great extent in humans or animals. Distribution patterns are generally similar; americium is found in highest concentrations in the skeleton, liver, and muscle of humans and animals. Although studies were not located regarding transfer of americium from mother to developing fetus, studies in animals suggest that americium could be incorporated by a fetus following inhalation exposure of the pregnant mother.

Methods for Reducing Toxic Effects. Topical applications of saline containing DTPA, tartaric acid, or citric acid (e.g., Schubert's solution) have been used to remove americium from the skin and wounds after accidental dermal exposures. These agents form stable, water soluble complexes with americium. Calcium or zinc complexes of DTPA have been used as chelating agents to accelerate the urinary excretion of americium. Hydroxypyridonate ligands such as octadentate 3,4,3-LI(1,2-HOPO) and hexadentate TREN-Me-3,2-HOPO) have been shown to be highly effective chelating agents in laboratory animals (Durbin et al. 1994; Stradling et al. 2000). Recent *in vitro* studies have indicated that octadentate 3,4,3-LI(1,2-HOPO) may be effective in decorporation of americium from bone tissues (Guilmette et al. 2000).

Children's Susceptibility. Some studies suggest that children, especially neonates, may be more susceptible than adults to radiation-induced adverse effects.. However, animal studies indicate that juvenile dogs are less susceptible than adults to americium-induced bone cancer (Lloyd et al. 1999). No direct evidence was located to indicate that the pharmacokinetics of americium in children may be different from that in adults. Based on dosimetric considerations related to differences in the parameters of available models, as well as studies in animals, it seems likely that children may be more susceptible to the radiological effects of americium than are adults by virtue of age-related differences in

pharmacokinetics. Absorption of ingested americium may be as much as 200 times greater in neonatal animals than in adults (Bomford and Harrison 1986; David and Harrison 1984; Sullivan et al. 1985).

As inherent in ICRP (1989, 1993) models, deposition of americium in bone occurs predominantly at bone surfaces that are actively undergoing resorption; therefore, exchanges between bone and soft tissue stores of americium would be expected to be more rapid during periods of active bone metabolism such as infancy and childhood, pregnancy, and menopause. Higher skeletal accumulation of americium has been observed in neonatal animals that received americium intravenously than in similarly exposed adult animals (Hollins et al. 1973; Schoeters et al. 1990; Stevens et al. 1977) and in young rats (3 months of age) compared to old rats (13 months of age) (Sontag 1983). This suggests the possibility that infants and children may accumulate higher concentrations of americium in bone than similarly exposed adults. Studies of other bone-seeking radionuclides provide further support for increased vulnerability during periods of rapid bone growth such as adolescence (Carnes et al. 1997; Lloyd et al. 1999).

Information on the transplacental transfer of americium in humans is not available. Studies in animals that received parenteral injections of americium have shown that absorbed americium is transferred to the fetus (Hisamatsu and Takizawa 1983; Paquet et al. 1998; Sasser et al. 1986; Schoeters et al. 1990; Weiss et al. 1980).

Information on the distribution of absorbed americium to mammary milk in humans is not available; however, maternal (oral or intravenous) exposures of animals, including cows and goats, have shown that transfer to milk occurs and that neonates can be exposed to americium during lactation (McClellan et al. 1962; Sasser et al. 1986; Sutton et al. 1979).

Exchanges between bone and soft tissue stores of americium would be expected to be more rapid during periods of active bone metabolism such as infancy and childhood, pregnancy, and menopause. Thus, it is possible that, in humans, some of the maternal bone americium stores may be transferred to the fetus during gestation and may be incorporated into fetal bone during the development of the fetal skeleton.

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

3.12.3 Ongoing Studies

No ongoing studies examining adverse health effects in mammalian species exposed to americium were identified in the Federal Research in Progress database (FEDRIP 2004) or are currently listed by the Argonne National Laboratory (ANL) for the Department of Energy (DOE).