

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to plutonium. Its purpose is to present levels of significant exposure to plutonium based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of plutonium and (2) a depiction of significant exposure levels associated with various adverse health effects.

Plutonium is a radioactive element. Radioactive elements are those that undergo spontaneous transformation (decay) in which energy is released (emitted) either in the form of particles, such as alpha or beta particles, or waves, such as gamma or X-ray. This transformation or decay results in the formation of new elements, some of which may themselves be radioactive, in which case they will also decay. The process continues until a stable (nonradioactive) state is reached (see Appendix B for more information).

Radionuclides can produce adverse health effects as a result of their radioactive properties. With toxicity induced by the chemical properties of an element or its compounds, the adverse effects are characteristic of that specific substance. With toxicity induced by radioactive properties, the adverse effects are independent of the chemical toxicity and are related to the amount and type of radiation absorbed by the target tissues or organs. While the chemical properties affect the distribution and biological half-life of a radionuclide and influence the retention of the radionuclide within a target organ, the damage from a type of radiation is independent of the source of that radiation. The adverse health effects reported in Chapter 2 are related to the radioactive properties of plutonium rather than its chemical properties. In this profile, there is little or no specific information regarding the influence of plutonium on specific target organs in humans, leading to reproductive, developmental, or carcinogenic effects. There is evidence, however, from the large body of literature concerning radioactive substances that alpha radiation can affect these processes in humans (BEIR IV 1988; UNSCEAR 1982) (see Appendix B for additional information on the biological effects of radiation).

Plutonium exists in several isomeric forms, the most important of which are plutonium-238 and plutonium-239. When plutonium decays, it emits primarily alpha particles (ionized helium atoms), except for plutonium-241 which decays by beta emission. Alpha particles are highly ionizing and, therefore, damaging, but their penetration into tissue is

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slight. Biological damage is limited to cells in the immediate vicinity of the alpha-emitting radioactive material.

The potential for adverse health effects caused by the plutonium isotopes is dependent on several factors including solubility, distribution in the various body organs, the biological retention time in tissue, the energy of the radioactive emission, and the half-life of the isotope (EPA 1977). A potential health hazard results when plutonium is inhaled and deposited in lung tissue or is ingested or enters the body through wounds. Subsequent translocation of some of the plutonium from the lungs to tissues and organs distant from the site of entry results in radiation damage to these tissues as well as to the lung. For the two most studied isotopes, plutonium-238 and plutonium-239, radioactive half-life (86 and 24,000 years, respectively) and biological retention time are very long, resulting in prolonged exposure of body organs to alpha radiation (EPA 1977). Plutonium isotopes generally exist as complexes with other elements or compounds (see Chapter 3 for information on chemical and physical properties of plutonium and plutonium compounds). Plutonium-238 compounds and certain plutonium-239 compounds, such as the nitrate forms, are more soluble in lung tissue than plutonium-239 dioxide. Thus, plutonium-239 dioxide will be retained longer in lung tissue following inhalation than the more soluble forms, plutonium-238 compounds or plutonium-239 nitrate. Insoluble plutonium is inhaled as particles. Particle size determines deposition patterns and consequently, clearance patterns from the lung; therefore, particle size is directly related to retention and the resulting radiological dose. These characteristics also affect the toxicity and target organs of the various isotopes.

Numerous studies have been conducted in laboratory animals to develop a better understanding of the physiological effects of exposure to plutonium. These studies have increased our understanding of the deposition of plutonium in various body organs and of the time of retention, as well as providing an extensive database on the adverse health effects of plutonium. The relevant toxicological properties of plutonium and significant health effects related to exposure to plutonium are described in this chapter.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral, and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate, and chronic.

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Levels of significant exposure for each exposure route and duration (for which data exist) 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 levels of exposure used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies 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 tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) are of interest to health professionals and citizens alike.

The activity of radioactive elements has traditionally been specified in curies (Ci). The curie is approximately 37 billion disintegrations (decay events) per second (3.7×10^{10} dps). In discussing plutonium, a smaller unit, the picocurie (pCi) is used, where 1 pCi is equal to 1×10^{-12} Ci. In international usage, the S.I. unit (the International System of Units) for activity is the Becquerel (Bq), which is equal to one disintegration per second or about 27 pCi. (Information for conversion between units is given in Chapter 9 and Appendix B.) In the text of this profile units expressed in pCi are followed by units in Bq contained in parentheses. The activity concentration is a description of the amount of plutonium deposited in lungs after inhalation exposure or administered to animals by the oral route or by other routes of exposure rather than an expression of dose. In radiation biology, the term dose refers specifically to the amount of energy imparted by the emitted radiation that is absorbed by a particular tissue or organ. This dose is expressed in rads (Grays).

2.2.1 Inhalation Exposure

Numerous inhalation studies in rats, mice, hamsters, dogs, and nonhuman primates have been, conducted or are still on-going. In the majority of these studies, the test animals received a single inhalation exposure to either plutonium-238 or plutonium-239, administered as the dioxide, the citrate, or the nitrate. Observation continued, or is

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continuing, for the lifespan of the animals. Among the issues studied were the comparative toxicity of plutonium-238 and plutonium-239, the effect of particle size on deposition and expressed toxicity, the effect of age at first exposure, the target organs and time-course of the disease process, and the differences in species sensitivity. In each case, animals were exposed by inhalation to an aerosol of plutonium particles of different aerodynamic sizes and to different amounts of radioactivity in the aerosol. Environmental levels (i.e., the amount of plutonium radioactivity present in the aerosol) were usually not given. Rather, the amount of plutonium was expressed as a "lung burden" or "initial alveolar deposition" or "initial lung deposition," i.e., the total amount of radioactivity retained in the lung after the exposure. Working from experiment-specific body weights, plutonium deposition levels in this profile have been expressed as pCi plutonium/kg body weight. When literature values were expressed as "radioactivity per gram of lung tissue," these values were also converted to pCi plutonium/kg body weight if lung weight or ratio of lung weight to body weight was given. Health effects associated with plutonium deposition, in units of pCi plutonium/kg body weight, for acute, intermediate, and chronic exposure duration (for which data exist) are presented in Table 2-1 and illustrated in Figure 2-1.

2.2.1.1 Death

Analyses of mortality among persons chronically exposed to plutonium in the workplace have been conducted. In the three occupational cohorts studied (Los Alamos Laboratory, Rocky Flats facility, and Hanford Plant), there were consistently fewer deaths than expected based on data for United States white males (Gilbert and Marks 1979; Voelz et al. 1983a, 1983b; Wilkinson et al. 1987). This phenomenon is generally attributed to the "healthy worker effect," which holds that individuals in the work force are healthier than those in the general population. However, in a refined cohort from the Rocky Flats facility, the mortality of plutonium-exposed workers was compared to that of unexposed workers from the same plant. It was reported that death from all causes was elevated in exposed individuals but the increase was not statistically significant (Wilkinson et al. 1987).

Statistically significant decreases in mean survival time in treated animals compared to controls have been reported in rats, mice, hamsters, dogs, and baboons following a single, acute inhalation exposure to plutonium-239 or plutonium-238. A single exposure to plutonium-239 resulting in deposition levels ranging from 2.3×10^4 to 7.2×10^6 pCi (8.5×10^2 to 2.7×10^5 Bq)/kg body weight produced a decrease in survival time in rats (Metivier et al. 1986; Sanders et al. 1976, 1988), in mice (Lundgren et al. 1987), in hamsters (in the high-dose group, males only) (Sanders 1977), in dogs (Dagle et al. 1988; Muggenburg et al. 1987a; Park et al. 1988), and in baboons (Metivier et

TABLE 2-1. Health Effects Associated with Plutonium Deposition - Inhalation

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (pCi/kg)	LOAEL (Effect)		Reference	Chemical Species
					Less Serious (pCi/kg)	Serious (pCi/kg)		
ACUTE EXPOSURE								
Death								
1	Rat	1d		1.7x10 ⁴		4.9x10 ⁵ (dec lifespan)	Metivier et al. 1986	²³⁹ PuO ₂
2	Rat	1d 30 min				2.5x10 ⁶ (dec lifespan)	Sanders et al. 1977	²³⁸ PuO ₂
3	Mouse	1d				2.1x10 ⁶ (dec lifespan)	Lundgren et al. 1987	²³⁹ PuO ₂
4	Hamster	1d 30 min				2.1x10 ⁴ (dec lifespan)	Sanders 1977	²³⁹ PuO ₂
5	Dog	1d				6.2x10 ³ (dec lifespan)	Park et al. 1988	²³⁹ PuO ₂
6	Dog	1d				2.8x10 ⁴ (dec lifespan)	Park et al. 1988	²³⁸ PuO ₂
Systemic								
7	Rat	1d 30 min	Resp			1.6x10 ⁶ (pneumonitis)	Sanders and Mahaffey 1979	²³⁹ PuO ₂
8	Rat	1d	Resp			1.6x10 ⁵ (fibrosis)	Sanders et al. 1988	²³⁹ PuO ₂
9	Rat	1d 30 min	Resp Other	2.5x10 ⁶		6.3x10 ⁵ (pneumonitis)	Sanders et al. 1977	²³⁸ PuO ₂
10	Rat	1d	Resp			4.3x10 ⁵ (inc collagen ct)	Metivier et al. 1978a	²³⁹ PuO ₂
11	Mouse	1d (days)	Resp Other	3.6x10 ³	8.4x10 ⁵ (biochem effects) 8.4x10 ⁵ (inc lung wt)		Talbot and Moores 1985	²³⁹ PuO ₂
12	Hamster	1dose 30 min	Resp Other	1.4x10 ⁶		1.4x10 ⁶ (metaplasia)	Sanders 1977	²³⁸ PuO ₂

TABLE 2-1 (continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (pCi/kg)	LOAEL (Effect)		Reference	Chemical Species
					Less Serious (pCi/kg)	Serious (pCi/kg)		
13	Hamster	1d 30 min	Resp Other	1.4x10 ⁶		1.4x10 ⁶ (pneumonitis)	Sanders 1977	²³⁹ PuO ₂
14	Dog	1d	Resp			1.0x10 ⁵ (pneumonitis)	Muggenburg et al. 1987a	²³⁹ PuO ₂
15	Dog	1d	Resp Hemato Hepatic		1.3x10 ⁵ (lymphopenia) 4.4x10 ⁵ (altered enz)	1.3x10 ⁵ (pneumonitis)	Dagle et al. 1988	²³⁹ Pu(NO ₃) ₄
16	Dog	1d	Hemato Hepatic		6.1x10 ³ (lymphopenia) 6.1x10 ³ (inc enzymes)		Park et al. 1988	²³⁸ PuO ₂
17	Dog	1d	Resp Hemato Hepatic	4.6x10 ⁵	6.1x10 ³ (dec lymphocytes)	4.6x10 ⁵ (pneumonitis)	Park et al. 1988	²³⁹ PuO ₂
18	Dog	1d	Resp		1.1x10 ⁸ (dec resp funct)		Muggenburg et al. 1988	²³⁹ PuO ₂
19	Dog	1d				1.0x10 ⁶ (fibrosis)	Mewhinney et al. 1987a	²³⁸ PuO ₂
Immunological								
20	Mouse	1d			4.5x10 ⁴ (dec macrophage)		Moores et al. 1986	²³⁹ PuO ₂
21	Hamster	1d			7.1x10 ⁴ (dec Ab form cell)		Bice et al. 1979	²³⁹ PuO ₂
22	Dog	1d				1.7x10 ³ (lymphadenopathy)	Park et al. 1988	²³⁹ PuO ₂
23	Dog	1d				6.1x10 ³ (lymphadenopathy)	Park et al. 1988	²³⁸ PuO ₂

TABLE 2-1 (continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (pCi/kg)	LOAEL (Effect)		Reference	Chemical Species
					Less Serious (pCi/kg)	Serious (pCi/kg)		
Cancer								
24	Rat	1d 30 min				3.1x10 ⁴ (CEL-lung)	Sanders et al. 1977	²³⁸ PuO ₂
25	Rat	1d				4.3x10 ⁴ (CEL-lung)	Sanders et al. 1988	²³⁹ PuO ₂
26	Rat	1d				1.7x10 ⁴ (CEL-lung)	Metivier et al. 1986	²³⁹ PuO ₂
27	Dog	1d				2.3x10 ⁴ (CEL-skeletal)	Dagle et al. 1988	²³⁹ Pu(NO ₃) ₄
28	Dog	1d				1.4x10 ³ (CEL-skeletal)	Park et al. 1988	²³⁸ PuO ₂
29	Dog	1d				2.1x10 ⁴ (CEL-lung)	Muggenburg et al. 1987a	²³⁹ PuO ₂
30	Dog	1d				1.9x10 ⁴ (CEL-liver)	Gillett et al. 1988	²³⁸ PuO ₂
31	Dog	1d				8.7x10 ⁴ (CEL-lung)	Park et al. 1988	²³⁹ PuO ₂
INTERMEDIATE EXPOSURE								
Death								
32	Mouse	1 yr bimonthly				4.1x10 ⁵ (dec lifespan)	Lundgren et al. 1987	²³⁹ PuO ₂
33	Hamster	1yr bimonthly		7.1x10 ⁴			Lundgren et al. 1983	²³⁹ PuO ₂

TABLE 2-1 (continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (pCi/kg)	LOAEL (Effect)		Reference	Chemical Species
					Less Serious (pCi/kg)	Serious (pCi/kg)		
Systemic								
34	Hamster	1 yr bimonthly	Resp			1.4x10 ⁴ (pneumonitis)	Lundgren et al. 1983	²³⁹ PuO ₂
Cancer								
35	Rat	Multiple				8.6x10 ⁴ (CEL-lung)	Sanders and Mahaffey 1981	²³⁹ PuO ₂
36	Mouse	1 yr bimonthly				1.8x10 ⁴ (CEL-lung)	Lundgren et al. 1987	²³⁹ PuO ₂

Ab form cell = antibody forming cells; biochem = biochemical; CEL = cancer effect level; ct = count; d = day; dec = decreased; enz = enzymes; funct = function; Hemato = hematological; inc = increased; LOAEL = lowest observed adverse effect level; min = minute; NOAEL = no observed adverse effect level; Resp = respiratory; wt = weight; yr=year

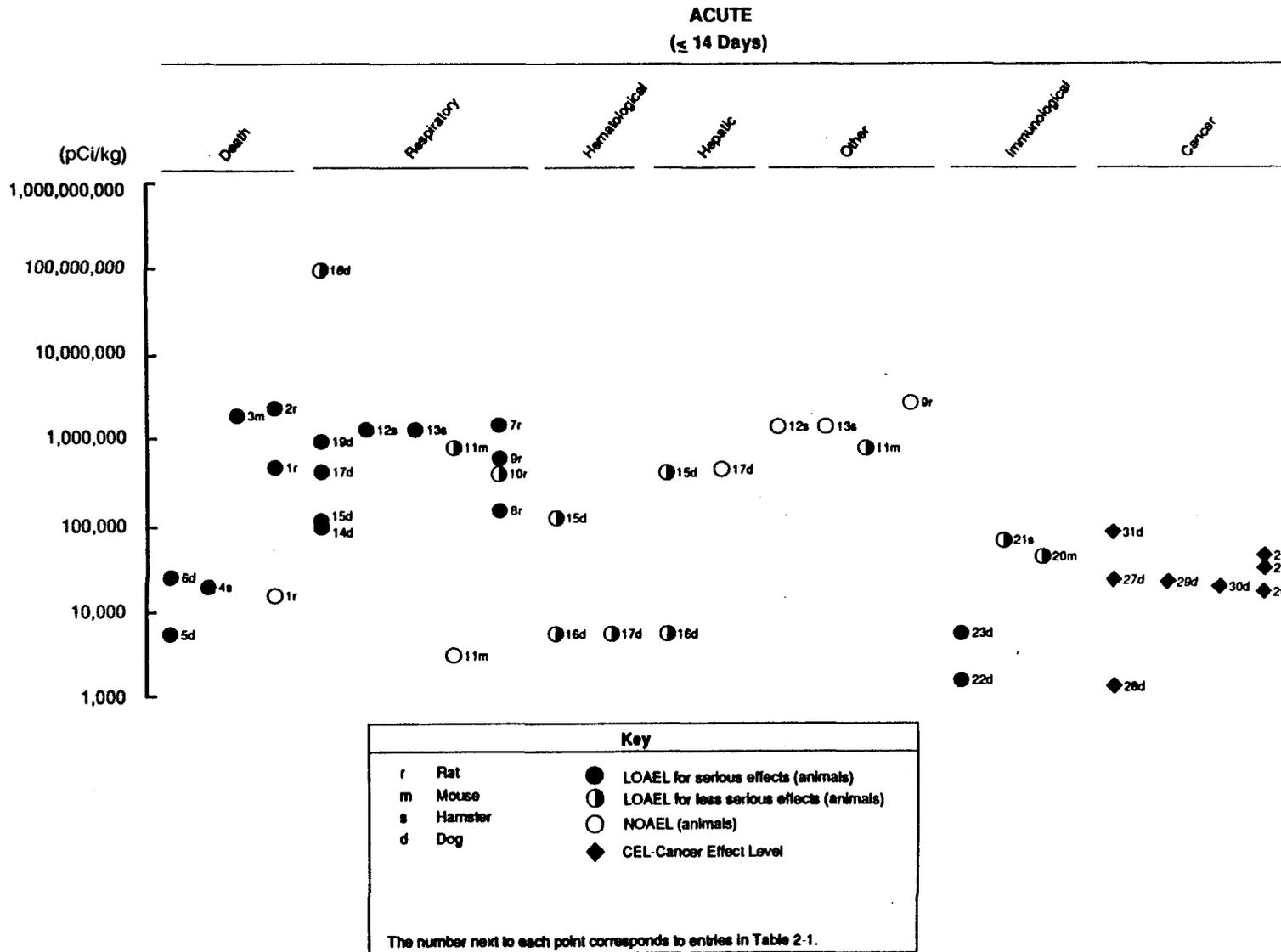


FIGURE 2-1. Health Effects Associated with Plutonium Deposition - Inhalation

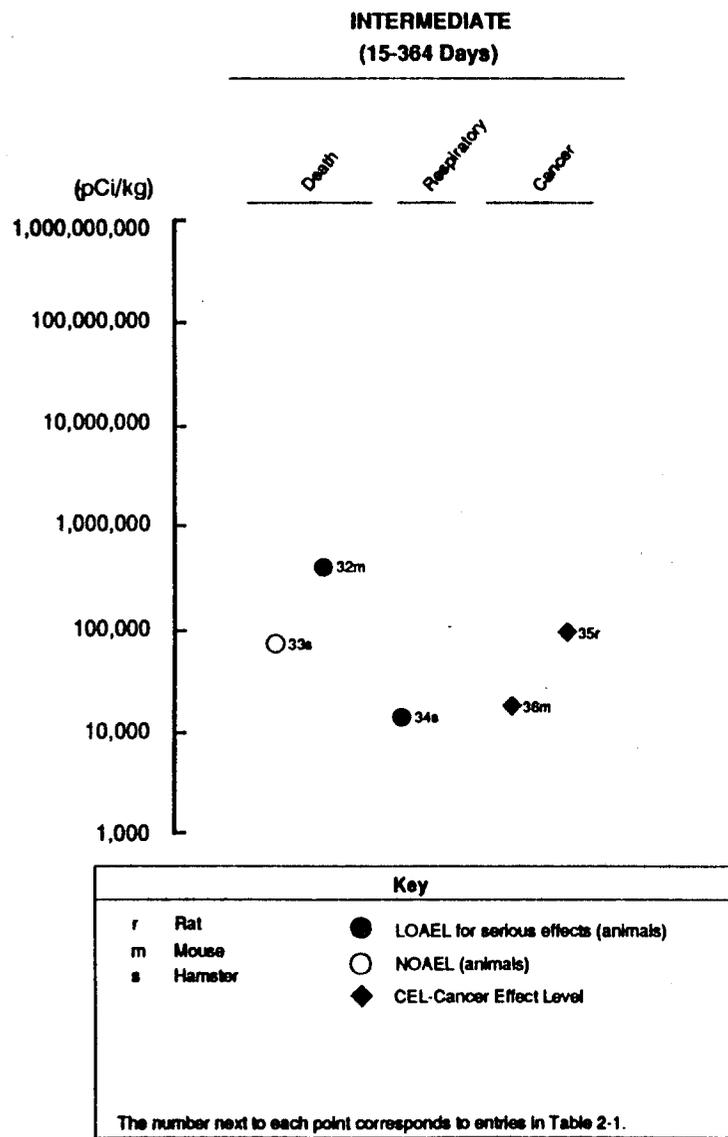


FIGURE 2-1 (Continued)

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al. 1974). In all species tested, death occurred within 1 to 3 years after exposure and was usually caused by radiation pneumonitis accompanied by edema, fibrosis, and other signs of respiratory damage. Survival time decreased in a dose-related manner at deposited levels in excess of approximately 1×10^4 pCi (3.7×10^2 Bq) plutonium-239 dioxide/kg body weight.

Similar results were observed in animals given a single, acute inhalation exposure to plutonium-238, as the more soluble dioxide or nitrate (Mewhinney et al. 1987a; Park et al. 1988; Sanders 1977; Sanders et al. 1977). Studies in dogs (Park et al. 1988) and hamsters (Sanders 1977) have demonstrated that plutonium-239 was more toxic than plutonium-238. The primary cause of death in animals treated with plutonium-238 was also radiation pneumonitis.

Exposure of hamsters for an intermediate duration (once every other month for a total of seven doses over 12 months) to plutonium-239 dioxide resulted in a statistically significant decrease in median survival time only in the highest exposure group [at deposition levels of 3.5×10^5 pCi (1.3×10^4 Bq) plutonium-239/kg body weight] (Lundgren et al. 1983). Hamsters receiving lower exposures [at deposition levels of 1.4×10^4 or 7.1×10^4 pCi (5.2×10^2 or 2.6×10^3 Bq) plutonium-239/kg body weight] had survival times comparable to controls. Similar exposure of mice (once every other month for a total of six doses over 10 months) to plutonium-239 [at deposited levels of 1.8×10^4 , 8.1×10^4 , or 4.1×10^5 pCi (6.7×10^2 , 3.0×10^3 , or 1.5×10^4 Bq) plutonium-239/kg body weight] resulted in statistically significant decreases in survival in all three exposure groups (Lundgren et al. 1987).

2.2.1.2 Systemic Effects

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

Respiratory Effects. No studies were located concerning respiratory effects in humans after inhalation exposure to plutonium.

Radiation pneumonitis, characterized by alveolar edema, fibrosis, and, in some cases, pulmonary hyperplasia and metaplasia, has been observed in dogs, mice, rats, hamsters, and baboons following exposure to high levels of plutonium-239 or plutonium-238 dioxide. In dogs, radiation pneumonitis and pulmonary fibrosis were two of the primary causes of death among high-dose groups receiving a lung deposition of approximately 1.0×10^6 pCi (3.7×10^4 Bq) plutonium-238/kg body weight (Mewhinney et al. 1987a) or 1.0×10^5 to 4.6×10^5 pCi (3.7×10^3 to 1.7×10^4 Bq) plutonium-239/kg body weight (Muggenburg et al. 1987a; Park et al. 1988). The time to death was inversely related to the initial lung

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burden; dogs that received approximately 1.0×10^6 pCi (3.7×10^4 Bq) plutonium-238/kg body weight were dead by 600 days post-exposure, while those receiving 2.1×10^5 pCi (7.8×10^3 Bq) plutonium-238/kg body weight survived 1,000 to 2,000 days (Mewhinney et al. 1987a). In dogs, neither the size of the particles (Muggenburg et al. 1987a) nor the age of the animal at initiation of treatment (Guilmette et al. 1987; Muggenburg et al. 1987b) altered the course of the respiratory effects. The pattern of disease in dogs 8 to 10 years old (Muggenburg et al. 1987b) and immature dogs (Guilmette et al. 1987) was similar to that seen in young adult dogs, that is, radiation pneumonitis occurred in the high-exposure groups resulting in shortened survival times. Lung carcinomas were observed in lower exposure groups in which dogs survived for a longer period of time (see Section 2.2.1.8 Cancer and Table 2-1).

Rats also developed radiation pneumonitis within 12 months after a single exposure that resulted in a deposited level of approximately 1.6×10^6 pCi (5.9×10^4 Bq) plutonium-239/kg body weight (Sanders and Mahaffey 1979). However, in another study, temporarily increased collagen deposition, but not pneumonitis, occurred in rats following deposition of 2.8×10^3 to 2.7×10^5 pCi (1.0×10^2 to 1.0×10^5 Bq) plutonium-239/kg body weight (Metivier et al. 1978a). Radiation pneumonitis and fibrosis were the major pathological findings and causes of death in male hamsters at deposited levels of 1.4×10^5 pCi (5.2×10^4 Bq) plutonium-239/kg body weight (Sanders 1977) or 1.7×10^6 pCi (6.3×10^4 Bq) plutonium-238/kg body weight (Mewhinney et al. 1986).

Baboons and monkeys displayed a respiratory disease pattern similar to that seen in dogs and rodents. Some baboons died of radiation pneumonitis accompanied by pulmonary edema within 50 days after a single exposure to plutonium-239 dioxide at deposited levels of 2.88×10^5 to 7.2×10^6 pCi (1.1×10^4 to 2.7×10^5 Bq)/kg body weight (Metivier et al. 1974; 1978b). Radiation pneumonitis and pulmonary fibrosis were also seen in Rhesus monkeys exposed to plutonium dioxide at deposited levels of 3.4×10^4 to 2.3×10^5 pCi (1.3×10^3 to 8.5×10^3 Bq)/kg body weight (Hahn et al. 1984; LaBauve et al. 1980). Death from pulmonary fibrosis occurred in Rhesus monkeys following lung deposition of 3.4×10^4 pCi (1.3×10^3 Bq) plutonium-239 dioxide/kg body weight (Hahn et al. 1984).

At levels below those that caused acute radiation pneumonitis, chronic alpha irradiation of lung tissue from the deposited plutonium produced interstitial fibrosis. The terminal stage of pneumonitis/fibrosis was characterized by an increased respiratory rate and decreased pulmonary compliance. The cardiopulmonary function of some of the dogs in the study by Muggenburg et al. (1986) was studied further (Muggenburg et al. 1988). Pulmonary dysfunction was observed in these animals and appeared to be a chronic form of radiation pneumonitis or pulmonary fibrosis. The authors noted that this chronic lung injury occurred at lower doses or after a long latency period and, unlike the radiation pneumonitis that was fatal to dogs usually within 1-2 years,

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occurred over the same time period and same doses as the pulmonary carcinoma.

Exposure of hamsters to plutonium-239 dioxide [at tissue deposition levels of 1.4×10^4 , 7.1×10^4 , or 3.5×10^5 pCi (5.2×10^2 , 2.6×10^3 , or 1.3×10^4 Bq) plutonium-239/kg body weight, once every other month for a total of seven doses over 12 months] resulted in several respiratory effects over lifetime observation (Lundgren et al. 1983). Radiation pneumonitis was observed at all dose levels. Bronchiolar hyperplasia was seen in all groups, including controls, but incidences were statistically significantly increased over controls only in the highest dose group. The highest dose group also showed a statistically significant increase in alveolar squamous metaplasia (Lundgren et al. 1983).

In a similar experiment, mice were exposed (once every other month for a total of six doses over 10 months) to plutonium-239 dioxide resulting in deposition levels ranging from 1.8×10^4 to 4.1×10^5 pCi (6.7×10^2 to 1.5×10^4 Bq) plutonium-239/kg body weight, and were observed for life (Lundgren et al. 1987). Radiation pneumonitis and fibrosis were seen only in the highest dose group. However, the incidence of bronchial hyperplasia was statistically significant in the mid- and high-dose groups [at deposition levels of 8.1×10^4 or 4.1×10^5 pCi (3.0×10^3 or 1.5×10^4 Bq) plutonium-239/kg body weight]. The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to plutonium.

In on-going studies in dogs (Dagle et al. 1988; Park et al. 1988; Ragan et al. 1986) the earliest observed biological effect was in the hematopoietic system. Aerosols of plutonium-239 or plutonium-238, as the dioxide (Park et al. 1988), or plutonium-239 nitrate (Dagle et al. 1988) were each administered at six treatment levels. With plutonium-239 or plutonium-238, as the dioxide, lymphopenia occurred in the four highest exposure groups [at deposited levels of approximately 6.1×10^3 to 4.6×10^5 pCi (2.3×10^2 to 1.7×10^4 Bq) plutonium/kg body weight] (Park et al. 1988), but only in the two highest dose groups with plutonium-239 nitrate [1.3×10^5 -to 4.3×10^5 pCi (4.8×10^3 to 1.6×10^4 Bq) plutonium-239 nitrate/kg body weight] (Ragan et al. 1986). The lymphopenia was doserelated and correlated both in magnitude and time of appearance postexposure with the initial lung burden for each plutonium isotope. The highest NOAEL values and all reliable LOAEL values for hematological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

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Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to plutonium.

In a study by Dagle et al. (1988), increases in liver enzymes occurred in dogs after a single exposure that resulted in deposition levels above 4.4×10^5 pCi (1.6×10^2 Bq) plutonium-239 nitrate/kg body weight, compared to untreated controls. In dogs, 4 to 13 years following a single inhalation exposure to plutonium-239 dioxide [at deposited lung tissue levels of 2.4×10^4 to 8.7×10^4 pCi (8.9×10^2 to 3.2×10^3 Bq) plutonium-239/kg body weight] the livers were congested, granular, and pigmented (Park et al. 1988).

Exposure of Syrian hamsters to plutonium-239 dioxide (once every other month for a total of seven doses over 12 months) resulted in a statistically significant increase in degenerative liver lesions in the highest exposure group [at deposition levels of 3.5×10^5 pCi (1.3×10^4 Bq) plutonium-239/kg body weight] (Lundgren et al. 1983). These lesions included degeneration, necrosis, fibrosis, and amyloidosis. However, Lundgren stated that the lesions observed in these hamsters were typical of those usually seen in aged Syrian hamsters. Hamsters receiving lower levels of deposited radioactivity [1.4×10^4 or 7.1×10^4 pCi (5.2×10^2 or 2.6×10^3 Bq) plutonium-239/kg body weight] exhibited nonsignificant increases in liver lesions.

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

Investigations of the radiation effects of plutonium in laboratory animals indicated that translocation of plutonium from the lungs to other tissues was dependent on several factors including the solubility of the plutonium isotope or compound. Translocation to the bone occurred with plutonium citrate and with plutonium nitrate (Bair et al. 1973). By 4,000 days post-exposure, osseous atrophy and radiation osteodystrophy occurred in dogs given a single inhalation exposure to plutonium-238 dioxide (Gillett et al. 1988). The dose which resulted in these specific effects was not reported. For further discussion of this study see Section 2.2.1.8.

2.2.1.3 Immunological Effects

No studies were located regarding the immunological effects in humans after inhalation exposure to plutonium.

Plutonium-239 was transported to the tracheobronchial and mediastinal lymph nodes where it concentrated with time, often reaching higher levels in the lymph nodes than in the lungs (Bair et al. 1973). Lymphadenopathy was associated with a high concentration of plutonium in

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the thoracic and hepatic lymph nodes of dogs at lung tissue deposition levels as low as 1.7×10^3 pCi (6.3×10^1 Bq) plutonium-239 dioxide/kg body weight or 6.1×10^3 pCi (2.3×10^2 Bq) plutonium-238 dioxide/kg body weight (Park et al. 1988). Radiation-related effects in dogs included atrophy and fibrosis of the tracheobronchial lymph nodes (Gillett et al. 1988). Decreases in pulmonary alveolar macrophages in mice (Moores et al. 1986) and depressed-antibody-forming cells in hamsters (Bite et al. 1979) were reported. In addition, decreases in primary antibody responses in dogs (Morris and Winn 1978) were also reported. The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

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

2.2.1.4 Neurological Effects

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

Epidemiological studies have thus far been limited and have not established conclusively a direct association between plutonium exposure by the inhalation route and increases in genetic effects. A dose-related increase in chromosomal aberrations was observed among 343 plutonium-exposed workers at the Rocky Flats facility. In this group, systemic and lung plutonium burdens of 18.6 to 571.4 pCi (0.69 to 21.2 Bq) plutonium/kg body weight were estimated based on urine analyses and lung deposition estimates (Brandom et al. 1979). Because the frequencies of aberrations were relatively low and the dose estimates imprecise, the authors advised caution regarding use of the data. A study of blood lymphocyte chromosomes of 54 plutonium workers in the United Kingdom was conducted by Tawn et al. (1985). (This study is a continuation of that reported in Schofield (1980).) Systemic body burdens of 114 to >570.8 pCi (4.3 to >21.1 Bq) plutonium/kg body weight were estimated based on urine analyses. While some differences in the distribution of aberrations were seen in the radiation exposed groups, the authors concluded that significant deposits of plutonium did not cause an increase in aberrations. In other studies, Manhattan Project plutonium workers (26 individuals) were followed for 27 to 32 years; no apparent correlation was observed between the frequency of chromosomal aberrations and plutonium body burdens [71.4 to 3.1×10^3 pCi (2.6 to 114.8 Bq) plutonium/kg body weight based on urine analyses] (Hempelmann et al. 1973; Voelz et al. 1979).

Chromosomal aberrations were observed in Rhesus monkeys and Chinese hamsters following inhalation exposure to plutonium. Increases in

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chromosomal aberrations in blood lymphocytes were seen in immature Rhesus monkeys in the high-exposure groups exposed for a single day to plutonium-239 dioxide [deposited levels of 5×10^4 to 5×10^5 pCi (1.9×10^3 to 1.9×10^4 Bq) plutonium-239 dioxide/kg body weight] at 1 and 3 months post-exposure, but not at lower levels (LaBauve et al. 1980). Dose-related increases in the frequency of chromosomal aberrations were observed in Chinese hamster blood cells 30 days after exposure of the animals to plutonium at deposited levels of 1×10^7 to 2.6×10^8 pCi (3.7×10^5 to 9.6×10^5 Bq) plutonium-239 dioxide/g of lung tissue (Brooks et al. 1976a).

2.2.1.8 Cancer

Epidemiological studies of occupational cohorts exposed to plutonium have been conducted at two plutonium processing plants, the Los Alamos National Laboratory and the Rocky Flats Nuclear Weapons Plant. A causal link between plutonium exposure and cancer has not been demonstrated in these studies, although there are some suggestions of effects. A prospective mortality study was begun in 1952 on a group of 26 subjects who worked with plutonium at Los Alamos Laboratory during World War II in the Manhattan Project. They have now been studied for 37 years (Voelz et al. 1985). Follow-up has included extensive medical examinations and urine analyses to estimate plutonium body burdens, which showed systemic plutonium deposition ranging from 2,000 to 95,000 pCi (74 to 3,500 Bq) plutonium with a mean of 26,000 pCi (9.6×10^2 Bq) plutonium. Mortality in this group as compared to that of United States white males in the general population was significantly less than expected (2.0 vs. 6.6). In addition, no malignant neoplasms have occurred during this extensive period of follow-up. Despite the fact that this study involves only a small number of individuals, it provides information about those who have encountered relatively high plutonium exposures (resulting in deposition of up to 95,000 pCi) and have been followed over a considerable length of time. A study of an additional cohort of 224 Los Alamos male workers was begun in 1974 (Voelz et al. 1983a). Average whole body deposition was estimated at 19,000 pCi (700 Bq) plutonium. Mortality, adjusted for age and year of death, was compared to that of United States males in the general population. Among the cohort, 43 deaths were observed as compared to 77 expected. The number of deaths due to malignant neoplasms among the cohort was also considerably lower than expected (8 vs. 15) including only one lung cancer death vs. five expected.

The studies at the Rocky Flats facility consisted of mortality studies of workers at the plant (Voelz et al 1983b; Wilkinson et al. 1987) and a study of residents living downwind from the facility (Johnson 1981, 1988). Voelz et al. (1983b) reported the results of a study of 7,112 workers employed at the Rocky Flats facility during 1952-1979. Observed deaths were significantly lower than expected (452 vs. 831). Malignant neoplasms were also lower than expected (107 vs. 167).

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In a re-analysis of the same Rocky Flats cohort, Wilkinson et al. (1987) investigated mortality patterns among those employed at the facility for at least 2 years. This reduced the cohort size to 5,413 white males. Comparisons of mortality through 1979 were made with expected mortality for United States males in the general population. In addition, employees were ranked according to plutonium body burden, estimated by urinalyses, as either less than 2,000 pCi (74 Bq) or greater than 2,000 pCi (74 Bq) plutonium body burden. Comparisons were made between these two exposure groups. When the cohort with at least 3 years of employment was compared to United States white males, the observed mortality was less than expected. However, the incidences of benign and unspecified neoplasms were greater than expected. These conclusions regarding mortality are in complete agreement with Voelz et al. (1983b). However, when the cohort reported by Wilkinson et al. (1987) was categorized by exposure [less than or greater than 2,000 pCi (74 Bq)] and the two groups compared, it was reported that the group with greater exposure had slightly elevated risk for mortality from all causes of death and from all lymphopoietic neoplasms (Wilkinson et al. 1987). However, the mortality ratios for lung, bone, and liver cancer were not elevated. The authors cautioned that comparisons between the two exposure groups were often based on small numbers of cases, so the precision of these observations is low. There were only four cases of cancers classified as lymphopoietic neoplasms. In addition, they suggested that the results could have been confounded by external radiation exposure (from working in the plutonium facility) or by potential interaction between plutonium radiation and external radiation.

A study of cancer mortality for 1969-1971 in residents near the Rocky Flats facility indicated a somewhat higher incidence than normal for all cancers in individuals living in the areas contaminated with plutonium (Johnson 1981). Tumors of the gonads (testes and ovaries), liver, pancreas, and brain contributed to the higher incidence, whereas the incidences of lung and bone tumors, frequently observed in laboratory animal studies, were not elevated. In a re-analysis of the 1969-1971 data, as well as cancer mortality in 1979-1981 (a more appropriate cancer latency period for the Rocky Flats area contamination), Crump et al. (1987) did not find an increase in the likelihood of developing cancer for those living near the Rocky Flats facility. Crump et al. (1987) attributed the findings of Johnson (1981) to the lack of consideration of confounding urban factors in the design of the study.

Case control studies have been conducted to evaluate the incidence of brain tumors and melanomas, in order to examine the potential associations with plutonium exposure. The study of brain tumors at the Rocky Flats facility and melanomas at Los Alamos did not reveal an association of either disorder with plutonium exposure (Reyes et al. 1983; Acquavella et al. 1983a).

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Two epidemiology studies have been conducted on a cohort of workers at the Hanford Plant, which produced plutonium in nuclear reactors. Because plutonium exposure was minimal, the studies primarily related to external radiation. Radiation work at Hanford includes reactor operation, chemical separation, fuel fabrication, and research. The radiation is primarily gamma, but also includes neutron, X-radiation, and tritium exposure (Gilbert and Marks 1979). Exposure levels of plutonium were not reported and individuals with plutonium body burdens comprised less than 3% of the cohort. In one study, a cohort of 12,500 white male workers employed at the Hanford Plant for at least 2 years was analyzed for mortality as well as cause of death (Gilbert and Marks 1979). The mean dose was reported to be 4.75 rem. Mortality from all causes was significantly less than that of United States white males. Death from malignant neoplasms of the pancreas and multiple myeloma occurred at rates higher than expected; deaths from these causes occurred in the group with a dose greater than 15 rem. This correlation was based on a small number of deaths (three each for cancer of the pancreas and multiple myeloma vs. 1 and 0.5 expected, respectively); however, only the increase in the incidence of multiple myeloma was statistically significant.

In a re-evaluation of the Hanford cohort, which included approximately 28,000 male and female workers, Kneale et al. (1981) detected a significant increase in the cancers in radiosensitive tissues in workers exposed to external radiation. Radiosensitive tissues grouped together in their analyses included cancers of the stomach, large intestine, pancreas, pharynx, lung, breast, reticuloendothelial system (lymphoma, myeloma, myeloid leukemia and others), and thyroid. Approximately 50% of these cancers were in the lung; however, smoking histories were not considered in the analysis. Of the male population, only 3% or 225 men had definite evidence of internal radiation. Due to this fact the authors stated that they could safely assume that the incidence of cancer from internal radiation was small compared with that associated with external radiation.

Studies have indicated that plutonium is a lung, skeletal, and liver carcinogen in animals depending on its chemical form, route of exposure, and species. Inhaled plutonium-239 dioxide is insoluble and is retained primarily in the lungs and associated lymph nodes (Muggenburg et al. 1987a; Park et al. 1988). Inhaled plutonium-238 is solubilized and is subsequently translocated from the lung to the bone and liver (Gillett et al. 1988). While the pattern of nonmalignant toxicity among the laboratory species tested was similar (i.e., radiation pneumonitis and pulmonary fibrosis occurred in the higher radiation dose groups in all species tested), species differences in the induction of cancer were apparent. With the exception of Syrian hamsters, cancer developed in animals in the lower exposure groups or in animals that survived initial radiation damage to the lungs.

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Experiments in dogs have provided the most extensive database on radiation-induced cancer following inhalation exposure to plutonium. The most frequently observed cancer in dogs treated with plutonium-239 dioxide was lung cancer. The majority of lung tumors in dogs were bronchiolar-alveolar carcinomas. In dogs treated with plutonium-238 or the more soluble forms of plutonium-239, such as the nitrate, plutonium translocates from the lungs to other sites, where liver and bone tumors, in addition to lung tumors, have been reported.

Lung tumors were the primary cause of death in dogs exposed to plutonium-239 dioxide at an initial lung deposition as low as 2.1×10^4 pCi (7.8×10^2 Bq) plutonium-239/kg body weight (Muggenburg et al. 1987a; Park et al. 1988). In the study by Park et al. (1988), early deaths among dogs in the highest dose group receiving plutonium-239 resulted from radiation pneumonitis accompanied by respiratory dysfunction, fibrosis, focal hyperplasia, and metaplasia. Increases in the incidence of lung cancer were statistically significant at three lower doses of 6.2×10^3 pCi/kg (2.3×10^2 Bq/kg), 2.4×10^4 pCi/kg (8.9 Bq/kg), and at 8.7×10^4 pCi/kg (3.2×10^3 Bq/kg)/kg body weight. The first lung tumor was found in a dog that died 37 months following exposure; ultimately, after 16 years post-exposure, 55 of the 136 dogs had lung tumors.

With exposure to plutonium-238 dioxide, the primary cause of cancer deaths was osteosarcomas rather than lung tumors. However, lung tumors frequently developed in dogs given a single inhalation exposure to plutonium-238 dioxide resulting in lung deposition levels as low as 1.4×10^3 pCi (5.2×10^1 Bq) plutonium-238/kg body weight (Gillett et al. 1988; Park et al. 1988). In the on-going study by Gillett et al. (1988), of 144 dogs at the beginning of the experiment, 112 died by day 4,000 post-exposure; of these, 100 had osteosarcomas and 28 had lung cancer. With increasing time after exposure, liver lesions increased in severity, with the first liver tumor observed after 3,000 days; the occurrence of primary liver tumors after inhalation exposure to plutonium-238 had not been reported previously.

Osteosarcomas were the principal cause of death among dogs given a single inhalation exposure resulting in deposited levels of 2.3×10^4 to 1.3×10^5 pCi (8.5×10^2 to 4.8×10^3 Bq) plutonium-239 nitrate/kg body weight, although some lung tumors were observed (Dagle et al. 1988). All dogs in the highest exposure group [4.2×10^5 pCi (1.6×10^4 Bq) plutonium-239 nitrate/kg body weight] died of radiation pneumonitis. Cancer mortality in the three lowest exposure groups were comparable to controls.

Statistically significant increases in lung cancer have been reported in rats, with lung deposition levels of 3.1×10^4 pCi (1.1×10^3 Bq) plutonium-238/kg body weight (Sanders et al. 1977) or greater than 3×10^4 pCi (1.1×10^3 Bq) plutonium-239/kg body weight (Sanders and Mahaffey 1979; Sanders et al. 1988). While pulmonary tumors in mice exposed to

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plutonium-239 dioxide increased with increasing initial lung deposition, the incidence of lung tumors in any treated group was not statistically significantly different from the untreated controls (Lundgren et al. 1987).

The pulmonary toxicity of plutonium-239 dioxide in Rhesus monkeys and baboons was similar to that of other species; however, they appear to be less sensitive to radiation-induced lung tumors than dogs and rats. A primary lung tumor occurred in one of nine Rhesus monkeys that survived for 9 years post-treatment (Hahn et al. 1984). Two of 32 baboons developed lung tumors (Metivier et al. 1974) at deposition levels of 2.88×10^5 to 7.2×10^6 pCi (1.06×10^4 to 2.67×10^5 Bq) plutonium-239 dioxide/kg body weight; these deposition levels are comparable to those that resulted in lung tumors in dogs.

Syrian hamsters appear to be resistant to lung tumor induction following inhalation of plutonium-239 or plutonium-238 particles. Hamsters were also resistant to radiation-induced lung cancer following exposure to other alpha-emitting radionuclides, such as radon and radon daughters (ATSDR 1990). No statistically significant increases in tumor incidence occurred in lifetime studies in hamsters that had received a single inhalation exposure to plutonium-238 dioxide or plutonium-239 dioxide at lung deposition levels of approximately 1.4×10^6 to 1.7×10^6 pCi (5.2×10^4 to 6.3×10^4 Bq) plutonium-238/kg body weight (Mewhinney et al. 1987a; Sanders 1977) or 1.4×10^6 pCi (5.2×10^4 Bq) plutonium-239/kg body weight (Sanders 1977).

Exposure of Syrian hamsters for an intermediate duration (once every other month for a total of seven doses over 12 months) to plutonium-239 dioxide, at deposited levels of 1.4×10^4 , 7.1×10^4 , or 3.5×10^5 pCi (5.2×10^2 , 2.6×10^3 , or 1.3×10^4 Bq) plutonium/kg body weight, resulted in several respiratory effects (see Section 2.2.1.2), but no lung tumors were observed in this study (Lundgren et al. 1983). The authors stated that the Syrian hamster may be an inappropriate animal model for lung cancer induction with alpha emitters.

Exposure of mice to plutonium-239 dioxide for an intermediate duration (once every other month for a total of six doses over 10 months) at deposited levels of 1.8×10^4 , 8.1×10^4 , or 4.1×10^6 pCi (6.7×10^2 , 3.0×10^3 , or 1.5×10^5 Bq) plutonium-239/kg body weight resulted in significant lung tumor development in the two lower dose groups (Lundgren et al. 1987). Early mortality precluded tumor development in the highest dose group. Pulmonary tumors (adenomas and adenocarcinomas) were seen in less than 2% of controls but in 13% of low-dose animals and 18% of mid-dose animals.

In a study designed to investigate the effect of temporal dosedistribution, rats were exposed to plutonium-239 dioxide once a month for 3 months with lung deposition levels totaling 8.6×10^4 pCi (3.2×10^3

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Bq) plutonium-239/kg body weight, or once a week (for up to 22 weeks) with lung deposition totaling 1.3×10^5 to 4.0×10^5 pCi (4.8×10^3 to 1.5×10^4 Bq) plutonium-239/kg body weight (Sanders and Mahaffey 1961). Lung tumor occurrence ranged from 19 to 60% in treated animals with tumors primarily categorized as adenocarcinomas and squamous carcinomas. No significant difference in lung tumor incidence was observed in mice exposed once a week versus mice exposed once a month for 3 months. Based on total alveolar deposition, a dose-dependent increase in the incidence of all lung tumors was observed. Untreated controls were included in the study, but tumor incidence for these animals was not reported.

2.2.2 Oral Exposure

Exposure by the oral route may occur; however, absorption of plutonium from the gastrointestinal tract appears to be limited (see Section 2.3). Health effects associated with oral exposure to plutonium are presented in Table 2-2 and Figure 2-2.

2.2.2.1 Death

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

Neonatal rats were given 3.3×10^8 pCi (1.2×10^7 Bq) plutonium-238 citrate/kg body weight by gavage (Fritsch et al. 1987). This single exposure to plutonium resulted in the death of 45% of the treated animals by 2 weeks post-exposure. No deaths were reported in groups given 1×10^5 pCi (3.7×10^3 Bq) plutonium-238/kg (Fritsch et al. 1987).

2.2.2.2 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 administration by gavage of 1×10^5 or 3.3×10^8 pCi (3.7×10^3 or 1.2×10^7 Bq) plutonium-238 citrate/kg body weight (Fritsch et al. 1987). In the lower treatment group, mild hypertrophy of the crypts of the small intestine, which form the secretions of the small intestine, was observed 11 days post-exposure. Total disappearance of epithelial cells and crypts, combined with intestinal hemorrhaging, was observed in the higher treatment group, also sacrificed at 11 days. However, neonatal rodents have immature and poorly enclosed crypts in the small intestine,

TABLE 2-2. Levels of Significant Exposure to Plutonium - Oral

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (pCi/kg)	LOAEL (Effect)		Reference	Chemical Species
					Less Serious (pCi/kg)	Serious (pCi/kg)		
ACUTE EXPOSURE								
Death								
1	Rat	(G) 1d		1.0x10 ⁵		3.0x10 ⁸	Fritsch et al. 1987	²³⁸ Pu citrate
Systemic								
2	Rat	(G) 1d	Gastro		1.6x10 ¹¹ (path change)		Sullivan et al. 1960	²³⁹ PuO ₂
3	Rat	(G) 1d	Gastro		1.0x10 ⁵ (hypertrophy)	3.3x10 ⁸ (intestinal hemor)	Fritsch et al. 1987	²³⁸ Pu citrate
			Other	1.0x10 ⁵		3.3x10 ⁸ (growth inhibit)		

d = day; (G) = gavage; Gastro = gastrointestinal; hemor = hemorrhaging; inhibit = inhibition; LOAEL = lowest observed adverse effect level; NOAEL = no observed adverse effect level; path = pathological

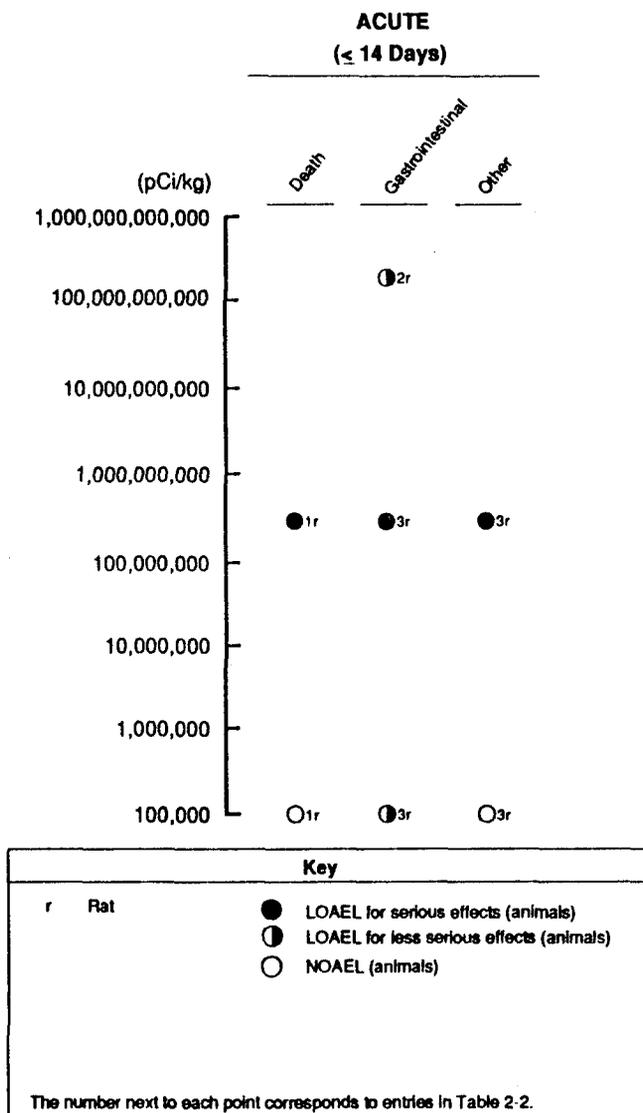


FIGURE 2-2. Health Effects Associated with Plutonium Deposition - Oral

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which is the main site of plutonium retention following oral exposure (see Section 2.3.2.4), as compared to other neonatal mammals. Therefore, neonatal rats could be expected to be more sensitive to the radiologic effects of plutonium than other neonates or adult mammals (Fritsch et al. 1987). Gastrointestinal effects have also been observed in adult rats given 1.6×10^{11} pCi (5.7×10^9 Bq) plutonium-239 dioxide/kg body weight. At 3 days post-exposure, there was an increase in neutrophils on the surface epithelium and superficial cellular layers of the large intestine (Sullivan et al. 1960). At 6 days post-exposure this increase was no longer observed.

Other Systemic Effects. No studies were located regarding other effects in humans or animals after oral exposure to plutonium. No studies were located regarding the following health effects in humans or animals after oral exposure to plutonium.

2.2.2.3 Immunological Effects

2.2.2.4 Neurological Effects

2.2.2.5 Developmental Effects

2.2.2.6 Reproductive Effects

2.2.2.7 Genotoxic Effects

2.2.2.8 Cancer

2.2.3 Dermal Exposure

2.2.3.1 Death

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

2.2.3.2 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.

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2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

2.2.4 Other Routes of Exposure

Health effects associated with plutonium administered by injection are presented in Table 2-3 and Figure 2-3.

2.2.4.1 Death

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

A significant decrease in lifespan was observed in rats, mice, and hamsters following a single injection of plutonium-239 at concentrations ranging from 2×10^5 to 7.5×10^7 pCi (7.4×10^3 to 2.8×10^5 Bq) plutonium-239/kg body weight given as the citrate (intravenous) or dioxide (intraperitoneal) (Ballou et al. 1967; Brooks et al. 1983; Sanders 1973a; Svoboda et al. 1980a, 1980b). Survival times decreased with increasing doses in rats and hamsters (Brooks et al. 1983; Sanders 1973a). Death resulted from bone marrow hypoplasia in hamsters approximately 400 days following an intravenous exposure [2×10^7 pCi (7.4×10^5 Bq) plutonium-239 citrate/kg body weight] (Brooks et al. 1982). In rats injected intraperitoneally at concentrations up to 8.3×10^6 pCi (3.1×10^5 Bq) plutonium-239 dioxide/kg body weight, death resulted mainly from large malignant abdominal tumors accompanied by hemorrhage-induced anemia approximately 350 to 580 days post-exposure (Sanders 1973a).

An age-dependent effect on lethality was observed in rats injected intravenously with 6×10^6 to 9×10^7 pCi (2.2×10^5 to 3.3×10^5 Bq) plutonium-239/kg body weight as the monomeric (citrate) or polymeric (nitrate) forms (Mahlum and Sikov 1974). Neonates were more susceptible to the lethal effects of the monomeric form of plutonium-239, while adults and weanlings were more susceptible to the polymeric form.

Animal studies indicate that the polymeric (nitrate) forms of plutonium-239 and plutonium-238 are more acutely toxic than the corresponding monomeric (citrate) forms (see Section 2.3.2.4). In rats, 30-day LD₅₀s for the monomeric [9.7×10^7 pCi (3.6×10^6 Bq)/kg] and

TABLE 2-3. Health Effects Associated with Plutonium Administration - Other Routes of Exposure

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (pCi/kg)	LOAEL (Effect)		Reference	Chemical Species
					Less Serious (pCi/kg)	Serious (pCi/kg)		
ACUTE EXPOSURE								
Death								
1	Rat	(IV) 1d		1.3x10 ⁸			Ballou et al. 1967	²³⁸ Pu citrate
2	Rat	(IV) 1d				9.7x10 ⁷ (30 day LD50)	Mahlum and Sikov 1974	²³⁹ Pu citrate
3	Rat	(IV) 1d				9.8x10 ⁷ (30 day LD50)	Mahlum and Sikov 1969a	²³⁸ Pu nitrate
4	Rat	(IV) 1d				1.6x10 ⁸ (30 day LD50)	Mahlum and Sikov 1969a	²³⁸ Pu citrate
5	Rat	(IV) 1d				4.7x10 ⁷ (30 day LD50)	Mahlum and Sikov 1974	²³⁹ Pu nitrate
6	Rat	(IV) 1d				7.9x10 ⁷ (dec lifespan)	Ballou et al. 1967	²³⁹ Pu citrate
7	Mouse	(IV) 1d				4.9x10 ⁶ (dec lifespan)	Svoboda et al. 1980a	²³⁹ Pu citrate
8	Hamster	(IV) 1d				2.0x10 ⁶ (dec lifespan)	Brooks et al. 1983	²³⁹ Pu citrate
Systemic								
9	Human	(IV) 1d	Hemato	7.3x10 ³			Langham et al. 1980	²³⁸ Pu or ²³⁹ Pu citrate
10	Rat	(IP) 1d	Resp	8.3x10 ⁶			Sanders 1975a	²³⁹ PuO ₂
11	Rat	(IV) 1d	Musc/skel			1.8x10 ⁷ (dec break strength)	Sikov and Mahlum 1976	²³⁹ Pu citrate
12	Rat	(IV) 1d	Hemato Hepatic			3.6x10 ⁷ (dec WBC & RBC count) 7.5x10 ⁷ (liver damage)	Ballou et al. 1967	²³⁸ Pu citrate

TABLE 2-3 (continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (pCi/kg)	LOAEL (Effect)		Reference	Chemical Species
					Less Serious (pCi/kg)	Serious (pCi/kg)		
13	Rat	(IP) 1d	Resp Hemato			2.0x10 ⁵ (pneumonitis) 8.2x10 ⁶ (lymphopenia)	Sanders 1973a	²³⁹ PuO ₂
14	Mouse	(IV) 1d	Hemato			3.6x10 ⁵ (dec stem cells)	Svoboda et al. 1987	²³⁹ Pu citrate
15	Hamster	(IV) 1d	Hepatic			2.0x10 ⁶ (hep degener)	Benjamin et al. 1976	²³⁹ Pu citrate
16	Dog	(IV) 1d	Musc/skel	3.0x10 ⁵		1.0x10 ⁶ (fractures)	Taylor et al. 1962	²³⁹ Pu citrate
17	Dog	(SB) 1d	Derm/oc			9.8x10 ⁴ (scarring)	Dagle et al. 1984	²³⁹ Pu nitrate
18	Dog	(IV) 1d	Hemato	9.0x10 ⁵		2.9x10 ⁶ (dec lymphocytes)	Dougherty and Rosenblatt 1971	²³⁹ Pu citrate
19	Dog	(IV) 1d	Musc/skel	1.0x10 ⁵			Bruenger et al. 1978	²³⁹ Pu citrate
20	Dog	(IV) 1d	Hepatic			3.0x10 ⁶ (func impair)	Cochran et al. 1962	²³⁹ Pu citrate
21	Dog	(IV) 1d	Hepatic	6.3x10 ²	1.9x10 ³ (nodules)		Taylor et al. 1986	²³⁹ Pu citrate
Immunological								
22	Dog	(SB) 1d				7.5x10 ⁵ (scarred lymph nodes)	Dagle et al. 1984	²³⁹ Pu oxide
Developmental								
23	Rabbit	(IV) 9,15,27,9 15-28 Gd				1.0x10 ⁷ (fetal lethal)	Kelman et al. 1982a	²³⁹ Pu citrate

TABLE 2-3 (continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (pCi/kg)	LOAEL (Effect)		Reference	Chemical Species
					Less Serious (pCi/kg)	Serious (pCi/kg)		
Cancer								
24	Rat	(IT) 1d				8.2x10 ⁴ (CEL-lung)	Sanders 1975b	²³⁹ PuO ₂
25	Rat	(IV) 1d				3.0x10 ⁵ (CEL-skeletal)	Sikov et al. 1978a	²³⁹ Pu citrate
26	Rat	(IP) 1d				2.0x10 ⁵ (CEL-abdominal)	Sanders 1973	²³⁹ PuO ₂
27	Rat	(IP) 1d				3.6x10 ⁶ (CEL-mammary)	Sanders 1974	²³⁸ PuO ₂
28	Mouse	(IP) 1d				3.2x10 ⁶ (CEL-skeletal)	Taylor et al. 1983	²³⁹ Pu citrate
29	Mouse	(IV) 1d				4.9x10 ⁶ (CEL-leukemia)	Svoboda et al. 1981	²³⁹ Pu citrate
30	Hamster	(IV) 1d				2.0x10 ⁶ (CEL-skeletal, liver)	Brooks et al. 1983	²³⁹ Pu citrate
31	Dog	(IV) 1d				1.0x10 ⁴ (CEL-skeletal)	Mays et al. 1987	²³⁹ Pu citrate
32	Dog	(IV) 1d				1.9x10 ³ (CEL-liver)	Taylor et al. 1986	²³⁹ Pu citrate
INTERMEDIATE EXPOSURE								
Cancer								
33	Mouse	(IP) 8 wk 2 d/wk 16 d				5.0x10 ⁴ (CEL-leukemia)	Humphreys et al. 1987	²³⁹ Pu nitrate

break = breaking; CEL = cancer effect level; d = day; dec = decreased; Derm/oc = dermal/ocular; func impair = functional; Hemato = hematological; hep degener = hepatic degeneration; (IP) = intraperitoneal; (IT) = intratracheal; (IV) = intravenous; LD50 = dose which produces lethal effects in 50% of the animals; LOAEL = lowest observed adverse effect level; Musc/skel = musculoskeletal; NOAEL = no observed adverse effect level; RBC = red blood cell; Resp = respiratory; (SB) = subcutaneous; WBC = white blood cell; wk = week

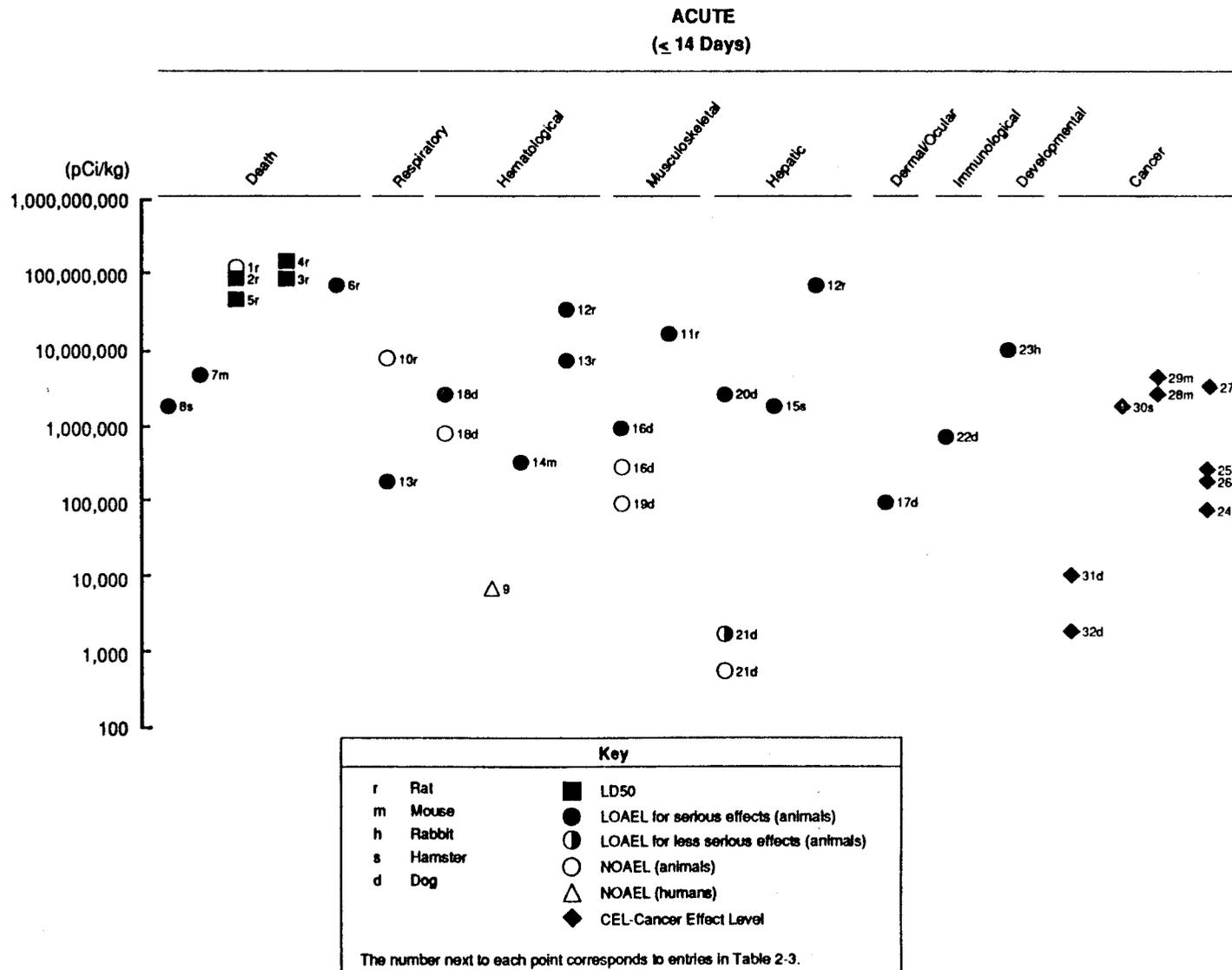


FIGURE 2-3. Health Effects Associated with Plutonium Deposition - Other Routes of Exposure

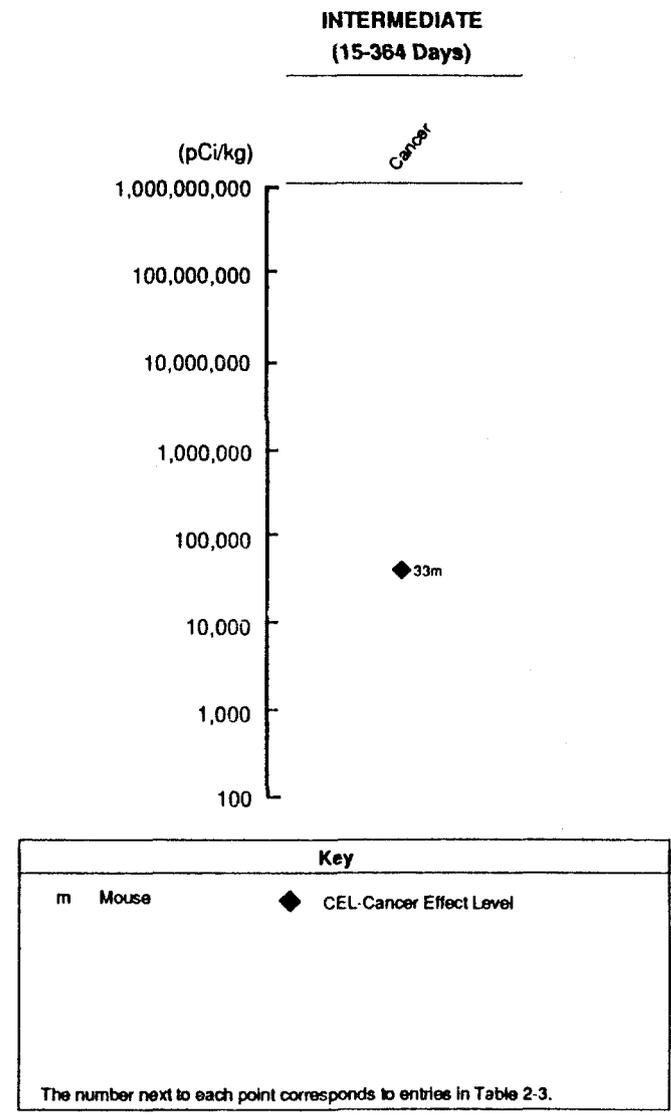


FIGURE 2-3 (Continued)

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polymeric [4.7×10^7 pCi (1.7×10^5 Bq)/kg] forms of plutonium-239 were lower than 30-day LD_{50} s for the corresponding forms of plutonium-238 [monomeric, 1.6×10^8 pCi (5.9×10^6 Bq)/kg; polymeric, 9.8×10^7 pCi (3.6×10^6 Bq)/kg] (Mahlum and Sikov 19696; 1974).

Plutonium-239 is more acutely toxic than an equivalent picocuric amount of plutonium-238 (Ballou et al. 1967). Survival times in rats given a single intravenous injection of 7.9×10^7 to 1.3×10^8 pCi (2.9×10^6 to 4.8×10^6 Bq) plutonium-239 citrate/kg body weight were decreased, while survival times of rats administered equivalent amounts, on a radioactivity basis, of plutonium-238 citrate were not reduced (Ballou et al. 1967).

2.2.4.2 Systemic Effects

No studies were located regarding cardiovascular or gastrointestinal effects in humans or animals after exposure to plutonium by other routes.

Respiratory Effects. No studies were located regarding respiratory effects in humans after exposure to plutonium by other routes. Increases in the incidence of pneumonitis, inflammation, and edema were observed in the lungs of rats following administration of 2×10^5 pCi (7.4×10^3 Bq) plutonium-239 dioxide/kg body weight as a single intraperitoneal injection (Sanders 1973a). However, the statistical significance of these increases in respiratory effects could not be determined based on the reported data.

Hematological Effects. No acute effects, as measured by evaluation of hematological end points, occurred in a case study of 18 humans following a single intravenous injection at levels ranging from 4×10^3 to 7.3×10^3 pCi (1.5×10^2 to 2.7×10^2 Bq) plutonium-238 or -239 citrate/kg body weight (Langham et al. 1980). (While reported in a memorial publication that republished Dr. Langham's work, this particular study was conducted in the early 1950s.) Thirty years following exposure to plutonium, 4 of the 18 individuals were still alive. One case could not be located for follow-up. The authors reported that plutonium could not be considered a contributing factor to the cause of death in the 13 cases (Rowland and Durbin 1976).

Anemia was observed in laboratory animals following a single injection of plutonium-238 or -239. Rats given a single intraperitoneal injection of plutonium-239 dioxide [8×10^6 pCi (3.0×10^5 Bq)/kg] or a single intravenous injection of plutonium-238 citrate [3.6×10^7 pCi (1.3×10^6 Bq)/kg] developed anemia (Ballou et al. 1967; Sanders 1973a; Sanders and Jackson 1972). In rats exposed intravenously, a decrease in viable bone marrow with replacement of marrow by a calcified plug

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accompanied the anemia (Ballou et al. 1967). Anemia, characterized by decreases in red blood cell volume, accompanied by increases in the number of new red blood cells (reticulocytes), was observed in dogs exposed to a single intravenous injection of 2.9×10^6 pCi (1.1×10^5 Bq) plutonium-239 citrate/kg (Dougherty and Rosenblatt 1971).

A decrease in the number of white blood cells, which continued to decrease with time post-exposure, was observed in rats given a single intravenous injection of 3.6×10^7 pCi (1.3×10^6 Bq) plutonium-238 citrate/kg (Ballou et al. 1967). Lymphopenia was observed in rats given a single intraperitoneal injection of 8.2×10^6 pCi (3.0×10^5 Bq) plutonium-239 dioxide/kg (Sanders 1973a; Sanders and Jackson 1972). Decreased white blood cell counts were also observed in dogs given a single intravenous injection of 2.9×10^6 pCi (3.7×10^3 Bq) plutonium-239 citrate/kg (Dougherty and Rosenblatt 1971).

Svoboda and co-workers (1979, 1980a, 1980b, 1982a, 1983, 1985, 1987) have conducted extensive research on mice concerning the effects of plutonium-239 on stem cells, the blood producing cells of the bone marrow. These effects on bone marrow are considered to be "preleukemic" by these authors (Svoboda and Kotaskova 1982). Administration of monomeric plutonium-239 citrate [3.6×10^5 pCi (1.3×10^4 Bq)/kg] as a single intravenous injection resulted in a decrease in the number of hematopoietic stem cells of the bone marrow in mice as soon as 4 weeks after exposure (Svoboda et al. 1987). This initial damage in one portion of the bone marrow appeared to be partially compensated, as exhibited by a slight increase in the number of stem cells (due to increased proliferative activity) in another part of the tissue by approximately 30 weeks post-exposure; however, the number of stem cells was still less than the number observed in untreated controls (Svoboda and Kotaskova 1982; Svoboda et al. 1979). The authors hypothesize that persistent radiological damage to the stem cells from plutonium-239 may lead to an early stage of leukemia (Svoboda and Kotaskova 1982). A similar decrease in stem cells was reported in mice given a single intravenous injection of polymeric plutonium-239 nitrate [5×10^6 to 1.5×10^7 pCi (1.9×10^5 to 5.6×10^5 Bq)/kg] (Joshima et al. 1981).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after exposure to plutonium by other routes.

Increased numbers of spontaneous fractures occurred in dogs given a single intravenous injection of 1×10^5 to 3×10^6 pCi (3.7×10^3 to 1.1×10^5 Bq) plutonium-239 citrate/kg body weight (Ta, et al. 1962). Total incidence of fractures decreased with decrease: dose with only one fracture observed in the two lowest treatment groups [1×10^5 and 3×10^5 pCi (3.7×10^3 and 1.1×10^4 Bq) plutonium-239/kg] combined.

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The anatomical range of the fractures increased with increasing dose. Plutonium exposure did not result in growth retardation in neonatal dogs as measured by the growth of long bones (Bruenger et al. 1978).

Age-dependent differences in the musculoskeletal effects induced by plutonium have been observed in adult, weanling, and neonatal rats given single intravenous injections of plutonium at concentrations ranging from 6×10^6 to 9×10^7 pCi (2.2×10^5 to 3.3×10^6 Bq) plutonium-239/kg body weight, administered in the monomeric or the polymeric forms (Mahlum and Sikov 1969b; Sikov and Mahlum 1976). Weanlings were more susceptible to the musculoskeletal effects of plutonium (Mahlum and Sikov 1969b), possibly due to the rapid growth of the bone cells, and greater radiosensitivity of these cells to plutonium. An increase in the incidence of spontaneous fractures was observed in weanlings, but not in adults or neonates, given the monomeric form of plutonium-239 (Sikov and Mahlum 1976). A decrease in the breaking strength of the femur was observed in weanling and adult rats, but was more pronounced in weanlings (Sikov and Mahlum 1976). In neonatal rats, the only musculoskeletal effects, which were mild and sporadic, were observed in the higher treatment groups administered greater than 6×10^7 pCi (2.2×10^6 Bq)/kg (Sikov and Mahlum 1976; Mahlum and Sikov 1969b).

Hepatic Effects. No studies were located regarding hepatic effects in humans after exposure to plutonium by other routes.

Hepatic damage was observed in rodents after a single intravenous injection of high levels of plutonium. Severe hepatic degeneration occurred in hamsters observed for life following administered levels as low as 2×10^6 pCi (7.4×10^4 Bq) plutonium-239 citrate/kg body weight (Benjamin et al. 1976). A single intravenous injection of 7.5×10^7 pCi (2.8×10^6 Bq) plutonium-239 citrate/kg resulted in damage to the liver parenchyma of rats as early as 15 days post-exposure (Ballou et al. 1967).

In studies in which dogs were given a single intravenous injection of plutonium-239 citrate, hepatic effects were observed to be dose-related. No hepatic effects were reported in dogs given 630 pCi (23 Bq) plutonium/kg body weight (Taylor et al. 1986), while gross and microscopic liver nodules and/or hyperplasia were observed by year 8 following injection of 1.9×10^3 to 3×10^5 pCi (7.0×10^1 to 1.1×10^4 Bq) plutonium-239/kg (Cochran et al. 1962; Taylor et al. 1986). At higher levels [1×10^6 and 3×10^6 pCi (3.7×10^4 and 1.1×10^5 Bq) plutonium-239/kg], functional impairment of the liver was observed 4 years post-exposure (Cochran et al. 1962). Some of the animals at the highest treatment level [3×10^6 pCi (1.1×10^5 Bq)/kg] had functional impairment, as well as shrunken livers and ascites, which the authors described as indicative of decompensated cirrhosis (Cochran et al. 1962).

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Renal Effects. No studies were located regarding renal effects in humans after exposure to plutonium by other routes.

Mild to severe chronic nephritis was observed in Sprague-Dawley rats following a single intraperitoneal injection of 2×10^5 pCi (7.4×10^3 Bq) plutonium-239 dioxide (Sanders 1973a). However, the statistical significance of these renal effects could not be determined based on the reported data. In addition, renal nephritis may be a common occurrence in the strain of rats used in this study.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after exposure to plutonium by other routes.

Loss of hair, thickening of the dermis, and focal scarring were observed around subcutaneous implants of plutonium-239 in dogs administered plutonium dioxide [7.5×10^5 pCi (2.8×10^4 Bq)/kg] or plutonium nitrate [9.8×10^4 pCi (3.6×10^3 Bq)/kg] (Dagle et al. 1984). These effects may have resulted from exposure to plutonium; however, the statistical significance of these dermal effects could not be determined based on the reported data.

Other Systemic Effects. Other systemic effects have been observed in rats following a single injection of plutonium. Mesothelial hyperplasia was observed in rats injected intraperitoneally with 8×10^6 pCi (3.0×10^5 Bq) plutonium-239 dioxide/kg (Sanders and Jackson 1972). A single intravenous injection of 6×10^5 to 9×10^7 pCi (2.2×10^5 to 3.3×10^6 Bq) plutonium-239 citrate/kg, administered as either the monomeric or polymeric form, resulted in a sex-related decrease in weight gain in weanling rats; the decrease in weight gain in males occurred at a lower level [6×10^5 pCi (2.2×10^4 Bq)/kg] than in females (1.8×10^7 pCi (6.7×10^5 Bq)/kg] (Mahlum and Sikov 1974). As seen with musculoskeletal effects (see previous section), weanlings were more susceptible to a decrease in weight gain following exposure to plutonium than adults or neonates. A decrease in weight gain was observed in adult rats following a single intravenous injection of 1.8×10^7 pCi (6.7×10^5 Bq) plutonium-239/kg or greater, administered in the monomeric form, but was not observed following administration of the polymeric form. Decreased weight gain in neonatal rats was observed only following lethal doses of plutonium-239 (Mahlum and Sikov 1974).

2.2.4.3 Immunological Effects

No studies were located regarding immunologic effects in humans after exposure to plutonium by other routes.

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Effects on some tissues of the immune system have been observed in dogs following a single subcutaneous injection of 7.4×10^5 pCi (2.7×10^4 Bq) plutonium-239 dioxide/kg (Dagle et al. 1984). The regional lymph nodes, which drained the injection sites of plutonium, were reduced in size in six of eight dogs exposed and in five of the dogs the lymph nodes consisted of only scar tissue (Dagle et al. 1984).

2.2.4.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after exposure to plutonium by other routes.

2.2.4.5 Developmental Effects

No studies were located regarding developmental effects in humans after exposure to plutonium by other routes.

Rabbits were given a single intravenous injection of 1×10^7 or 4×10^7 pCi (3.7×10^5 or 1.5×10^6 Bq) plutonium-239/kg, administered in the monomeric form, on various days of gestation (Kelman et al. 1982a). Fetal weights of the offspring of does given 4×10^7 pCi (1.5×10^6 Bq) plutonium-239/kg were significantly decreased compared to the fetal weights of the offspring of does given 1×10^7 pCi (3.7×10^5 Bq) plutonium-239/kg or the offspring of untreated controls. In contrast, fetal weights of does given 1×10^7 pCi (3.7×10^5 Bq) plutonium-239/kg were significantly increased above controls. The number of litters containing dead fetuses was significantly increased in the group of dams given 1×10^7 pCi (3.7×10^5 Bq) plutonium-239/kg on gestation days 15 to 28. Rabbits given either 1×10^7 or 4×10^7 pCi (3.7×10^5 or 1.5×10^6 Bq)/kg on gestation days 9 to 28 had significantly fewer fetuses. No teratogenic effects of plutonium-239 were observed (Kelman et al. 1982a).

2.2.4.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after exposure to plutonium by other routes.

In mice, dominant lethality has been shown to result from plutonium exposure. Fetal intrauterine deaths occurred in female mice mated with male mice treated 4 weeks prior to mating. Male mice were given (intravenously) plutonium-239 at levels ranging from 1.6×10^6 to 1.6×10^7 pCi (5.9×10^4 to 5.9×10^5 Bq) plutonium-239/kg body weight (Lüning et al. 1976a, 1976b). The effects of the dominant lethal mutations were also observed when untreated females were mated with male mice from the F1 generation. Exposure of male mice to higher doses of plutonium-239 resulted in sterility 12 weeks post-exposure (Lüning et al. 1976a, 1976b). Exposure of female mice to plutonium also resulted in dominant lethal mutations (Searle et al. 1982). Female mice intravenously

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injected with 2×10^7 pCi (7.4×10^5 Bq) plutonium-239 citrate/kg body weight exhibited a marked oocyte killing which resulted in a reduction in the number of mice which became pregnant, compared with the controls. Both pre- and post-implantation dominant lethals were induced at long periods (12 weeks) after intravenous exposure to plutonium.

2.2.4.7 Genotoxic Effects

Open wounds represent a significant route through which plutonium workers might be exposed to plutonium alpha-particles. Chromosomal aberrations were observed in lymphocytes among 8 plutonium workers in the United Kingdom occupationally exposed to plutonium with the primary routes of exposure through wounds, punctures, or abrasions [estimated body burdens from 2.1×10^4 to 4×10^4 pCi (7.8×10^2 to 1.5×10^3 Bq) plutonium, based on urine analyses]. 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).

Increased chromosomal aberrations were observed in liver tissue of Chinese hamsters intravenously given plutonium-239 or plutonium-238, as the citrate or the dioxide, to achieve levels ranging from 7×10^2 to 2×10^4 pCi (2.6×10^1 to 7.4×10^2 Bq) plutonium-239 or plutonium-238/g of liver tissue (Brooks et al. 1976a) or 2×10^6 pCi (7.4×10^4 Bq) plutonium-239 citrate/kg of body weight (Benjamin et al. 1976). The frequency of aberrations was much higher in hamsters exposed by intravenous injection to plutonium-239 or plutonium-238 citrate, than in hamsters exposed to plutonium-239 or plutonium-238 dioxide (Brooks et al. 1976b). No statistically significant increases in the incidence of chromosomal aberrations per spermatogonia cell were observed in mice or hamsters following intravenous administration of plutonium-239 citrate [2×10^3 pCi (7.4×10^1 Bq) plutonium-239/kg body weight], compared to untreated controls (Brooks et al. 1979).

Other genetic effects attributed to plutonium are dominant lethality and chromosome translocations in spermatocytes. Fetal intrauterine death occurred in female mice mated with male mice treated 4 weeks prior to mating. Male mice were given (intravenously) plutonium-239 at levels ranging from 1.6×10^5 to 1.6×10^7 pCi (5.9×10^4 to 5.9×10^5 Bq) plutonium-239/kg body weight (Lüning et al. 1976a, 1976b). The effects of the dominant lethal mutations were also observed when untreated females were mated with male mice from the F1 generation. Exposure of male mice to higher doses of plutonium-239 resulted in sterility 12 weeks post-exposure (Lüning et al. 1976a, 1976b).

Increased frequency of reciprocal translocations in spermatogonia was observed in male mice 6 to 18 weeks after intravenous injection of 1×10^7 pCi (3.7×10^5 Bq) plutonium-239 citrate/kg body weight (Beechey et al. 1975). An increase in the frequency of heritable translocations was

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also observed in male mice intravenously injected with 1×10^7 pCi (3.7×10^5 Bq) plutonium-239 citrate/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 4×10^6 pCi (1.5×10^5 Bq) plutonium-239/kg body weight (Searle et al. 1976).

Exposure of mice to 3.6×10^5 pCi (1.3×10^4 Bq) plutonium-239 citrate/kg body weight resulted in increased chromosomal aberrations in bone marrow cells (Svoboda et al. 1987). The highest incidence of these mutations was observed in the early days following exposure to plutonium.

2.2.4.8 Cancer

No studies were located regarding cancer effects in humans after exposure to plutonium by other routes.

Following a single intravenous injection of plutonium-239 citrate, osteosarcomas were found in mice [3.2×10^5 pCi (1.2×10^4 Bq)/kg] (Taylor et al. 1983), rats [3×10^5 pCi (1.1×10^4 Bq)/kg] (Sikov et al. 1978a), hamsters [2×10^6 pCi (7.4×10^4 Bq)/kg] (Brooks et al. 1983), and dogs [1×10^4 pCi (3.7×10^2 Bq)/kg] (Mays et al. 1987). Latency periods for the induction of these bone tumors were not reported. However, lifespan was significantly shortened only in hamsters. Lifespan studies in beagle dogs provided evidence that certain skeletal sites were more prone to develop plutonium-induced osteosarcomas than others (Miller et al. 1986). In these dogs, most osteosarcomas originated in trabecular (spongy) bone areas, such as the ends of long bones, the pelvis, vertebrae, and the area surrounding the marrow of the bone (endosteal surfaces) (Miller et al. 1986). Because these areas may have a greater blood flow, a greater amount of plutonium may deposit in these areas of the bone (see Section 2.3.2.4).

Induction of osteosarcomas following a single injection of plutonium-239 appeared to be age-dependent as well as sex-dependent. A statistically significant increase in the incidence of bone tumors was observed in adult and weanling rats given a single intravenous injection of 3×10^5 pCi (1.1×10^4 Bq) plutonium-239 citrate/kg (Sikov et al. 1978a). At higher levels [3×10^6 to 3×10^7 pCi (1.1×10^5 to 1.1×10^6 Bq) plutonium-239/kg via intracardiac injection], a nonsignificant increase in the incidence of bone tumors was observed in neonatal rats. The anatomical distribution of these bone tumors was markedly influenced by age at time of injection. In neonates one-third of all tumors were in the head while older groups had bone tumors primarily in the extremities or vertebrae (Sikov et al. 1978a). A statistically significant increase in the incidence of bone tumors was observed in female mice, but not in male mice given a single intraperitoneal injection of plutonium-239 citrate (9×10^5 pCi (3.3×10^4 Bq)/kg] (Taylor et al. 1981a). Females may

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be more sensitive to the toxic bone effects following a single exposure to plutonium-239 because the induction of osteosarcomas could be estrogen related (Taylor et al. 1981a).

Liver tumors have been observed in dogs following a single intravenous injection of plutonium-239. A statistically significant increase in the incidence of hepatic tumors, mostly bile duct tumors, has been observed in dogs given 1.9×10^3 pCi (7.0×10^1 Bq) plutonium-239 citrate/kg body weight (Taylor et al. 1986). These tumors were observed primarily in the lower dose groups following long latency periods. Most of the liver tumors observed were in dogs sacrificed due to bone cancer; however, liver tumors were primary liver tumors and not metastases.

Liver and bone tumors were observed in hamsters administered a single intravenous injection of 2×10^6 pCi (7.4×10^4 Bq) plutonium-239/kg body weight, administered as plutonium citrate (monomeric) (Brooks et al. 1983). However, in hamsters given a single intravenous injection of 2×10^6 pCi (7.4×10^4 Bq) plutonium-239 dioxide/kg (polymeric), a significant increase in the incidence of liver tumors was observed with no accompanying bone tumors (Brooks et al. 1983).

No conclusive evidence exists that plutonium induces leukemia in laboratory animals. However, in mice with a high spontaneous incidence of leukemia (ICR mice), administration of plutonium as a single intravenous injection [4.4×10^6 pCi (1.8×10^5 Bq) plutonium-239 citrate/kg] decreased the latency period for the appearance of leukemia (Svoboda et al. 1981).

Various types of tumors have been observed in rats following a single intraperitoneal injection of plutonium dioxide. A dose-dependent increase in the incidence of mesotheliomas and soft-tissue sarcomas was observed in rats given 2×10^5 to 8×10^6 pCi (7.4×10^3 to 3.0×10^5 Bq) plutonium-239 dioxide/kg (Sanders 1973). Death in many of the treated rats resulted from large malignant abdominal tumors. It appears that plutonium-239 particles, administered as plutonium dioxide, can produce mesotheliomas in the abdominal cavity, but a greater radiation dose is needed to induce mesotheliomas than is needed to induce sarcomas (Sanders 1973). An increase in the incidence of mammary tumors was observed in rats given 3.6×10^6 pCi (1.3×10^5 Bq) plutonium-238 dioxide/kg (Sanders 1974).

2.3 TOXICOKINETICS

In radiation biology the term dose has a specific meaning. Dose refers to the amount of radiation absorbed by the organ or tissue of interest and is expressed in rads (grays). For example, estimation of this radiation dose to lung tissue or specific cells in the lung from a given exposure to plutonium is accomplished by modeling the sequence of events involved in the inhalation, deposition, clearance, and decay of

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plutonium within the lung. While based on the current understanding of lung morphometry and experimental data on plutonium toxicokinetics, different models make different assumptions about these processes, thereby resulting in different estimates of dose and risk. Other models estimate dose from ingestion of plutonium. These models are described in numerous reports including Bair (1985), EPA (1988), ICRP (19783, James (1988), and NEA/OECD (1983). In this section the toxicokinetics of plutonium is described based on the available experimental data rather than on descriptions derived from models.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

The most common route of exposure to plutonium is inhalation. The absorption of plutonium following inhalation was dependent on its physicochemical properties including isotope number, the mass deposited, valence, chemical compound, and particle size (Bair et al. 1962b; Guilmette et al. 1984). Depending on the plutonium compound, it may be either soluble or insoluble. Plutonium as the citrate or nitrate was more soluble than the dioxide compound. Plutonium dioxides prepared at temperatures of 700°C or higher had a slower absorption rate compared to air-oxidized forms (Sanders and Mahaffey 1979). The absorption of plutonium was also dependent upon its respirable fraction, or that fraction of the total concentration of plutonium which may deposit in the nonciliated part of the lung. The respirable fraction of plutonium is composed of particles less than 10 pm Activity Median Aerodynamic-Diameter (AMAD), which indicates that only particles less than 10 pm AMAD would be retained in the nonciliated part of the lung and would be available for absorption (NEA/OECD 1981; Volchok et al. 1974).

The more soluble the form of plutonium, the more rapidly and extensively it was absorbed by the lungs (Ballou et al. 1972; Dagle et al. 1985). The insoluble forms of plutonium were absorbed from the lungs very slowly (Bair et al. 1962b; Bair and Willard 1962; Guilmette et al. 1984; Park et al. 1985) with the majority being deposited in the tracheobronchial region and then removed by the mucociliary apparatus. Insoluble particles may be engulfed by macrophages and alveolar cells (Metivier et al. 1980a; Sanders and Adey 1970) and taken up into the reticuloendothelial system (Leggett 1985).

Plutonium-238 administered as the soluble nitrate or as the less soluble dioxide form to dogs was absorbed from the lungs more rapidly than the corresponding forms of plutonium-239, possibly due to the lower mass of plutonium-238 (Dagle et al. 1983; Park et al. 1972) or more likely, due to the higher specific activity of plutonium-238. However, when plutonium-239 nitrate was administered to rats, it was absorbed more readily than the plutonium-238 nitrate (Morin et al. 1972).

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2.3.1.2 Oral Exposure

Absorption of plutonium from the gastrointestinal tract was minimal and was dependent on age, chemical properties, stomach content, dietary iron intake, and nutritional factors (Bomford and Harrison 1986; Harrison et al. 1986; Stather et al. 1980; Sullivan and Ruemmler 1988; Sullivan et al. 1983; Weeks et al. 1956). Oxidation state, administration media, extent of polymer formation, rate of hydrolysis, and mass administered did not appear to effect the absorption of plutonium (Carritt et al. 1947; Harrison and David 1987; Larsen et al. 1981; Stather et al. 1980, 1981).

Absorption of plutonium was slightly increased when administered in a citrate or nitrate solution and when administered as a very acidic solution (Weeks et al. 1956). Absorption of 0.003 to 0.01% of the administered plutonium citrate or nitrate has been reported in rats and hamsters (Carritt et al. 1947; David and Harrison 1984; Katz et al. 1955; Stather et al. 1981).

The absorption of plutonium after oral administration was age-related in laboratory animals. From 3 to 6% of administered plutonium may be absorbed by neonatal rats, hamsters, guinea pigs, and dogs (Cristy and Leggett 1986). A rapid decrease in absorption has been seen with increasing age. In hamsters between 1 day and 30 days of age, absorption of plutonium decreased from 3.5 to 0.003% of the administered dose (David and Harrison 1984).

Gastrointestinal absorption increased when plutonium was administered on an empty stomach. In hamsters that had been fasted for 8 to 24 hours, absorption increased to 0.1 to 0.15% of the administered plutonium citrate or ascorbate compared to 0.01% in animals which had not been fasted (Harrison et al. 1986).

Absorption of plutonium from the gastrointestinal tract was dependent on iron status. A four-fold increase in plutonium absorption occurred in rats that were iron deficient compared to those with normal iron status (Ragan 1977; Sullivan et al. 1986). Absorption of plutonium in nursing neonates of iron deficient dams was twice as much as neonates of iron-replete dams (Sullivan et al. 1986).

2.3.1.3 Dermal Exposure

The absorption of plutonium following dermal exposure was very limited. The amount absorbed depended on the thickness of the skin, the area of the skin exposed, the mass applied, the integrity of the skin, and the solution in which the plutonium is dissolved. Plutonium absorption through the intact palmar skin of a human was found to be less than 0.0002%/hr when administered as the nitrate in a 0.4N nitric acid solution (Langham 1959). Plutonium has been found to migrate down

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hair follicles (Weeks and Oakley 1955) and into sweat and sebaceous glands (Buldakov et al. 1970).

2.3.1.4 Other Routes of Exposure

The absorption of plutonium after exposure was dependent on the route of administration. Intravenous injection delivered plutonium directly into the blood stream where it may then distribute in the body. Injection of plutonium into the peritoneal cavity (Sanders 1975a; Sanders and Jackson 1972) or into the muscle (Nenot et al. 1972) resulted in phagocytosis of particles which then enter the blood stream through the lymphatics. Intramuscular injection of plutonium-238 citrate to monkeys resulted in absorption of 95% of the administered dose from the site of injection in 10 days (Durbin et al. 1985). Absorption of plutonium after intraperitoneal injection was dependent on iron status. A two-fold increase in plutonium absorption occurred in rats which were iron-deficient compared to those with normal iron status (Ragan 1977).

Absorption of plutonium through wounds has occurred in humans occupationally exposed (Hammond and Putzier 1964). Experiments in animals where plutonium-239 as the nitrate or dioxide was injected under the skin have been conducted to simulate this exposure. From these studies it has been found that about 80% of the administered plutonium nitrate or dioxide was absorbed (Dagle et al. 1984).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

The distribution of plutonium following absorption from the lungs was dependent on the physicochemical form deposited. In general, plutonium was distributed to the skeleton, liver, and lymph nodes; however, some plutonium has been found in all tissues. Information from humans who have been occupationally exposed to plutonium indicated that the highest concentrations of the absorbed plutonium were found in the tracheal-bronchial lymph nodes, followed by the liver, skeleton, and kidneys (Lagerquist et al. 1973). However, a more recent study by McInroy et al. (1989) reports that plutonium deposition in a small number of former nuclear industry workers was greatest, exclusive of the respiratory tract, in the skeleton followed by the liver, striated muscle, and other organs and tissues. These authors suggested that muscle and other soft tissues may act as a long-term storage depot for plutonium. Results from studies in laboratory animals indicated that absorption of the more soluble forms of plutonium led to greater distribution in the skeleton and liver (Dagle et al. 1985; Morin et al. 1972), while the less soluble dioxide form was distributed to a greater extent to the trachea-bronchial lymph nodes and the liver (Bair et al.

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1966; Park et al. 1972). Distribution to the bone was greater with plutonium-238 nitrate than with plutonium-239 (Morin et al. 1972) and with the air-oxidized form of both plutonium-238 and plutonium-239 compared to the high-fired form (Sanders and Mahaffey 1979).

Particle size did not appear to affect distribution to the liver and skeleton in dogs (Guilmette et al. 1984). An age-related effect on distribution to the bone was reported by Guilmette et al. (1986). In immature dogs, a five-fold increase in distribution to the bone was seen compared to that in young adult dogs. Most information available on the distribution of plutonium following inhalation exposure is from studies where plutonium-239 dioxide was administered in a single dose to dogs. Additional information is also available on other chemical compounds, and isotopes in rodent species (Buldakov et al. 1972; Nenot et al. 1972; Sanders 1973b; Sanders et al. 1977).

The distribution of plutonium within the lungs after inhalation exposure was also dependent on several variables. In rats a more uniform exposure of lung cells occurred from administration of the air-oxidized form compared to the high-fired form (Sanders and Mahaffey 1979). Initially after exposure to the dioxide form, distribution in the lungs of hamsters was random with particles becoming more clumped with time (Diel et al. 1981).

The distribution of plutonium in the liver differed between the nitrate and dioxide forms. Administration of the nitrate form to dogs resulted in diffusely distributed activity found as single tracks, while administration of the dioxide form resulted in localized activity found as "alpha stars" with radioautography (Dagle et al. 1985).

2.3.2.2 Oral Exposure

In rats and dogs following absorption of plutonium from the gastrointestinal tract, up to 95% of the absorbed dose has been found to be distributed to the skeleton (Carritt et al. 1947; Larsen et al. 1981; Toohey et al. 1984). Plutonium was also distributed to a less extent to the liver, carcass, and soft tissues (Carritt et al. 1947; Katz et al. 1955; Larsen et al. 1981; Sullivan et al. 1984). The distribution of plutonium-237 in a bicarbonate solution administered via a gelatin capsule was greatest to the axial skeleton (Toohey et al. 1984).

2.3.2.3 Dermal Exposure

At early times after dermal exposure of rabbits to plutonium-239 nitrate, activity in blood was uniformly distributed, but later changed to a nonuniform distribution (Khodyreva 1966). Distribution of plutonium was greatest to the skeleton followed by muscle tissue, liver, kidney, spleen, heart, and lungs (Khodyreva 1966). In an earlier study in rats, the absorption of plutonium through intact skin did not appear

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to result in distribution to the liver as compared to absorption through skin damaged by punctures or wounds where deposition in the liver was seen (Oakley and Thompson 1956).

2.3.2.4 Other Routes of Exposure

The distribution of plutonium was studied in terminally ill patients who had been given an intravenous injection of plutonium (Langham et al. 1980). Blood concentrations decreased rapidly (0.3% remained in the blood after 30 days). At death, which occurred from 16 to 450 days after injection, an average of 56% of the administered plutonium was in the bone marrow and on bone surfaces, while 23% was in the liver (Langham et al. 1980).

Although exposure by injection routes in humans is not likely, data from distribution studies in laboratory animals provides insight into the toxicokinetics of plutonium in the body. In dogs, once plutonium entered the blood stream, it was bound to transferrin, a serum transport protein (Stevens et al. 1968). Plutonium competed with iron for the transferrin in the blood. If transferrin was saturated with iron, then more plutonium would deposit in the liver and not in the bone (Ragan 1977). Similar binding of plutonium to transferrin was observed in human blood serum (Stover et al. 1968a).

In laboratory animals that received plutonium by intravenous injection, most plutonium was deposited in the liver and skeleton. No differences in distribution between plutonium-238 and plutonium-239 were reported in mice (Andreozzi et al. 1983); however, Ballou et al. (1967) reported that in rats deposition in the liver and other soft tissues was twice as great after intravenous administration of plutonium-239 than after administration of plutonium-238. In dogs, the concentration of plutonium polymer decreased in the lungs, spleen, and liver with time and increased in the skeleton and kidney (Stevens et al. 1976).

The distribution of plutonium after intravenous injection was age-dependent. The distribution of different chemical forms of administered plutonium did not differ in neonates, and activity was more uniformly distributed than in weanlings and adults (Mahlum and Sikov 1974; Sikov and Mahlum 1976). In immature dogs, increased deposition of plutonium was associated with bones that were undergoing active growth (Bruenger et al. 1978). The concentration of plutonium in the skull of neonates was twice as great as that in young adults, but distribution to the liver was not as great in neonates as in other age groups (Bruenger et al. 1978). Age at time of injection influenced distribution between the skeleton and the liver (Bruenger et al. 1980; Lloyd et al. 1978a, 1978b). In rats plutonium distribution within bone was different in weanlings compared to adults. In weanlings, there was a tendency for localization on periosteal surfaces and plutonium was seen in compact bone at earlier times (Sikov and Mahlum 1976).

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In dogs and mice administered plutonium-239 as the citrate or as the polymer by intravenous injection, 15 to 31% or 55 to 70%, respectively, of the injected dose was distributed to the liver after 6 days (Baxter et al. 1973; Stover et al. 1959). In rats at 30 days post-exposure to plutonium as the citrate or as the polymer, 9.6 or 40%, respectively, was distributed to the liver (Carritt et al. 1947). The distribution of activity in the liver was uniform following administration of the citrate and nonuniform after administration of the polymer (Baxter et al. 1973; Brooks et al. 1983; Cochran et al. 1962).

The percent of plutonium-239, administered by intravenous injection as the citrate or as the polymer, that distributed to the skeleton of dogs and mice was 2.8 to 3.1% or 0.1 to 0.2%, respectively, after 6 days (Baxter et al. 1973). In rats 30 days after exposure to plutonium-239 as the citrate or as the polymer, 56.9 or 29.4%, respectively, distributed to the bone (Carritt et al. 1947). In dogs plutonium distribution in the skeleton was greatest to the trabecular or "spongy" bone and more was found in the red bone marrow, which is perfused with blood, compared with yellow or fatty bone marrow (Smith et al. 1984; Wronski et al. 1980). The rate of deposition in bone may be related to the rate of blood flow to bone, and in mice there appears to be a threshold rate for blood flow below which plutonium will not deposit to bone (Humphreys et al. 1982).

A small fraction of the plutonium taken in has been found to distribute to the gonads of mice following intravenous exposure. In mice exposed to plutonium-239 citrate, about 0.02 to 0.06% of the administered dose was distributed to the testes (Andreozzi et al. 1983; Ash and Parker 1978; Green et al. 1976). In the testes, plutonium was associated with the interstitial tissue (Ash and Parker 1978; Brooks et al. 1979; Green et al. 1976). Plutonium has also been measured in the ovarian tissue of mice exposed to plutonium-239 citrate (Green et al. 1977).

Plutonium-239 citrate has been shown to cross the placental membrane and has been found in the fetus in both mice and baboons following intravenous injection (Green et al. 1979; Sikov et al. 1978b; Weiss and Walburg 1978). The fractional placental transfer of plutonium citrate was found to be inversely proportional to the administered dose (Weiss and Walburg 1978). The greatest amounts of plutonium were found in the fetal membranes followed by the placenta and then the fetus (Sikov et al. 1978b). Plutonium was distributed to the gastrointestinal tract, liver, and mineralized areas of the bone in the fetus (Green et al. 1979).

After the absorption of plutonium from a wound site, it may be absorbed in the blood stream and distributed to the regional lymph nodes, liver, spleen, skeleton, and other tissues. In dogs exposure to plutonium dioxide through a wound resulted in greater distribution to

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the lymph nodes and less to the skeleton as compared with exposure to plutonium nitrate (Dagle et al. 1984). Distribution to the spleen of dogs exposed to the dioxide form was greater than to the skeleton, while distribution to the spleen of dogs exposed to the nitrate form was less than to the skeleton. Comparable amounts of both forms were distributed to the liver and the skeleton (Dagle et al. 1984).

2.3.3 Metabolism

Plutonium occurs naturally in several valence states, but in the body the most common state is (IV) due to stabilization by ligands and complexing agents (ICRP 1972). Plutonium does not exist as a simple ion at physiological pH and, therefore, tends to hydrolyze and form polymers. The tendency for plutonium to hydrolyze should increase with increasing atomic number because the hydrolytic behavior is determined by ionic charge and size (ICRP 1972). When plutonium is complexed with citrate, it is less likely to form polymers and remains more soluble in the body.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Elimination of plutonium following exposure by inhalation appears to be dependent upon the form of plutonium and may vary among species. After inhaled exposure to plutonium, the clearance pattern from the lungs appeared to be biphasic. In rats, the half-time for clearance of plutonium-238 or -239 dioxide from the lungs for the first phase was from 20 to 30 days and for the second phase was from 180 to 250 days (Sanders et al. 1976, 1977, 1986). In the first phase, 70 to 76% of the plutonium was removed with the remainder of that excreted removed in the second phase. Retention of plutonium in the body after it translocates to other tissues may be very long. In dogs exposed to plutonium-239 dioxide, 85% of the administered amount was retained in the body 9 to 10 years after exposure (Park et al. 1972). Retention of plutonium dioxide in the lungs of dogs was not constant over time, which may be related to an increased rate of solubilization of the particles with time, resulting in greater translocation to other organs (Hahn et al. 1981). The retention half-time increased with increasing particle size (Bair et al. 1962b; Guilmette et al. 1984). The retention half-time for the plutonium-239 isotope was greater than for the plutonium-238 isotope (Park et al. 1972). With repeated exposure to plutonium-239 dioxide, it appeared that each administered amount was retained independently with its own retention characteristics (Diel and Lundgren 1982).

The excretion of plutonium by humans approximately 30 years after occupational exposure to plutonium particles, primarily by inhalation, appeared to indicate that more plutonium was cleared in the urine than in the feces (Voelz et al. 1979). However, Leggett (1985) stated that,

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at equilibrium, 4 times more plutonium was eliminated in the feces than in the urine. In laboratory animals, the primary route of excretion of plutonium was reportedly through the feces. From 10 to 35 times more plutonium was excreted in the feces than in the urine in dogs and rats (Bair and McClanahan 1961; Diel and Lundgren 1982; Sanders et al. 1976, 1977). In rats exposed by inhalation or intramuscular injection, greater amounts of plutonium have been found in the feces as soon as 6 days following inhalation exposure. This may be due to the removal of particles from the respiratory tract by the mucociliary elevator and the consequent swallowing of these particles or due to biliary clearance (Morin et al. 1972).

2.3.4.2 Oral Exposure

Most of plutonium administered to dogs in a bicarbonate solution by the oral route was eliminated in the feces, with an average excretion of 98% of the administered dose after 5 or 6 weeks (Toohey et al. 1984). In mice and rats total retention of plutonium varied from 0.17 to 0.24% of the administered activity and was not dependent on oxidation state or on the medium in which it was administered (Larsen et al. 1981). Retention in the liver of mice and rats was 0.036 and 0.054%, respectively, of the initial dose (Larsen et al. 1981) and in the skeleton plus liver of fasted dogs was 0.063% of the administered dose (Toohey et al. 1984).

Retention of plutonium in rat neonates was 100 times greater than in adults (Sullivan et al. 1984). More plutonium was found in the wall of the small intestine than in the walls of the stomach and large intestine of rats (Fritsch et al. 1988).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or laboratory animals after dermal exposure to plutonium.

2.3.4.4 Other Routes of Exposure

Little information is known about the excretion of plutonium in humans after exposure through other routes. From terminally ill humans who were administered an intravenous injection of plutonium it appeared that the major route of elimination was in the urine (Langham et al. 1980). The biological half-time in these individuals was estimated to be 118 years and the retention half-time in the liver was estimated to be greater than 1 year. Data from humans occupationally exposed through wounds indicated that excretion patterns could not be predicted following this type of exposure (Hammond and Putzier 1964).

From injection studies in laboratory animals it was found that retention was dependent on the isotope, chemical form, and sex. In dogs

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plutonium-239 was retained longer than plutonium-237 (Bair et al. 1974). The retention of plutonium-242 and plutonium-244 was similar, and was longer than the retention time for plutonium-236 and plutonium-239 (Guilmette et al. 1978). In mice no difference was seen in fractional retention at low and high doses (Andreozzi et al. 1983). In hamsters more plutonium administered intravenously in an insoluble form (plutonium dioxide) was retained than plutonium administered in a soluble form (plutonium citrate) (Brooks et al. 1976b). Retention after intraperitoneal injection of mice and hamsters may be sex-dependent; females retained more in the liver than males (Smith et al. 1976, 1978). However, retention after intravenous injection was not sex-dependent (Smith et al. 1978). Total retention and liver retention increased with age (Bruenger et al. 1980; David and Harrison 1984).

The whole body retention of intravenously administered plutonium-237 and/or -239 citrate in dogs varied from approximately 85% to almost 100% (Bair et al. 1974; Lloyd et al. 1976, 1984) with liver retention of about 25% (Bair et al. 1974; Lloyd et al. 1976, 1984; Stover et al. 1962) and skeletal retention of about 50% (Bruenger et al. 1980; Lloyd et al. 1978a, 1978b, 1984). Liver retention was found to be dose-dependent (Stover et al. 1962). In hamsters, the whole body retention of plutonium-239 dioxide was approximately 100% (Brooks et al. 1983). Plutonium was found to be retained for an indefinite time in the testes and ovaries of mice and rats (Green et al. 1977; Miller et al. 1989; Taylor 1977). Retention at the site of administration after exposure which simulated wounds was from 16 to 21% of the administered dose (Dagle et al. 1984).

The half-life for removal of plutonium was very long. In mice the biological half-life of plutonium-238 or 239 citrate in the skeleton was one to two times the animal's lifespan and in the liver the half-life was 350 days (Andreozzi et al. 1983). In dogs the half-life of plutonium-239 citrate in the liver was 3,081 days, in the spleen was 995 days, and in the kidney was 1,520 days (Stover et al. 1968b). A long effective half-life has been reported in hamsters with 85% of injected plutonium-239 citrate still in the bone and liver 700 days after administration (Benjamin et al. 1976).

In mice plutonium-239 administered as a polymer in a non-citrate solution was cleared from the blood rapidly, 99% in 15 minutes, while only 20% of plutonium administered as a monomer in a citrate solution was cleared in the same time (Baxter et al. 1973). Most plutonium was retained in the body, and the remainder was excreted. In mice, hamsters, and dogs from 10 to 30% of plutonium was excreted primarily in feces (Baxter et al. 1973; Brooks et al. 1983; Lloyd et al. 1976, 1978b, 1984). Plutonium was also shown to be removed from the body through lactation; however, the amount of plutonium in milk was not reported (Taylor 1980). In nursing rats administered plutonium-239 citrate, the total body burden was decreased 10% by lactation (Taylor 1980).

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2.4 RELEVANCE TO PUBLIC HEALTH

Plutonium isotopes are products of neutron absorption processes in nuclear reactors generated by nuclear processes. Exposure to plutonium in environmental media poses the potential for causing adverse health effects. Plutonium and other alpha-emitting radionuclides (ATSDR 1990) exert their biological effects after entering the body and depositing in radiosensitive tissues. Inhalation is the primary route of plutonium exposure for humans in either occupational or environmental settings. Translocation from the lungs to other organs in the body depends on a variety of factors including the solubility of the plutonium compound and the particular plutonium complex. Plutonium is not readily absorbed from the gastrointestinal tract or through intact skin.

Plutonium emits ionizing radiation primarily in the form of alpha particles. The type and severity of the biological response to this radiation will depend not only on the amount of radiation emitted but also on the radiosensitivity of the tissue and contact (retention) time. In general, tissues undergoing rapid cell regeneration are more radiosensitive than slower or nonregenerating cell systems (see Appendix B).

Animal studies have demonstrated that exposure to high radiation doses of plutonium isotopes have resulted in decreases in lifespan, diseases of the respiratory tract, and cancer. The target tissues appear to be the lungs and associated lymph nodes, the liver, and bones. However, these observations in animals have not been corroborated by epidemiological investigations in humans exposed to smaller amounts of plutonium.

Death. No deaths in humans specifically associated with plutonium have been reported following acute plutonium exposure. Epidemiological studies of occupational cohorts did not report any increases in deaths due to nonmalignant diseases. However, the highest radiation levels reported in workers were 100- to 1,000-fold lower than the radiation levels that resulted in death (due to respiratory failure) in some laboratory animals. Acute exposures to high levels of plutonium isotopes, administered as dioxides, citrates, or nitrates, were fatal to several laboratory species when exposure occurred by the inhalation, oral, or injection routes. Survival time was radiation dose-related for all of these routes of exposure. By the inhalation route in animals, nonmalignant respiratory disease was characterized by radiation pneumonitis, pulmonary fibrosis, alveolar edema, and occasionally hyperplasia and metaplasia with death occurring within weeks or months of the initial exposure to high concentrations. It is likely that mortality due to radiation-induced sickness, such as radiation pneumonitis, could occur in humans at sufficiently high radiation doses. Such amounts of radiation, however, would be expected to occur only with

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an extremely large accidental release but not at the radiation levels attributable to plutonium currently identified in the ambient environment.

Respiratory Effects. Neither deaths due to respiratory disease nor reduced respiratory function have been reported among the occupationally exposed cohorts-. Respiratory diseases characterized by pneumonitis, fibrosis, edema, and respiratory dysfunction have been reported in all laboratory species tested following acute exposure to high concentrations of plutonium by the inhalation or injection routes. The severity of the respiratory disease and the time to death from respiratory disease correlated with the activity concentration. Induction of this type of respiratory disease in humans could occur at high exposure levels, which greatly exceed those commonly found in the environmental setting. However, the radiation dose that might result in either pulmonary dysfunction or pulmonary disease in humans has not been specifically identified. A no observed adverse effect level (NOAEL) was not established with certainty based on the data from animal studies. The types of adverse respiratory effects observed appear to be consistent with the pattern of alpha radiation damage that may occur in slower regenerating tissues such as the lungs (see Appendix B). That being the case, production of respiratory tissue damage in the lungs may occur but may not be immediately apparent, especially at low environmental exposures.

Hematological Effects. No acute hematological effects were observed among human volunteers given a single injection of plutonium, but no follow-up study was conducted to assess the possibility of delayed effects. No adverse hematological effects were reported among the various occupational cohorts who underwent medical examinations. There is considerable evidence from animal experiments that plutonium produces adverse effects in the hematopoietic system. Lymphopenia was the most common finding following inhalation exposure in animals, while anemia, bone marrow depression, and decreases in white blood cells and hematopoietic stem cells occurred following injection of plutonium in animals. The lymphopenia was dose-related and correlated both in magnitude and time of appearance post-exposure with the initial lung burden of inhaled plutonium. Hematological abnormalities have occurred in human populations following exposure to external radiation (i.e., gamma and high-energy beta), and blood-forming cells could be a target for internally deposited alpha radiation (see Appendix B); however, the relevance of the hematological effects seen in animals at high doses to potential health effects in humans environmentally exposed to plutonium is unclear.

Hepatic Effects. Adverse hepatic effects associated with plutonium exposure have not been reported in humans. There is evidence in animals that inhalation or injection of plutonium results in degenerative liver

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injury and functional impairment of the liver. It is likely that these effects are directly related to the radiation toxicity of plutonium (since liver tumors have been observed), rather than a secondary response to other adverse biological events in the body, although the liver is expected to be less radiosensitive than more rapidly regenerating cells. Subtle changes in liver function as a result of low doses of plutonium have not been evaluated. It is unclear from the reported literature whether complete liver function tests were performed in the occupational cohorts under investigation. As with the other nonstochastic biological effects discussed, the level below which hepatic effects are unlikely to occur has not been clearly defined; therefore, the effects of plutonium on hepatic function and histology at levels encountered in the environment have not been identified.

Musculoskeletal Effects. Adverse musculoskeletal effects associated with plutonium exposure have not been reported in humans. There is limited evidence of noncancerous bone damage and no evidence of muscle damage in laboratory animals exposed to plutonium. Muscle tissue is considered to be relatively resistant to the effects of alpha radiation (see Appendix B); therefore, damage to muscle tissue is not expected in animals and should not be of concern to individuals exposed to plutonium in the environment. Bone damage occurred in animals given plutonium by the inhalation route and the injection route. The more soluble forms of plutonium resulted in bone damage when inhaled. Spontaneous fractures, which were age-dependent, along with atrophy and osteodystrophy, were seen at high radiation doses. These skeletal effects may be due to radiation damage to rapidly dividing osteoblasts especially in the ends of long bones; therefore, children could be a sensitive subpopulation and could be more sensitive to radiation-induced bone damage.

Gastrointestinal Effects. Adverse gastrointestinal effects associated with plutonium exposure have not been reported in humans. Gastrointestinal effects in animals have been reported only in an oral study in neonatal rats. Because the epithelial cells of neonatal rodents are immature and poorly enclosed, these cells may be more sensitive to radiation damage in the neonate than in the adult, so it is possible that infants would represent a sensitive subpopulation among people exposed to plutonium by the oral route. Gastrointestinal absorption is limited, and translocation to other organ systems is also limited. The probability of exposure of humans to plutonium by the oral route is expected to be small; however, if it were to occur, localized radiation damage to the epithelial cells of the stomach may occur.

Immunological Effects. Adverse immunological effects associated with plutonium exposure have not been reported in humans. Immunotoxicity has been observed in several species administered plutonium by inhalation and in dogs given plutonium by injection.

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Plutonium is translocated from the lungs to the tracheobronchial and mediastinal lymph nodes, and has also been found in the hepatic lymph nodes. Immunotoxicity ranged from alterations in antibody-forming cells to atrophy and fibrosis of lymph glands. The animal data present a consistent view that plutonium affects immune function either by destruction of lymph nodes or circulating lymphocytes or other alterations in immune system competence. The implications of this for human health are unknown; however, it is possible that if alterations in immune system competence were to occur, then the ability to respond to other disease situations unrelated to plutonium could be affected. The immunotoxicity which occurred in laboratory animals was observed at concentrations lower than those that resulted in overt clinical (respiratory) effects. These findings suggest that individuals exposed to plutonium could develop subtle changes in the immune system that may reduce immune competence at doses that may not induce overt signs of toxicity.

Genotoxic Effects. Tables 2-4 and 2-5 present the results of *in vitro* and *in vivo* genotoxicity studies, respectively. Epidemiological studies do not provide evidence that plutonium produces genetic damage in humans. In particular, the data from persons involved in the Manhattan project after a 30-year follow-up have been negative. In vitro tests using human lymphocytes irradiated with plutonium-238 or plutonium-239 demonstrated increases in sister chromatid exchange (Aghamohammadi et al. 1988) and chromosomal aberrations (Purrott et al. 1980), respectively. In vitro studies have also shown a dose-related linear increase in mutation frequencies at the hypoxanthine-guanine phosphoribosyl transferase locus in cultured human fibroblasts (Chen et al. 1984).

The animal in vivo and in vitro studies are in agreement. Plutonium induced chromosomal aberrations in several species in vivo and in the corresponding cell lines when cultured in vitro. Chromosomal aberrations (Welleweerd et al. 1984) and gene mutations (Thacker et al. 1982) were seen in Chinese hamster cells cultured in vitro. Plutonium was not genotoxic using the Ames test for mutagenicity in several strains of Salmonella typhimurium (Fritsch et al. 1980).

Cancer. Epidemiological studies of occupational cohorts with long-term exposure to plutonium include those of workers at Los Alamos National Laboratory, Rocky Flats Nuclear Weapons Plant, or Hanford Weapons Plant and the cohort involved in the original Manhattan project at Los Alamos. None of these studies has demonstrated an unequivocal association between exposure to plutonium and mortality from cancer at any anatomical location in workers after 30 or more years. These

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TABLE 2-4. Genotoxicity of Plutonium In Vitro

End Point	Species/Test System	Result	Reference
Prokaryotic organisms:			
Gene mutation	<u>Salmonella typhimurium</u> / TA-100, TA-98, TA-1535, TA-1537, TA-1538, TA-2420, TA-2421	-	Fritsch et al. 1980
Mammalian cells:			
Gene mutation	Chinese hamster/ovary cell line	+	Fritsch et al. 1980
Chromosomal aberrations	Human/lymphoblastic cell line	+	Fritsch et al. 1980
	Human/lymphocytes	+	Purrott et al. 1980
	Chinese hamster/M3-1 cells	+	Welleweerd et al. 1984
Gene mutation	Human/embryonic skin fibroblasts	+	Chen et al. 1984
	Chinese hamster/ovary cell line	+	Barnhart and Cox 1979
	Chinese hamster/V79-4 cells	+	Thacker et al. 1982
DNA damage	Chinese hamster/V79- 379A cells	+	Prise et al. 1987
Reduction in radio- resistance	Mouse-rat/hybrid cell line	+	Robertson and Raju 1980
Sister chromatid exchanges	Human/lymphocytes	+	Aghamohammadi et al. 1988

- = negative result
+ = positive result

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TABLE 2-5. Genotoxicity of Plutonium In Vivo

End Point	Species/Test System	Result	Reference
Mammalian systems:			
Chromosomal aberrations	Chinese hamster/ testes	-	Brooks et al. 1979
	Mouse/testes	+	Brooks et al. 1979; Beechey et al. 1975
	Chinese hamster/liver cells	+	Benjamin et al. 1976; Brooks et al. 1976b
	Mouse/bone-marrow cells	+	Svoboda et al. 1987
	Syrian hamster/lung cells	+	Stroud 1977
	Chinese hamster/blood cells	+	Brooks et al. 1976a
	Human/peripheral lymphocytes	(+)	Brandon et al. 1979; Tawn et al. 1985
	Human/whole blood	-	Hempelmann et al. 1973; Voelz et al. 1979
	Human/blood lymphocytes	+	Schofield et al. 1980
	Monkey/blood lymphocytes	+	LaBauve et al. 1980
Dominant lethal	Mouse/germ cells	-	Searle et al. 1976
	Mouse/germ cells	+	Lüning et al. 1976a, 1976b
	Mouse/ovaries	(+)	Searle et al. 1982
Reciprocal/ chromosome translocation	Mouse/spermatogonia	+	Beechey et al. 1975; Generoso et al. 1985
		-	Searle et al. 1976

+ = positive result

- = negative result

(+) = positive or marginal result

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studies have one or more of the same limitations inherent in other epidemiological studies. These include small cohort size, poorly defined exposure information, or insufficient follow-up periods. However, the Rocky Flats study was extensive and exposures were documented from health physics records. One limitation of the Rocky Flats study is that the worker cohort was divided into only two exposure categories based on body burden, less than or greater than 2,000 pCi (74 Bq) plutonium. The authors concluded that the study suggested an increased risk of lymphopoietic cancers based on a total of four such lymphopoietic neoplasms, one each of lymphosarcoma/reticulosarcoma, non-Hodgkin's lymphoma, multiple myeloma and myeloid leukemia. However, no elevated cancer incidences were noted in tissues with the highest concentrations of plutonium (tracheobronchial lymph nodes, lungs, liver, and bone) as demonstrated in autopsy samples.

In contrast, the results from numerous animal studies are conclusive. Plutonium at the concentrations administered produced lung, liver, and bone cancers primarily when administered by the inhalation or injection routes in dogs, mice, rats, and nonhuman primates. Only Syrian hamsters appeared to be resistant to plutonium-induced tumors, even though hamsters developed the same nonmalignant respiratory effects. The current understanding of radiation-induced carcinogenesis is that it is a stochastic process, that is, one without a threshold for developing cancer. Mechanistically, plutonium should be considered to have the potential to cause cancer due to the emission of alpha particles (ATSDR 1990). While it is true that cancer in animals resulted from extremely large concentrations that are orders of magnitude higher than any occupational or environmental exposure (except under an accident scenario), it is appropriate and health protective to assume that some level of risk of cancer exists from exposure of humans to plutonium.

2.5 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 or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid 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 (e.g., high urinary levels of phenol

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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 biologic 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 2.5.1.

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 epithelium cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not 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 2.5.2.

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. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Plutonium

Biomarkers of exposure to plutonium include the presence of plutonium in urine, which is identified by measuring alpha activity. From the levels of radioactivity in the urine, body burdens of plutonium may be estimated by the use of models. Body burdens of plutonium in several populations, including workers at Los Alamos National Laboratory, the Rocky Flats facility, and the Hanford facility, have been estimated from urinalysis data. However, whole body burdens determined from selected tissues obtained at autopsy have generally been lower than those estimated from urinalysis data (Voelz et al. 1979). The presence of radioactivity from plutonium in urine is specific to plutonium exposure. Plutonium may be found in the urine after any exposure duration (e.g., acute, intermediate, chronic). Although it can be assumed that exposure to greater levels of plutonium would result in the presence of greater levels of radioactivity in the urine, no information was located to directly quantify this relationship.

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2.5.2 Biomarkers Used to Characterize Effects Caused by Plutonium

Limited information is available regarding biomarkers of effect of plutonium exposure. The presence of chromosome aberrations has been reported in laboratory animals following exposure to plutonium. Chromosome aberrations have also been reported in humans following exposure through open wounds, but evidence from epidemiologic studies where exposure occurred via inhalation have been equivocal (Brandon et al. 1979; Hempeimann et al. 1975; Tawn et al. 1985; Voelz et al. 1979). Although the presence of chromosome aberrations could be considered a biomarker of effect, the number of chemicals that could cause this effect is so great that the effect would not be considered plutonium-specific. In dogs, the earliest observed biological effect of exposure to plutonium is a dose-related lymphopenia that correlated in magnitude and time of appearance post-exposure with initial lung burden (Park et al. 1988; Ragan et al. 1986). Although there is currently no information in humans regarding the occurrence of this effect, the presence of lymphopenia in humans following plutonium exposure might be a potential biomarker of effect.

Biomarkers of effect for plutonium exposure may exist but were not located in the reviewed literature. For more information on biomarkers of effects for the immune, renal, and hepatic systems see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for biomarkers of effect for the neurological system see OTA (1990). For more information on health effects following exposure to plutonium see Section 2.2.

2.6 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 plutonium-239 dioxide, appeared to inhibit the clearance of plutonium (Talbot et al. 1987). At 49 days post-exposure, animals exposed to plutonium and cigarette smoke retained approximately 20% more plutonium than those animals exposed to plutonium alone.

Exposure to inhaled plutonium-239 dioxide 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 plutonium-239 dioxide alone (Metivier 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 plutonium-239 dioxide 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 (Sanders 1973a).

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A decrease in median survival time was observed in rats injected intravenously with plutonium-239, 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 15 days) following exposure of the rats to plutonium-239, the number of deaths occurring before 40 days was reduced.

Exposure of rats to plutonium-239 dioxide and asbestos by intraperitoneal injection resulted in a higher incidence of abdominal tumors compared to animals exposed to plutonium-239 dioxide alone (Sanders 1973a). 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 plutonium-239 oxide 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 those exposed to plutonium only (Sanders 1975b).

An increased incidence of metaplasia was observed in rats exposed via inhalation to a single exposure of plutonium-239 dioxide followed by administration of 1 or 10 mg vitamin C/ml of drinking water for 1 year post-exposure, compared to those animals exposed to plutonium only (Sanders and Mahaffey 1963). However, the incidence of squamous cell carcinomas in animals exposed to plutonium and vitamin C decreased with increasing dose of vitamin C. The authors state that vitamin C may interfere with the progression of squamous cell metaplasia to squamous cell carcinoma.

Studies in laboratory animals have also shown the influence of metals on the toxicokinetics of plutonium. Pretreatment of rats with a subcutaneous injection of cadmium or copper followed by an intravenous injection of plutonium-239 or plutonium-238 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). Copper pretreatment appeared to increase the retention of plutonium in the liver, while cadmium pretreatment appeared to decrease plutonium retention in the liver. These differences in retention of plutonium in the liver may reflect different properties of the respective metalbinding proteins or different mechanisms of action (Volf 1980).

Exposure of rats via inhalation to beryllium oxide followed by exposure to plutonium-239 oxide resulted in increased retention of plutonium in the lungs of rats and subsequently, increased translocation of plutonium to thoracic lymph nodes as compared to plutonium-treated, controls (Sanders et al. 1978). Although lung retention of plutonium was increased and beryllium and plutonium are both considered to be lung

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carcinogens, combined exposures of beryllium and plutonium-239 did not significantly increase the incidence of lung tumors in rats, compared to rats treated with plutonium only (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 plutonium-239 and were sacrificed 1 or 41 days post-exposure (Mahlum and Hess 1978). In animals given ethanol for 6 weeks, retention of plutonium in the liver was increased at 1 day post-exposure, but returned to normal 41 days post-exposure, compared to animals exposed to plutonium only. At 1 day post-exposure, 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 post-injection (Mahlum and Hess 1978).

Animal studies have been conducted to study the relative hazards of "diffuse" vs. "localized" irradiation of the lung (Anderson et al. 1979) to determine if there is a "hot particle" or "hot spot" effect. In these studies, hamsters were exposed by instillation or intravenous injection to plutonium-238 or -239 oxide contained in zirconium dioxide spheres. Following "localized" exposure, the incidence of lung tumors was significantly increased (3/102) only at the highest exposure [3.5×10^6 pCi (1.3×10^5 Bq) plutonium-238/kg body weight]. However, following "diffuse" exposure, a significant increase in the incidence of lung tumors was observed at exposures of 8.4×10^5 pCi (3.1×10^4 Bq) plutonium-238/kg body weight and 9.4×10^5 pCi (3.5×10^4 Bq) plutonium-239/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. Exposure of young adult beagle dogs to a single intravenous injection of polymeric plutonium-239 plus plutonium-237 as a tracer, 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% plutonium-237 excretion, respectively, vs. 7.1% plutonium excretion at 24 hours post-exposure 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.

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2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Children may be particularly susceptible to the adverse effects of plutonium. Cells are replicating much faster in growing children than in adults. Rapidly regenerating cells are more radiosensitive than slowly regenerating cells (see Appendix B). 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 Ragan (1977) have demonstrated that iron-deficient mice absorbed four times as much plutonium from the gastrointestinal tract as mice with normal iron levels. Therefore, persons who are iron deficient may absorb more plutonium (Sullivan and Rummeler 1988).

2.8 ADEQUACY OF THE DATABASE

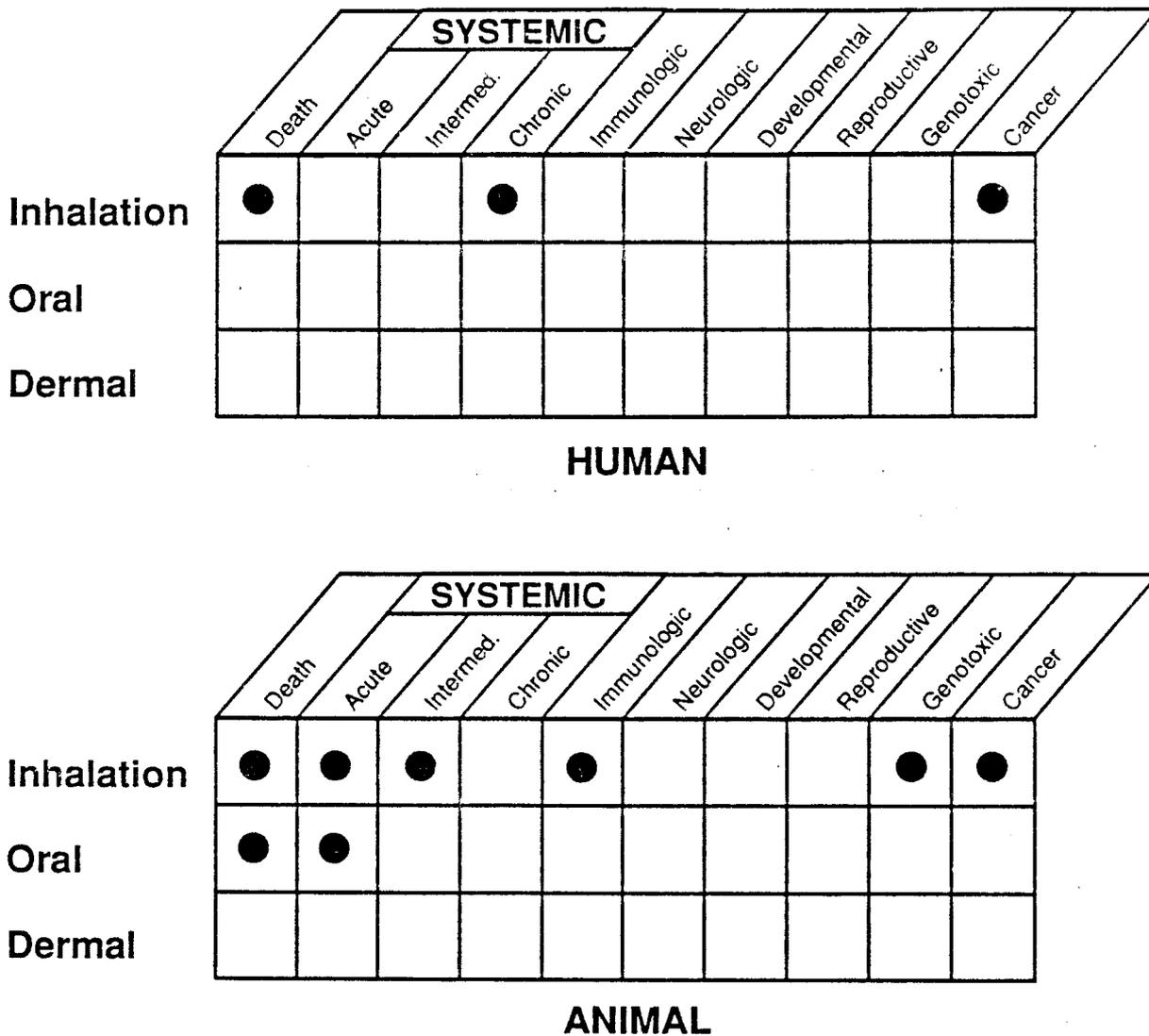
Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of plutonium is available. Where adequate information is not available, ATSDR, 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 or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.8.1 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 2-4. 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 imply anything about the

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● Existing Studies

FIGURE 2-4. Existing Information on Health Effects of Plutonium

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quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

Figure 2-4; 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 exposure. No information on health effects in humans after acute or intermediate 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 inhalation exposure and limited information on acute oral exposure.

2.8.2 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

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exposure concentrations would be useful in determining any dose-response relationship for adverse health effects.

Intermediate-Duration Exposure. Limited data from intermediate-Duration exposure studies in laboratory animals indicate that the lung is the target organ for inhaled plutonium. In one study, hamsters developed pneumonitis following intermittent exposure to plutonium. However, no data are available on effects of inhalation exposure for this duration in humans. Kinetics studies in animals exposed by inhalation are extensive but all are single-exposure studies. No information is available in animals or humans following intermediate-duration exposure by the oral or dermal routes. A single kinetics study in rats exposed to plutonium by the oral route for an intermediate period indicated that significant deposition was found in the gastrointestinal tract, the skeleton, and soft tissues. Because limited or no data are available on systemic effects or kinetics following intermediate-duration exposure by all three routes, studies to provide such data would be useful. These data could be used to predict human health effects from exposure for this duration in populations living near hazardous waste sites and in the workplace, and to determine the relative contribution of each of the three routes of exposure to these adverse health effects.

Chronic Duration Exposure and Cancer. No information on noncancer health effects following chronic exposure of animals or humans to plutonium by any route exists. Epidemiological studies generally report only mortality from cancer and do not report deaths from noncancer causes or other noncancer adverse effects that may have been identified. Limited kinetics studies of occupationally exposed individuals indicate that plutonium concentrations were higher in the lungs and trachealbronchial lymph nodes than in any other single organ, indicating that the lung would be the target organ for inhaled plutonium. However, no noncancer effects were reported in these individuals. Studies of kinetics following exposure by any route in laboratory animals are only for single exposures. Due to the general lack of data on noncancer health effects following chronic exposure, results of tests in animals exposed chronically to plutonium would be informative. Although, such tests may be difficult to design and carry out due to the radioactive nature of plutonium, it would be useful to compare such data to noncancer adverse effects which are commonly reported in single-dose studies. These studies would also be useful in evaluating toxicity, other than cancer, to the general public, as well as occupationally exposed individuals. In addition, it would be worthwhile to report information on noncancer effects seen in follow-up of existing occupational cohorts or new cohorts.

Studies in rats and dogs exposed to plutonium for 1 day have indicated that plutonium via inhalation causes cancer. At various times

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following high doses of plutonium, tumors were found primarily in the lung, but also in the skeleton and liver. Chronic studies of animals exposed to plutonium via inhalation would be useful in order to compare the type of cancers that may occur and the onset of these effects to those reported in single-dose studies. Epidemiological studies have been equivocal. Most epidemiological studies of occupationally exposed individuals have consistently reported fewer cancer deaths in exposed cohorts than in an unexposed cohort or in the normal population. However, these epidemiological studies have many confounding factors including small cohort size, poorly defined exposure information, insufficient follow-up period, or possible concurrent exposure to external radiation. In one epidemiological study, the authors report a suggested increased risk of lymphopoietic cancers. However, the incidence of this type of cancer was based on limited data, and no increase in cancer incidence was noted in tissues with the highest concentration of plutonium as demonstrated in autopsy samples. Chronic animal studies at low radiation doses would be useful to provide information to assist in the interpretation of inconclusive carcinogenicity information from existing epidemiologic studies. No information is available on kinetics or development of cancer in animals or humans following oral or dermal exposure. Although acute studies report that absorption via these routes is much less than absorption via inhalation, chronic animal studies would provide information on kinetics and possible carcinogenicity of plutonium by these routes.

Genotoxicity. Epidemiological studies of occupationally exposed cohorts have reported equivocal results concerning exposure to plutonium and increased incidence of chromosomal aberrations. However, *in vitro* tests using human lymphocytes irradiated with plutonium demonstrated increases in sister chromatid exchange. Laboratory animals have exhibited increased chromosomal aberrations in blood lymphocytes following exposure to plutonium by inhalation. Other effects seen *in vivo* in 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 individuals occupationally exposed would be useful, and would hopefully clarify the equivocal reports of previous studies.

Reproductive Toxicity. There are no data 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, significant fetal deaths were reported and were attributed to dominant lethality. Kinetics 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 (more than 575 days) (Green et al 1977; Taylor 1977). Although this

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route of exposure is not relevant to humans, results of these studies would indicate that studies to evaluate reproductive effects in laboratory animals following single, repeated, or multi-generation exposure to plutonium via inhalation or ingestion would be worthwhile.

Developmental Toxicity. There are no data 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 showed that plutonium crosses the placenta and is retained in the fetus (Green et al 1977; Sikov et al 1978b). These studies would indicate that additional data are needed to evaluate developmental effects in laboratory animals following single or repeated exposure to plutonium via inhalation or ingestion.

Immunotoxicity. There are no data available regarding 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 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 function of the immune system would be useful.

Neurotoxicity. No studies have been done 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, tests of the neurotoxicity of plutonium may not be 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 Los Alamos National Laboratory, the Rocky Flats Facility, and the Hanford Facility, as well as the cohort involved in the original Manhattan project at Los Alamos. These studies have failed to demonstrate an unequivocal association between exposure to plutonium and mortality from cancer following occupational exposure. However, these studies contain many limitations including small cohort size, poorly defined exposure information, or insufficient follow-up periods. Because these occupational cohorts have

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been exposed to plutonium levels many times higher than environmentally exposed populations, continuation of the follow-up of these cohorts would generate useful information. Examination of these cohorts for end points-other than cancer, such as genetic effects and effects on the immune system, would be useful.

Epidemiological studies in which humans were occupationally exposed to plutonium attempted to correlate adverse health effects with body burdens of plutonium. However, definite correlations between plutonium exposure and body burdens have not been reported. Further information in this area is needed. Epidemiological studies in which activity concentrations in the workplace are reported also are needed. If an epidemiological study were conducted in which activity concentrations the workplace were known, attempts could be made to correlate exposure levels with body burdens, as well as with health effects. Isolated measurement of plutonium levels resulting from fallout have been made air, water, food, and soil. Overall, information regarding levels of plutonium in the environment is limited. If epidemiologic data could provide dose-response information, additional studies on environmental levels could provide information to evaluate the extent of the hazard associated with environmental plutonium exposure or exposure to individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect. Currently, the only biomarker of exposure that has been identified is the presence of radioactivity released by plutonium, in the urine. The presence or this activity in the urine is specific to plutonium exposure and can be used to monitor short-term, intermediate, or long-term exposure. Although the detection of plutonium radioactivity in the urine is not a direct measurement of exposure, estimates may be derived using mathematical models. Other biomarkers of exposure may exist, such as the presence of plutonium in blood, bone, teeth, or hair.

Biomarkers of health effects resulting from plutonium-released radiation are not known. It is possible that early damage to bone marrow resulting from radiation exposure may be indicated by a decrease in stem cells or by a decrease in the number of red blood cells (Joshima et al. 1981). It is also possible that abnormal sputum cytology may be used as an early indicator of radiation damage to lung tissue (ATSDR 1990). Although a decrease in stem cells and abnormal sputum cytology may indicate exposure to radiation, additional research to determine if these methods are reliable and to correlate these effects with plutonium exposure levels would be worthwhile.

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

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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. Studies of age-related changes in the toxicokinetics of plutonium would be very valuable, especially those age-related differences that may indicate enhanced exposure or susceptibility. Very 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. There is limited information regarding comparative toxicokinetics among laboratory animal species and humans. However, similar target organs have been identified among laboratory animals exposed to plutonium. Toxic effects that have been observed in animals have not been observed in humans. In addition, hamsters develop many of the toxic effects in the lung following exposure to inhaled plutonium, but have not been found to develop lung tumors. This may be indicative of differences in anatomy and physiology or species sensitivity. Information to help identify the appropriate animal model to provide insight into the toxicokinetics of plutonium compounds in humans would be useful.

2.8.3 On-going Studies

G.L. Voelz (Los Alamos National Laboratory) is investigating the correlation between low-level plutonium and/or external radiation exposure and lung cancer incidence or other diseases among current and former workers at Rocky Flats, Los Alamos, Mound, Savannah River, Oak Ridge, and Hanford.

Mechanisms of alpha-emitting and bone-seeking radionuclide-induced skeletal cancers are being investigated by W.S. Jee (University of Utah) in humans and dogs.

The long-term toxicity of inhaled plutonium-239 dioxide (B.A. Muggenburg and his colleagues, Inhalation Toxicology Research Institute and F.W. Bruenger, University of Utah) in juvenile and mature beagle dogs is being studied. Influence of age at the time of exposure is the focus of the studies. Studies by Muggenburg include single and multiple exposure of rats, Syrian hamsters, and mice to plutonium-239 dioxide aerosols similar to human exposure.

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J.H. Diel (Inhalation Toxicology Research Institute) has been studying health effects in laboratory animals following repeated exposure to insoluble plutonium over a long fraction of their lifetime. Single exposures at comparable radiation dose levels are included for comparison. Experiments using rats and dogs are still in progress. whereas experiments using mice and hamsters have been completed.

The effects of inhaled plutonium-239 nitrate (G.E. Dagle, Pacific Northwest Laboratories), or plutonium-239 dioxide or plutonium-238 dioxide (J.F. Park, Pacific Northwest Laboratory), on lifespan have been under investigation in beagle dogs. The current investigation by Dagle involves determining the interrelationship of lung cancer, bone cancer, and noncancerous lesions in dogs exposed to low levels of plutonium. Park is continuing to investigate the mechanisms of lymph node damage and lymphopenia in these animals. The role of oncogenes in plutonium-induced cancers will be examined in both studies by Dagle and Park. Furthermore, M.E. Frazier (Pacific Northwest Laboratory) is studying whether oncogenes are activated in plutonium-induced lung cancer or whether oncogene activation is a cause or an effect of cancer development.

An extensive investigation of the effects of lifetime inhalation of low-levels of plutonium-239 dioxide ($5 \times 10^{+2}$ to 1.9×10^{-5} pCi (1.9×10^1 to 7.0×10^3 Bq) initial alveolar depositions] in rats is in progress by C.L. Sanders (Pacific Northwest Laboratory).

Among the few studies in progress pertaining to plutonium genotoxicity is the investigation of heritable plutonium-induced gene mutations, chromosome aberrations, and dominant lethal mutations in mice (P.B. Selby, Oak Ridge National Laboratory). P.G. Kale at Hampton University is studying the genetic effects of plutonium in *Drosophila*. Special emphasis will be placed on the dose-response relationship in predicting consequences of low-level plutonium exposures.

Current studies by S.E. Dietert at Hanford Environmental Health Foundation focus on elucidating the biokinetics and dosimetry of plutonium and related elements in humans. The study includes determining the distribution and concentration of transuranic elements in man by radiochemical analysis of donated autopsy tissues from occupationally exposed individuals. The uptake and distribution patterns of plutonium and other actinides in humans are being studied by J.F. McInory (Los Alamos National Laboratory). N.P. Singh at the University of Utah is studying the biological half-lives of plutonium in liver and bone of the general population of northern Utah.

M.F. Sullivan at Pacific Northwest Laboratory is investigating the transfer factors involved in the absorption of plutonium in animals and other actinides across the gastrointestinal tract under conditions that may be experienced by humans (such as the oxidation state of plutonium,

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fasting, high acidity, iron and calcium deficiency). Plutonium gastrointestinal tract absorption is being studied in three baboons in order to obtain information on possible human gastrointestinal tract absorption of plutonium (M.H. Battacharyya, Argonne National Laboratory).

R.G. Cuddihy at Inhalation Toxicology Research Institute is studying the mechanisms involved in the deposition and clearance of inhaled plutonium in the respiratory tract of rats and other animals.

E. Shek (Pharmatec) is investigating methods for improving gastrointestinal tract absorption of orally administered chelating agents, which bind metals such as plutonium and facilitate excretion from the body. New actinide-chelating agents produced by microorganisms are being tested by P.W. Durbin at Lawrence Berkeley Laboratory. It is assumed that these agents bind plutonium(IV) and enhance its excretion. Another study by Durbin includes the development of metabolic models for plutonium and other radionuclides in order to verify and/or modify metabolic models currently recommended by the International Commission on Radiation Protection (ICRP) for these radioelements.

S.C. Miller (University of Utah) is determining the localization and distribution of plutonium-239 and other actinides in tissue, cellular, and subcellular compartments of the gonads (testes and ovaries) in different species and in human tissue.

R.E. Filipy (Pacific Northwest Laboratory) is continuing the investigation of the effects of cigarette smoke on rats and dogs exposed to plutonium as compared to sham-exposed animals or those exposed to plutonium alone. The findings of the study will contribute to the understanding of the potential health effects of inhaled plutonium among the cigarette-smoking population.