3. HEALTH EFFECTS

3.1 INTRODUCTION

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

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

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

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

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

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

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

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

3.2 DISCUSSION OF HEALTH EFFECTS OF PLUTONIUM BY ROUTE OF EXPOSURE

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

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

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

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

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

3.2.1 Inhalation Exposure

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

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

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

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

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

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

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

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

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

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

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

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

3.2.1.1 Death

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Studies in Animals.

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

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

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

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

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

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

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

3.2.1.2 Systemic Effects

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

Respiratory Effects.

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

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

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

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

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

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

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

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

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

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

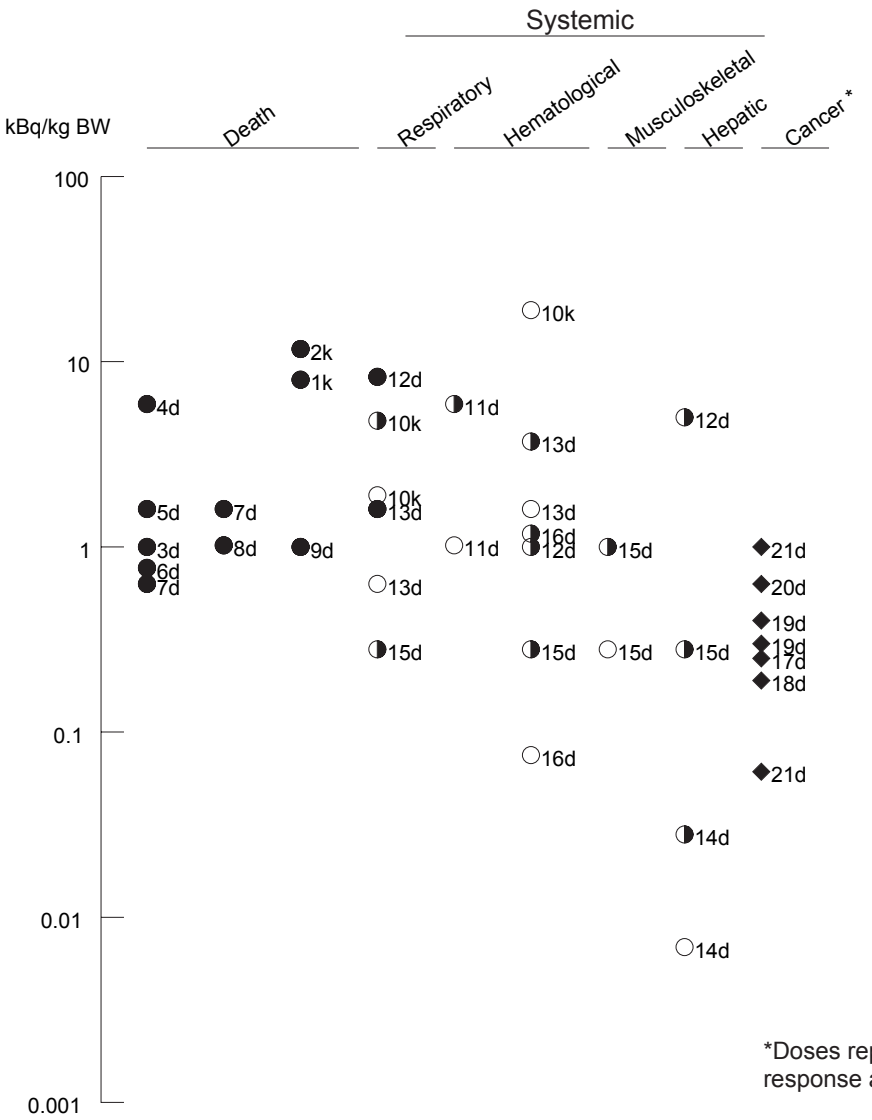
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (kBq/kg)	LOAEL			Reference Chemical Form	Comments
					Less Serious (kBq/kg)	Serious (kBq/kg)			
21	Dog (Beagle)	once 10-30 min				1	(CEL: bone tumors)	Park et al. 1997 238PuO2	Group mean ILB.
						0.061	(CEL: lung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

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

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

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

Acute (≤14 days)



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

c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

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

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

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

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

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

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

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

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

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

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

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

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

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

Cardiovascular Effects.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Musculoskeletal Effects.

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

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

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

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

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

Hepatic Effects.

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

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

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

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

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

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

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

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

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

Endocrine Effects.

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

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

3.2.1.3 Immunological and Lymphoreticular Effects

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

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

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

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

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

3.2.1.4 Neurological Effects

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

3.2.1.5 Reproductive Effects

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

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

3.2.1.6 Developmental Effects

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

3.2.1.7 Cancer

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.2.2 Oral Exposure

3.2.2.1 Death

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

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

3.2.2.2 Systemic Effects

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

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

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

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

3.2.2.3 Immunological and Lymphoreticular Effects

3.2.2.4 Neurological Effects

3.2.2.5 Reproductive Effects

3.2.2.6 Developmental Effects

3.2.2.7 Cancer

3.2.3 Dermal Exposure

3.2.3.1 Death

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

3.2.3.2 Systemic Effects

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

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

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

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

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

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

3.3 GENOTOXICITY

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

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

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

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

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

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

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

— = negative result; + = positive result

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

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

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

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

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

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

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

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

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

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

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

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

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

3.4 TOXICOKINETICS

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

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

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

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

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

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

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

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

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

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

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

3.4.1.2 Oral Exposure

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

excretion of $^{239+240}$Pu to that of the excretion predicted to occur if absorption had been complete. The latter was predicted using kinetic models of excretion of absorbed plutonium (Durbin 1972; Talbot et al. 1987, 1993). The reported mean absorption fraction was 1.7×10^{-4} (range: 0.2×10^{-4}–4.9×10^{-4}) for subjects who ingested winkles. The estimated mean absorption fraction for subjects who ingested cockles was 3.4×10^{-4} (range up to 7×10^{-4}) based on the kinetic model of Durbin (1972), which predicts approximately 1.1% of the body burden eliminated in 7 days, or 1.9×10^{-4} (range up to 3.9×10^{-4}), based on the kinetic model of Talbot et al. (1987, 1993), which predicts approximately 2% of the body burden eliminated in 7 days.

Gastrointestinal absorption was also measured in three adult male volunteers following ingestion of a plutonium citrate solution along with food (Popplewell et al. 1994). Based on comparisons between measured urinary plutonium excretion for 8 or 9 days postingestion and similar assessments following intravenous injection of plutonium citrate 6 months later, calculated fractional absorption of ingested plutonium ranged from 2×10^{-4} to 9×10^{-4}.

The gastrointestinal absorption fraction has also been estimated in human populations, based on analyses of inhalation and ingestion intakes, biological monitoring of plutonium excretion in urine or measurements of body burdens at autopsy. These estimates rely on model-based assumptions regarding the deposition of inhaled plutonium and the absorption fraction for plutonium deposited in the respiratory tract. Sun and Meinhold (1997) conducted an analysis of data on 34 residents of Rongelap Island who were exposed to plutonium fallout during and following the nuclear bomb detonations in the Marshall Islands. Based on measurements of urinary plutonium excretion and assumptions regarding the deposition and absorption of inhaled plutonium, the gastrointestinal absorption fraction (for diet and soil, combined) was estimated to be approximately 4.2×10^{-4} (range: 1.7×10^{-4}–7.1×10^{-4}). Mussalo-Rauhamaa et al. (1984) conducted an analysis of plutonium body burdens in Finnish Lapps and, along with estimates of inhalation and dietary intake of plutonium (primarily from consumption of reindeer), and assumptions regarding elimination rate of plutonium, estimated the gastrointestinal absorption fraction to range from approximately 8×10^{-4} to 9×10^{-4}.

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

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

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

3.4.1.3 Dermal Exposure

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

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

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

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

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

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

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

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

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

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

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

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

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

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

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

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

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

3.4.2.2 Oral Exposure

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

3.4.2.3 Dermal Exposure

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

3.4.2.4 Other Routes of Exposure

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

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

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

3.4.3 Metabolism

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

3.4.4 Elimination and Excretion

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

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

3.4.4.1 Inhalation Exposure

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

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

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

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

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

3.4.4.2 Oral Exposure

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

3.4.4.3 Dermal Exposure

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

3.4.4.4 Other Routes of Exposure

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

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

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

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

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

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

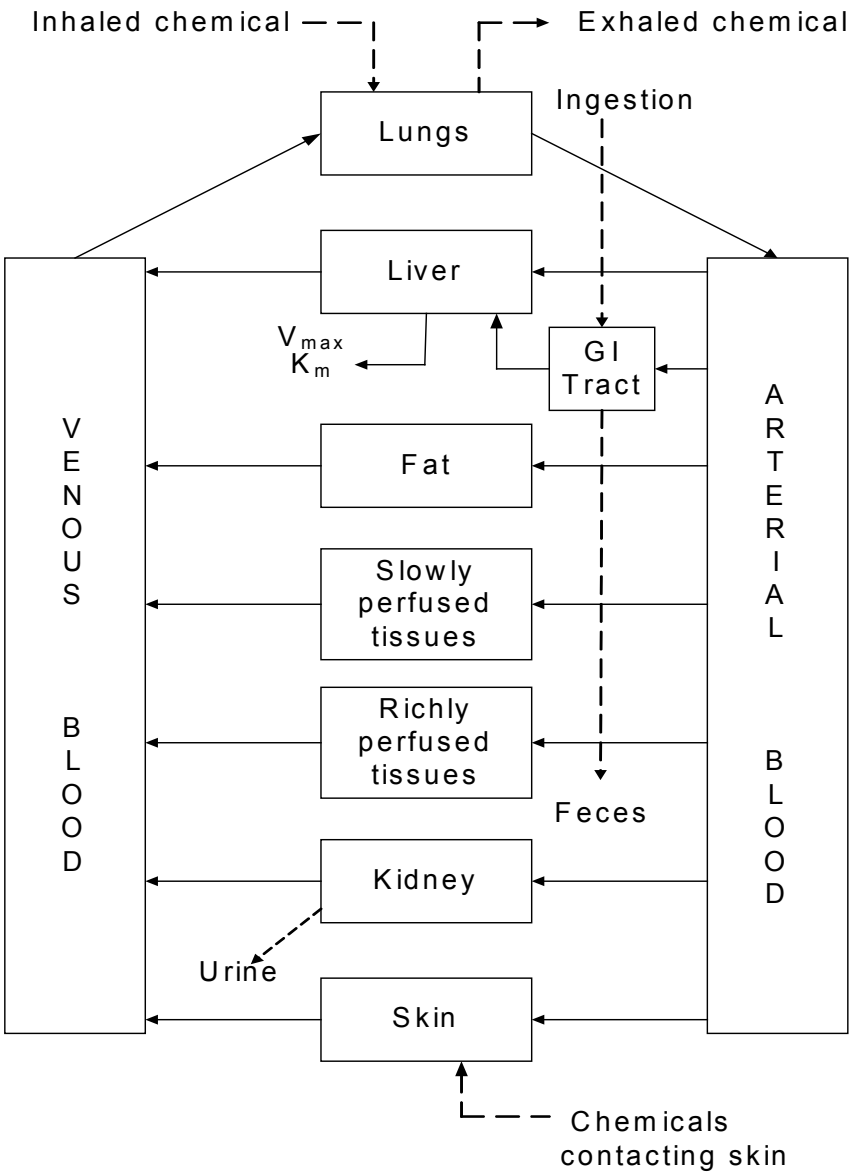
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety; and (2) the target tissue dose and observed responses (Andersen and Krishnan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

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

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

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

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



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

Source: adapted from Krishnan and Andersen 1994

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

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

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

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

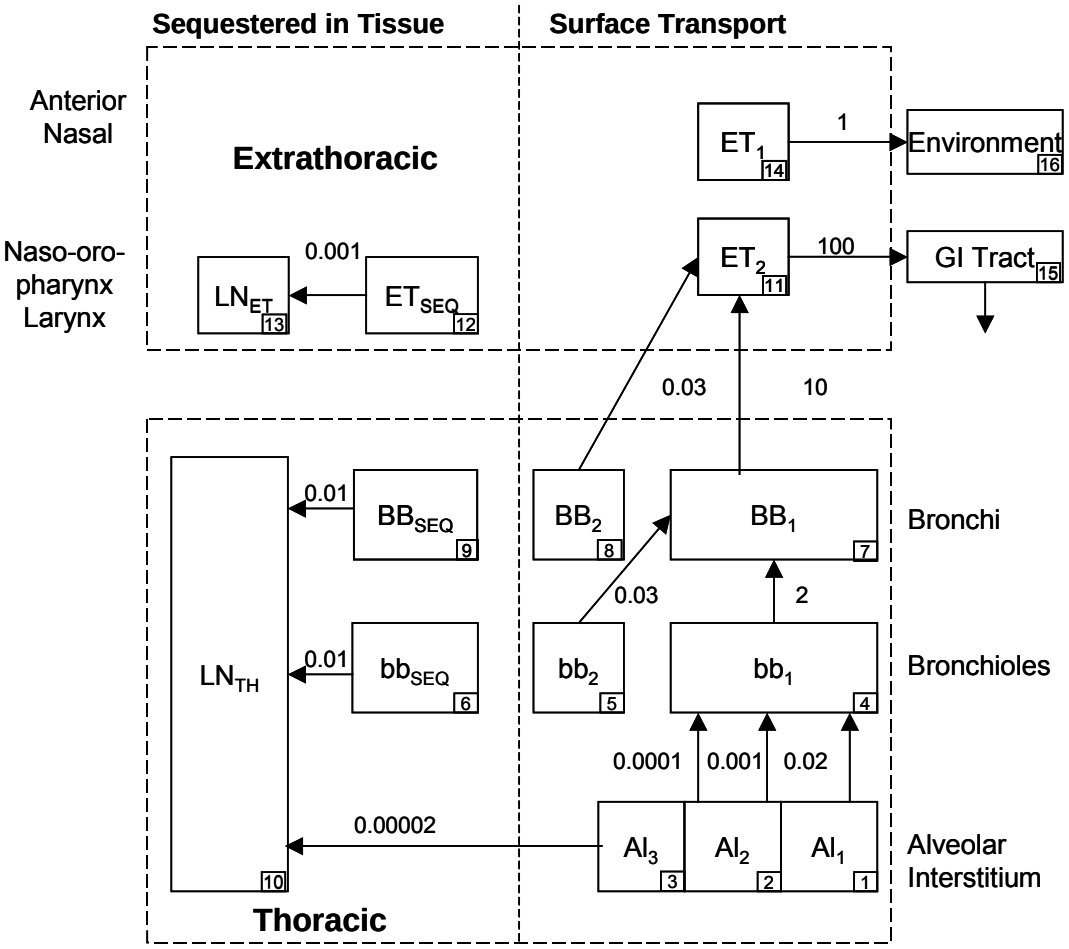
Human Respiratory Tract Model for Radiological Protection (ICRP 1994b)

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

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

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

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



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

Source: ICRP 1994b

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

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

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

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

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

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

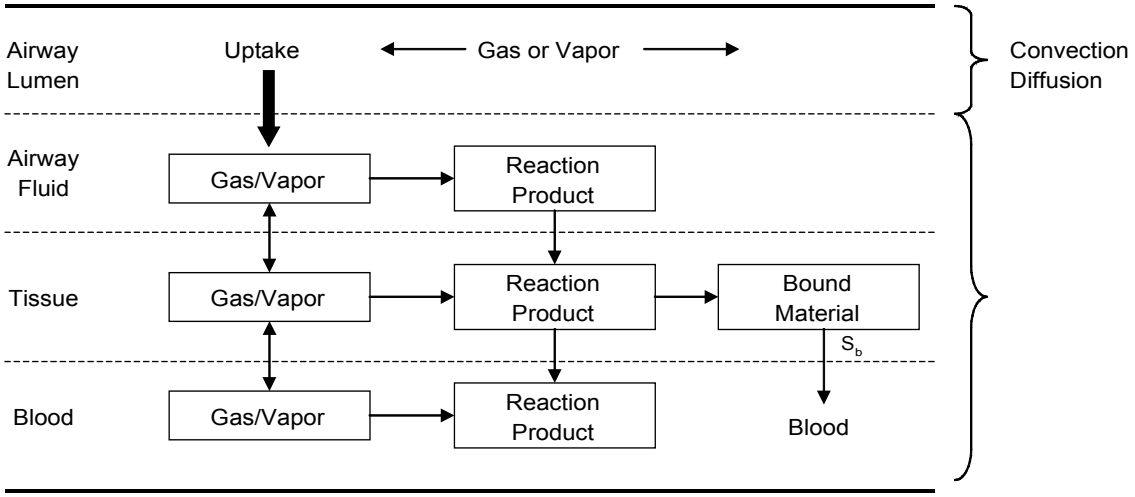
- Type SR-1 compounds include soluble or reactive gases and vapors which are expected to be taken up by the respiratory tract tissues and may deposit in any or all of the regions of the respiratory tract, depending on the dynamics of the airways and properties of the surface mucous and airway tissues,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

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

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

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

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



Source: ICRP 1994b

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

Part A

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

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

Part B

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

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

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

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

where

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

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

Source: ICRP 1994b

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

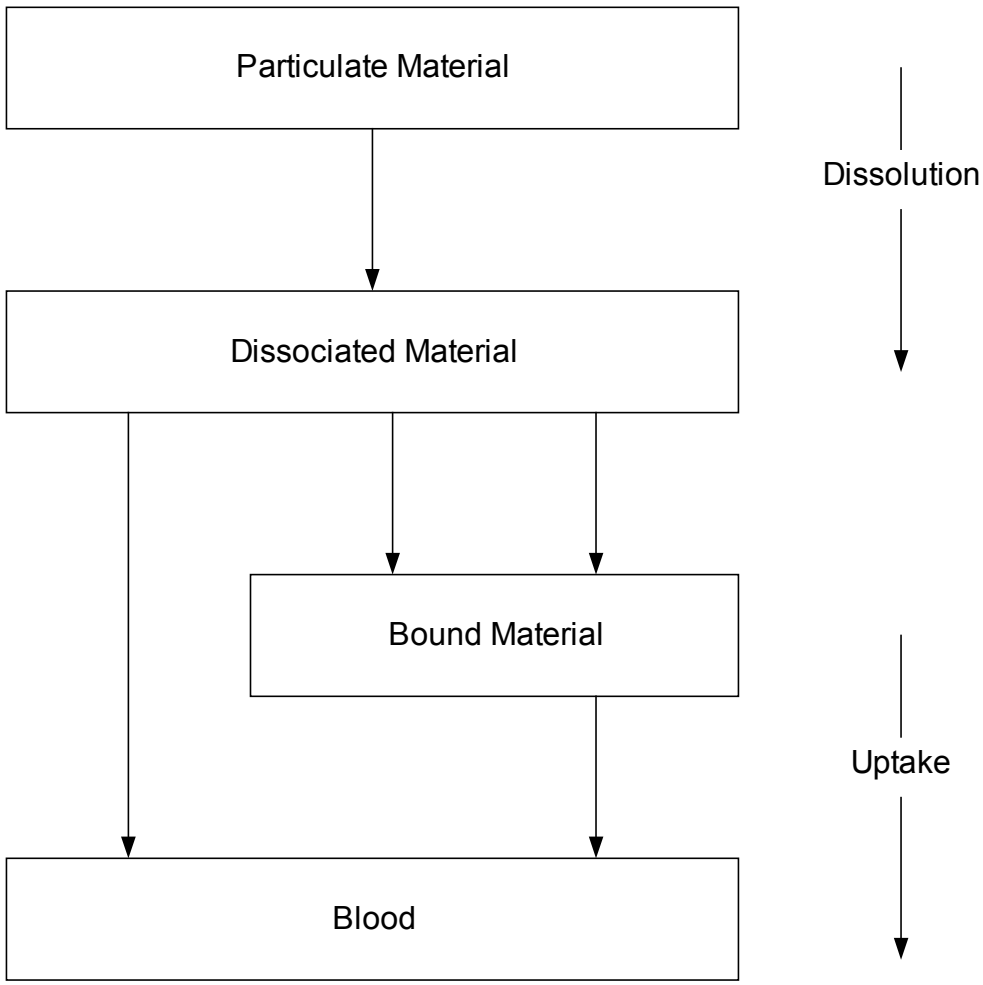
Ciliary action removes deposited particles from both the bronchi and bronchioles. Though it is generally thought that mucociliary action rapidly transports most particles deposited here toward the pharynx, a fraction of these particles is cleared more slowly. Evidence for this is found in human studies.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

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

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

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

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



Source: ICRP 1994b

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

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

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

ICRP (1994a) Plutonium Biokinetics Model

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

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

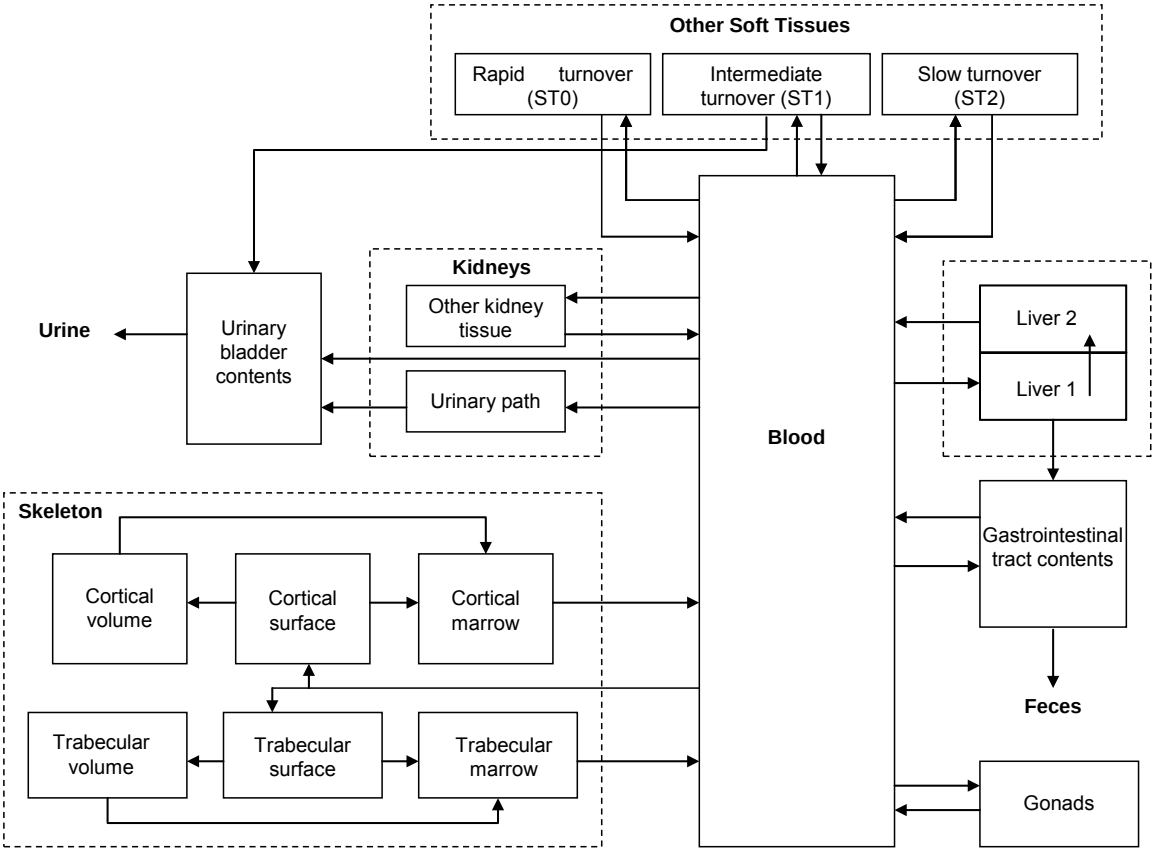
	Age					
Parameter[b]	3 months	1 year	5 years	10 years	15 years	Adult
Soft tissue (ST0) to blood	6.93×10^{-1}	6.93×10^{-1}	6.93×10^{-1}	6.93×10^{-1}	6.93×10^{-1}	6.930×10^{-1}
Soft tissue (ST1) to blood	4.75×10^{-4}	4.75×10^{-4}	4.75×10^{-4}	4.75×10^{-4}	4.75×10^{-4}	4.75×10^{-4}
Soft tissue (ST2) to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

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

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

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

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



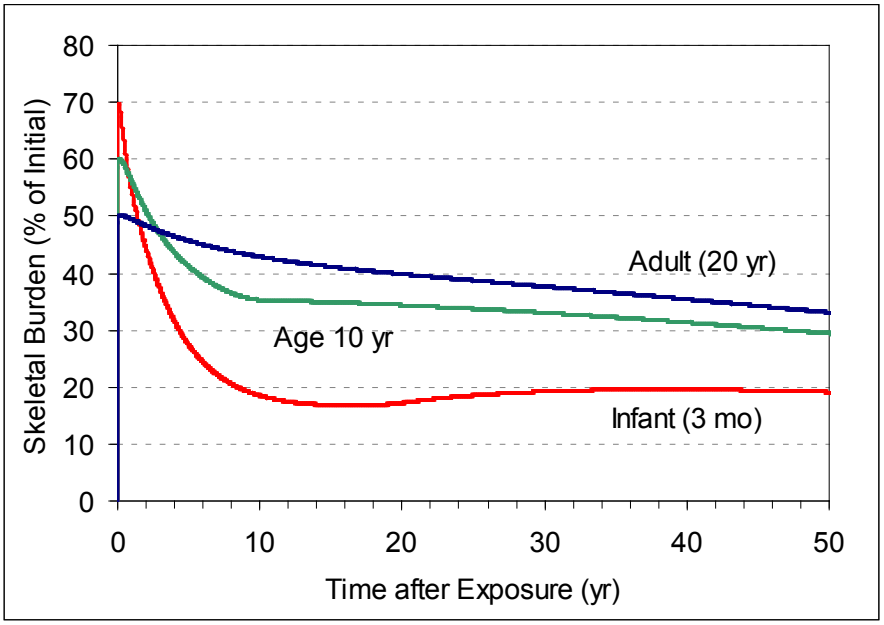
*See Table 3-8 for parameter values.

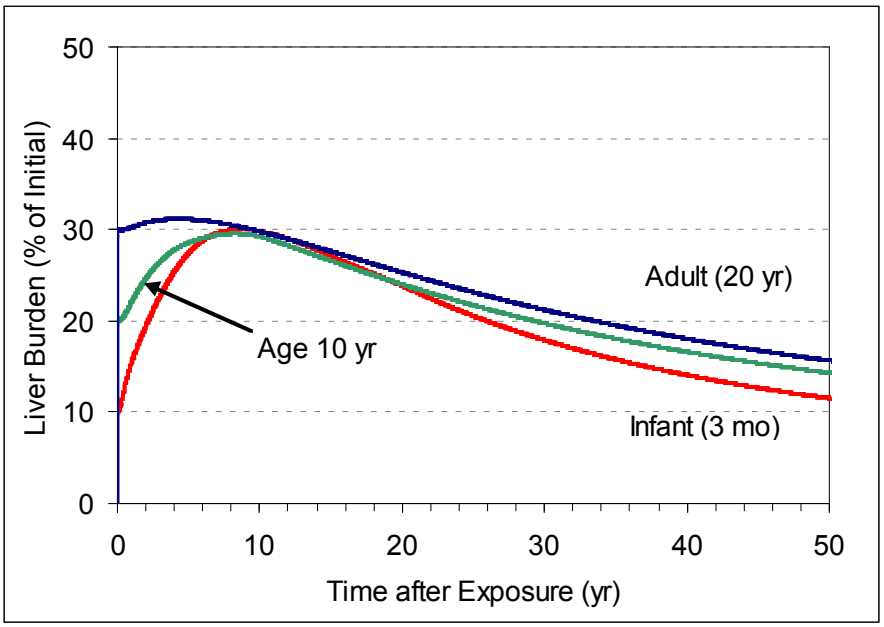
Bone is divided into trabecular and cortical components, with each further divided into bone surface, bone volume, and bone cavity (marrow compartment). Initial deposition of plutonium is assumed to occur from blood directly to bone surfaces, where it can be transferred to bone marrow or to bone volume.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

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

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

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





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

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

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

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

Luciani and Polig (2000) Plutonium Biokinetics Model

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

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

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

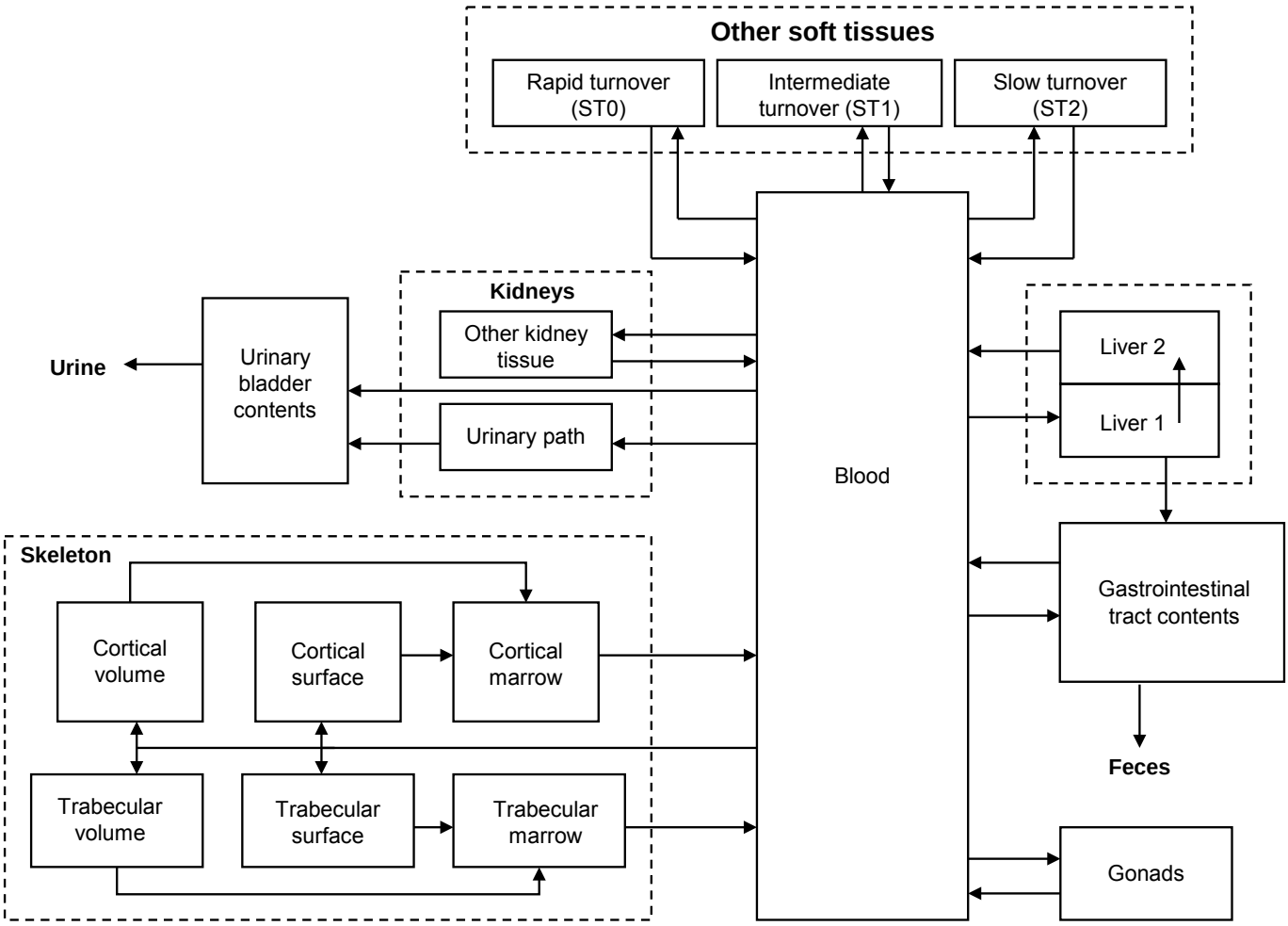


Table 3-9. Comparison of Parameters of ICRP (1994a) Model and Luciani and Polig (2000) Model of Plutonium Biokinetics in Humans[a]

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

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

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

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

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

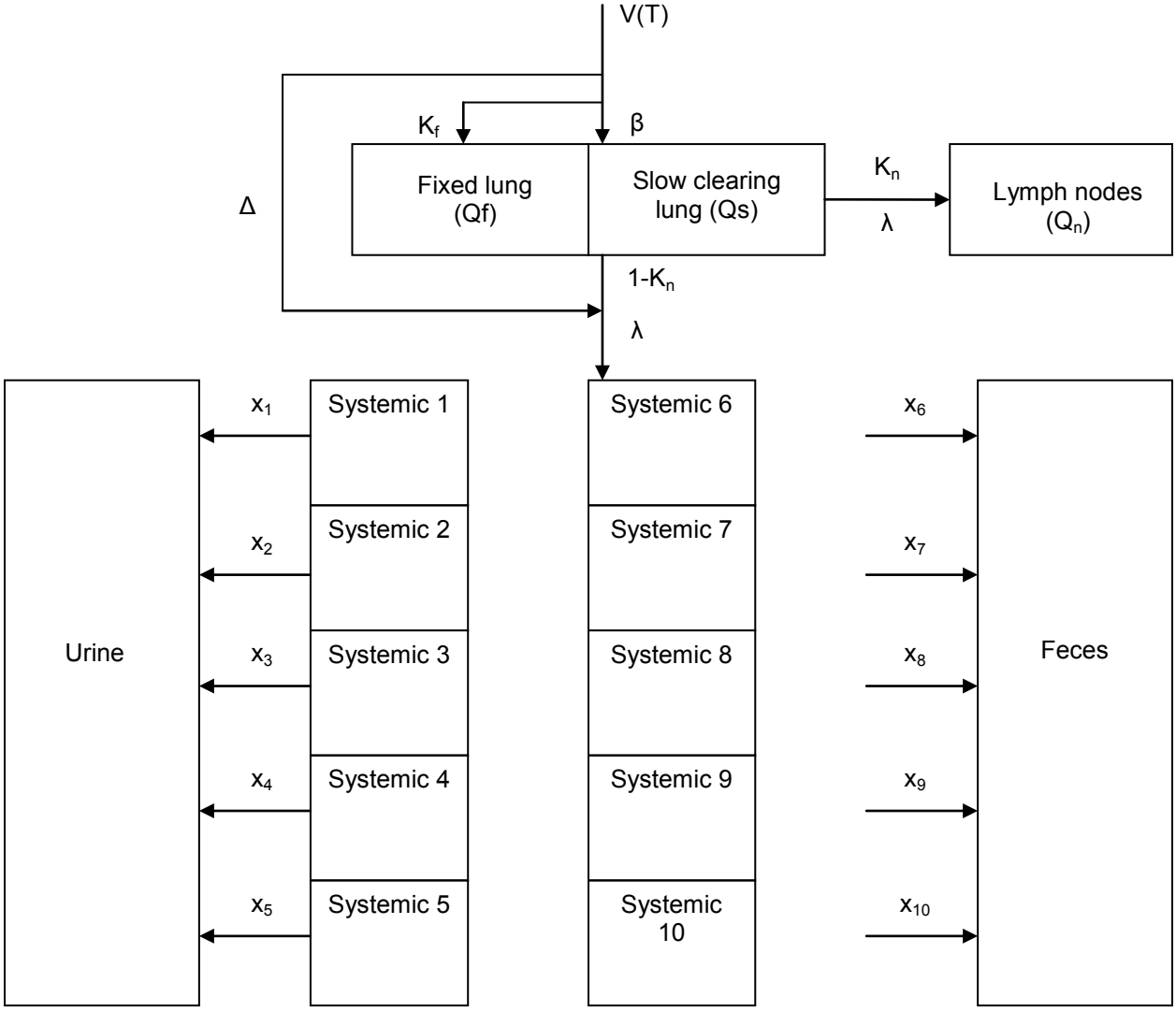
Species Extrapolation. The model is intended for applications to human dosimetry. Applications to other species would require consideration of species-specific adjustments in model parameters.

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

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

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

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



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

Source: Khokhryakov et al. 2002

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

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

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

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

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

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

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

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

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

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

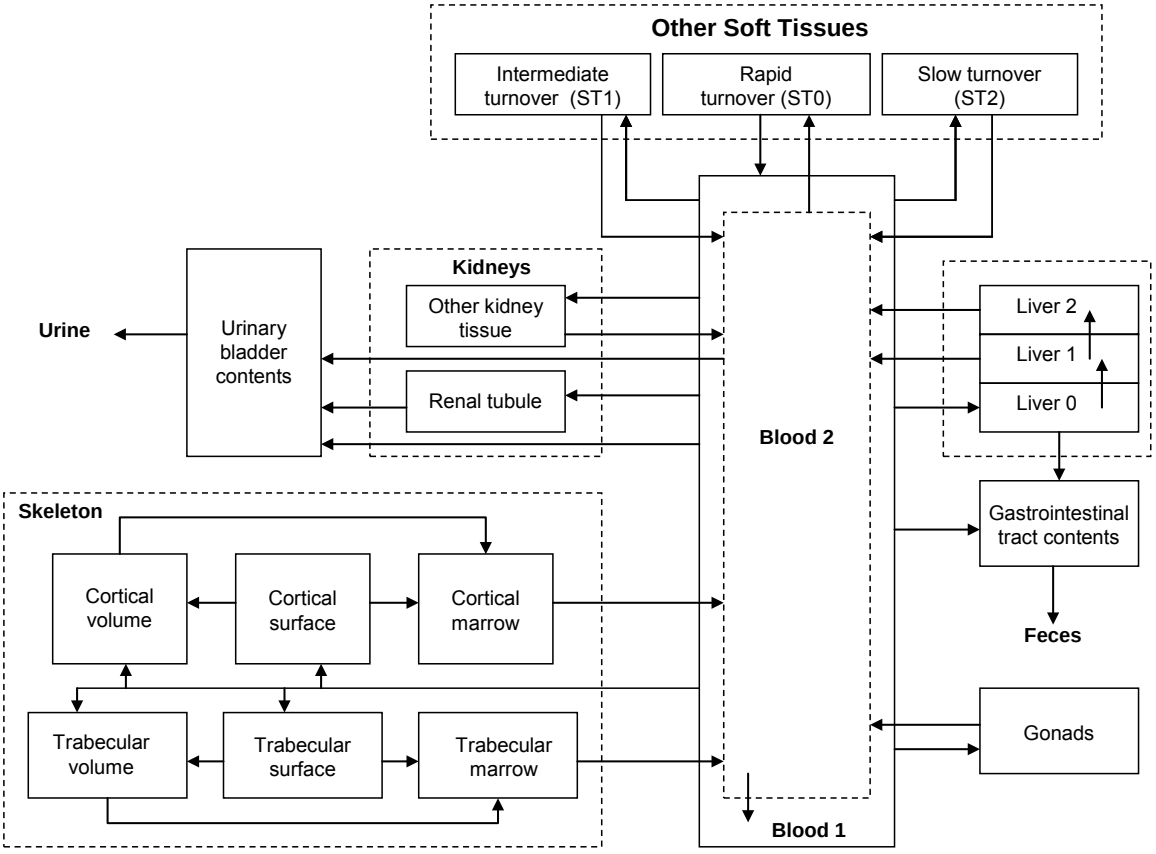
Source: Khokhryakov et al. 2002

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

Leggett et al. (2005) Plutonium Biokinetics Model

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

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



*See Table 3-11 for parameter values.

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

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

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

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

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

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

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

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

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

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

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

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

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

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

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

Distribution.

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

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

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

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

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

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

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

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

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

3.5.2 Mechanisms of Toxicity

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

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

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

3.5.3 Animal-to-Human Extrapolations

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

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

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

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

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

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

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

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

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

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

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

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

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

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

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Plutonium

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

3.8.2 Biomarkers Used to Characterize Effects Caused by Plutonium

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

3.9 INTERACTIONS WITH OTHER CHEMICALS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

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

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

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

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

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

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

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

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

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

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

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

3.11.1 Reducing Peak Absorption Following Exposure

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

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

3.11.2 Reducing Body Burden

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

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

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

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

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

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

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

3.12 ADEQUACY OF THE DATABASE

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

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

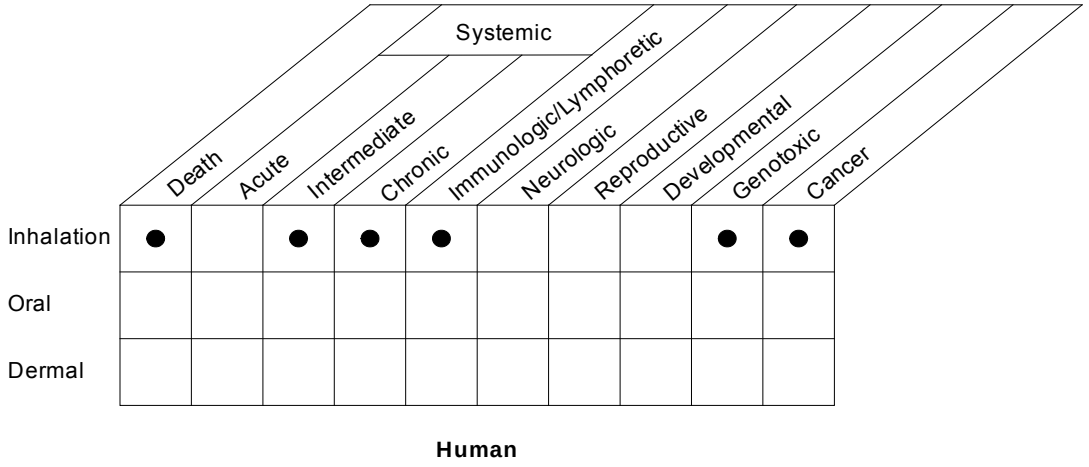
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

3.12.1 Existing Information on Health Effects of Plutonium

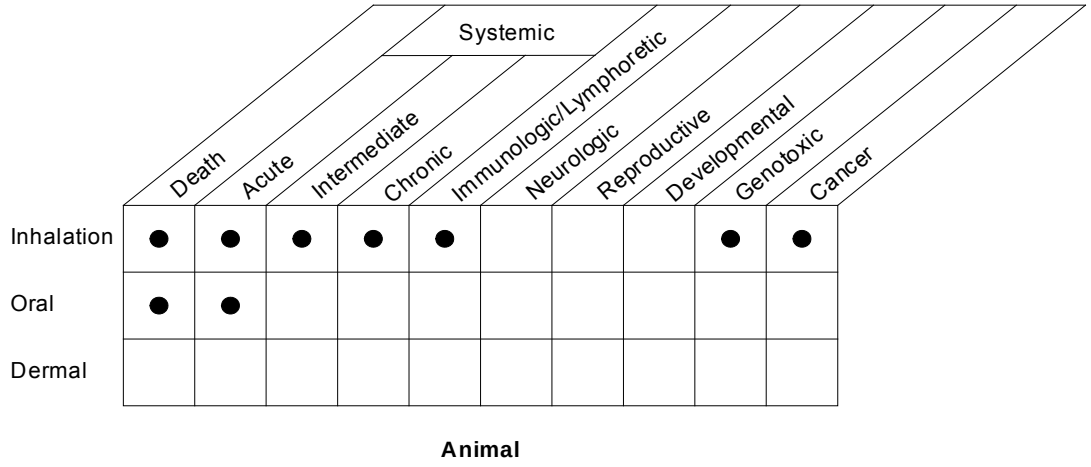
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to plutonium are summarized in Figure 3-11 for radioactive plutonium. The purpose of this figure is to illustrate the existing information concerning the health effects of plutonium. Each dot in the figure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

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

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



Human



Animal

● Existing Studies

3.12.2 Identification of Data Needs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Biomarkers of Exposure and Effect.

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

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

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

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

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

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

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

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

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

3.12.3 Ongoing Studies

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

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

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