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2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PLUTONIUM IN THE UNITED STATES

Plutonium is primarily a human-made radioactive element of the actinide series and was the first human-made element to be synthesized in weighable amounts. Plutonium was first synthesized by the bombardment of uranium with deuterons (^2H) by Seaborg and co-workers in 1940. Although 20 isotopes of plutonium ($^{228-247}\text{Pu}$) have been identified, the alpha-emitting ^{238}Pu and ^{239}Pu isotopes are the ones most commonly encountered and widely studied for potential adverse health effects. The isotope ^{239}Pu was first used in fission weapons beginning in 1945 and is produced during the bombardment of uranium (^{235}U) by neutrons in nuclear reactors. Approximately one-third of the total energy produced in a typical commercial nuclear power plant comes from the fission of ^{239}Pu produced from ^{235}U . The isotope ^{238}Pu has been used as a heat source in nuclear batteries to produce electricity in devices such as unmanned spacecraft and interplanetary probes. Plutonium is a carefully regulated material under government and International Atomic Energy Agency (IAEA) control and has no commercial usage, with the exception of small quantities used in research laboratories. Approximately 1,855 metric tons of plutonium was estimated to exist worldwide at the end of 2003; most of which was found in spent fuel from nuclear power plants. A plutonium production rate of 70–75 metric tons/year was estimated for reactors worldwide in 2003.

The main sources of plutonium in the environment are releases from research facilities, nuclear weapons testing, waste disposal, nuclear weapons production facilities, and accidents. Atmospheric testing of nuclear weapons, which ended in 1980, is the source of most of the plutonium in the environment worldwide, which released approximately 10,000 kilograms of plutonium. Trace amounts of plutonium (including ^{238}Pu , ^{239}Pu , ^{240}Pu , and ^{241}Pu) are found worldwide, mostly due to fallout from atmospheric nuclear testing. Trace amounts of ^{239}Pu are found in naturally occurring uranium ores, although in such small amounts that extraction is not practical. Small amounts of ^{244}Pu also exist in nature from remnants of primordial stellar nucleosynthesis and from “natural” reactors such as the Oklo natural reactor in the African nation of Gabon, which existed about 2 billion years ago. Plutonium released to the atmosphere reaches the earth's surface through wet and dry deposition to the soil and surface water. Once in these media, soluble plutonium can sorb to soil and sediment particles or bioaccumulate in terrestrial and aquatic food chains.

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Humans may be exposed to plutonium by breathing air, drinking water, or eating food containing plutonium; however, the levels of plutonium in air, water, soil, and food are generally very low, and of little health consequence. Average plutonium levels in surface soil from fallout range from 0.01 to 0.1 picocuries (pCi) per gram of soil (1 picocurie equals one-trillionth [10^{-12}] of a curie). In general, plutonium concentrations in air are low. Baseline ^{239}Pu concentrations in air ranging from 1.6×10^{-6} to 3.8×10^{-6} pCi per cubic meter of air (pCi/m³) have been reported.

2.2 SUMMARY OF HEALTH EFFECTS

Risks for adverse outcomes of plutonium exposures are strongly dependent on radiation doses received by specific tissues and organ systems. Most of the body burden of plutonium resides in the skeleton and liver, and following inhalation exposures, in the lung and lung-associated lymph nodes. As a result, these tissues receive relatively high radiation doses following exposures to plutonium. Radiation-induced toxicity to these tissues has been documented in human epidemiological studies and in animal models. The relatively high radiation doses received by bone, liver, and lung lend greater credibility to the epidemiological findings for these tissues than for outcomes in other tissues that receive much smaller radiation doses. All epidemiological studies that have reported adverse outcomes in these tissues have studied populations (i.e., workers in plutonium production and processing facilities) that experienced exposures and radiation doses that greatly exceed those experienced by the general public. Accordingly, risks for these outcomes in the general population are substantially lower than reported for these more highly exposed worker populations.

Death. Possible associations between exposure to plutonium and mortality have been examined in studies of workers at the U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (e.g., Mayak) and the United Kingdom (e.g., Sellafield). The Mayak studies provide relatively strong evidence for an association between cancer mortality (bone, liver, lung) and exposure to plutonium. Plutonium dose-response relationships for lung cancer mortality have been derived from studies of Mayak workers, who received much higher uptakes of plutonium compared to other epidemiological cohorts (i.e., mean body burdens 0.09–9.2 kBq, with much higher individual exposures [up to 470 kBq] in relatively large numbers of these workers). Excess relative risk estimated in three studies (adjusted for smoking) were 3.9 per Gy (95% confidence interval [CI]: 2.6–5.8) in males, and 19 per Gy (95% CI: 9.5–39) in females (attained age 60 years), 4.50 per Gy (95% CI: 3.15–6.10) in males, and 0.11 per Sv (95% CI: 0.08–0.17) or 0.21 per Sv (95% CI: 0.15–0.35), depending on the smoking-radiation interaction model that was assumed (these estimates per Sv correspond to 2.2 or

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4.3 per Gy, respectively, assuming a quality factor of 20 for α -radiation). The excess relative risk per Gy in Mayak workers declined strongly with attained age.

Decreased survival was noted in beagle dogs exposed to plutonium aerosols ($^{238}\text{PuO}_2$, $^{239}\text{PuO}_2$, or $^{239}\text{Pu}(\text{NO}_3)_4$) at levels resulting in initial lung burdens in the range of ≥ 1 kBq/kg body weight. Early deaths were attributed to radiation pneumonitis and decreased survival late in life was typically associated with tumor development.

Cancer. Possible associations between exposure to plutonium and cancer mortality and morbidity have been examined in studies of workers at the U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). Compared to studies of U.K. and U.S. facilities, the Mayak cohorts had relatively high uptakes of plutonium (i.e., mean body burdens as high as 9.2 kBq, with much higher individual uptakes [up to 470 kBq] in relatively large numbers of these workers). Collectively, the Mayak studies provide evidence for an association between cancer mortality (lung, liver, bone) and uptake of plutonium. Studies of U.K. and U.S. facilities have examined cohorts of workers who had substantially lower estimated plutonium uptakes and corresponding internal radiation doses than the Mayak cohorts (e.g., Sellafield: ≤ 1 kBq in 97% of the assessed workers; Los Alamos: mean body burden 0.970 kBq, range 0.05–3.18 kBq). Although a significantly higher incidence of cancer mortality in certain groups of plutonium workers has been found in some studies, higher cancer incidence and/or risks for tissues that received the highest plutonium radiation doses (i.e., lung, liver, bone) have not been found, making causal connections of these outcomes to plutonium exposure more uncertain. The Sellafield study is by far the strongest of these studies and did not find associations between plutonium exposure and cancers to tissues receiving the highest radiation doses from plutonium.

Plutonium dose-response relationships for lung cancer mortality and morbidity have been corroborated in three Mayak studies. Estimated excess relative risk in these three studies (adjusted for smoking) were as follows: (1) 3.9 per Gy (95% CI: 2.6–5.8) in males, and 19 per Gy (95% CI: 9.5–39) in females; (2) 4.50 per Gy (95% CI: 3.15–6.10) in males; and (3) 0.11 per Sv (95% CI: 0.08–0.17) or 0.21 per Sv (95% CI: 0.15–0.35), depending on the smoking-radiation interaction model that was assumed (these estimates per Sv correspond to 2.2 or 4.3 per Gy, respectively, assuming a quality factor of 20 for α -radiation).

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The risks of mortality and morbidity from bone and liver cancers have also been studied in Mayak workers. Increasing estimated plutonium body burden was associated with increasing liver cancer mortality, with higher risk in females compared to males. Relative risk for liver cancer for a cohort of males and females was estimated to be 17 (95% CI: 8.0–26) in association with plutonium uptakes >7.4 kBq; however, when stratified by gender, the relative risk estimates for females was 66 (95% CI: 16–45) and higher than for males, 9.2 (95% CI: 3.3–23). Risk of bone cancer mortality in this same cohort (n=11,000) was estimated to be 7.9 (95% CI: 1.6–32) in association with plutonium uptakes >7.4 kBq (males and females combined). Risks of leukemia mortality, in the same cohort, were not associated with internal plutonium exposure. In a case control study of Mayak workers, the odds ratio for liver cancer was 11.3 (95% CI: 3.6–35.2) for subjects who received doses >2.0–5.0 Gy (relative to 0–2.0 Gy) and the odds ratios for hemiangiosarcomas were 41.7 (95% CI: 4.6–333) for the dose group >2.0–5.0 Gy, and 62.5 (95% CI: 7.4–500) for the dose group >5.0–16.9 Gy; doses were estimated based on periodic urine sampling.

Consistent with findings from human epidemiological studies, results of animal studies show that tissue location of plutonium-induced cancer is compound-dependent. A significant amount of plutonium from the relatively soluble $^{238}\text{PuO}_2$ and $^{239}\text{Pu}(\text{NO}_3)_4$ compounds is distributed to bone and liver, whereas the relatively insoluble $^{239}\text{PuO}_2$ is primarily retained within the lungs and associated lymph nodes. Bone tumors (predominantly osteosarcomas) were the primary cause of cancer deaths in dogs exposed once to $^{238}\text{PuO}_2$ aerosols; lung tumor incidences were also relatively high in these dogs, and liver tumors appeared to be a contributing cause of death in a few $^{238}\text{PuO}_2$ -exposed dogs. The pattern of tumor development in dogs exposed to $^{239}\text{Pu}(\text{NO}_3)_4$ was similar to that of dogs exposed to $^{238}\text{PuO}_2$, with tumors observed in lung, bone, and liver (principally of bile-duct epithelium). Bone tumors were the main cause of death in the exposure groups with mean initial lung burdens of 1 and 5.9 kBq/kg. In contrast to the high incidences of bone tumors in the dogs exposed to $^{238}\text{PuO}_2$ or $^{239}\text{Pu}(\text{NO}_3)_4$ aerosols, cancer deaths in dogs exposed to aerosols of the relatively insoluble $^{239}\text{PuO}_2$ were predominantly associated with lung tumors consisting mainly of bronchiolo-alveolar carcinomas.

Respiratory Effects. Possible associations between exposure to plutonium and respiratory tract disease have been examined in studies of workers at U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). Collectively, these studies have not found significant associations between mortality rates from respiratory tract disease, other than cancer, and exposures to plutonium among workers at these facilities. Possible associations between exposure to plutonium and pulmonary fibrosis

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

Radiation pneumonitis has been observed following inhalation exposure of dogs, nonhuman primates (monkeys and baboons), and rodents to plutonium (primarily insoluble) compounds, and was identified as the primary cause of death in some dogs and nonhuman primates that inhaled $^{238}\text{PuO}_2$, $^{239}\text{PuO}_2$, or $^{239}\text{Pu}(\text{NO}_3)_4$. Results of lifetime studies in dogs indicate that radiation pneumonitis in the $^{239}\text{PuO}_2$ -exposed dogs occurred at lower initial lung burdens and had a shorter time to onset following exposure to $^{239}\text{PuO}_2$ compared to that observed in $^{238}\text{PuO}_2$ - or $^{239}\text{Pu}(\text{NO}_3)_4$ -exposed dogs. This observation is consistent with the toxicokinetic differences observed for inhaled plutonium compounds, showing that inhaled $^{239}\text{PuO}_2$ is cleared from the lung more slowly than $^{238}\text{PuO}_2$ and $^{239}\text{Pu}(\text{NO}_3)_4$. Because reports of radiation-induced pneumonitis in the dogs primarily focused on mortality, dose-response data for nonfatal radiation pneumonitis are lacking.

Hematological Effects. Possible associations between exposure to plutonium and mortality from hematopoietic diseases have been examined in studies of workers at plutonium production and/or processing facilities in the United States (Rocky Flats), United Kingdom (Sellafield). Collectively, these studies have not found significant associations between mortality rates from diseases of blood or blood-forming organs and exposures to plutonium among workers at these facilities.

Compound-dependent decreased numbers of selected white blood cells were observed in dogs exposed to plutonium aerosols. Primary hematological effects following pulmonary deposition of $^{238}\text{PuO}_2$ and $^{239}\text{Pu}(\text{NO}_3)_4$ were lymphopenia and neutropenia, whereas lymphopenia was the primary hematological effect of inhaled $^{239}\text{PuO}_2$. Persistent hematological effects occurred in $^{238}\text{PuO}_2$ - and $^{239}\text{PuO}_2$ -exposed dogs with initial lung burdens as low as 0.28 kBq/kg initial lung burdens that elicited hematological effects in $^{239}\text{Pu}(\text{NO}_3)_4$ -exposed dogs appeared to be somewhat higher (mean initial lung burdens ≥ 5.91 kBq/kg).

Hepatic Effects. Possible associations between exposure to plutonium and mortality from liver disease (e.g., liver cancer) have been examined in studies of workers at U.S. plutonium production and/or

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processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). Collectively, these studies have not found significant associations between mortality rates for liver disease, other than cancer, and exposures to plutonium among workers at these facilities.

Elevated serum liver enzymes (indicative of adverse liver effects), were the most consistent indicators of non-neoplastic liver effects in dogs exposed to aerosols of $^{238}\text{PuO}_2$ and $^{239}\text{Pu}(\text{NO}_3)_4$ at levels resulting in mean initial lung burdens ≥ 0.36 and ≥ 0.19 kBq/kg, respectively. No consistent changes in serum liver enzymes were seen in $^{239}\text{PuO}_2$ -exposed dogs. Although elevated liver enzymes may serve as indicators of hepatotoxicity, clinical signs of liver dysfunction (i.e., ascites, icterus clotting disorders) were not observed in the $^{238}\text{PuO}_2$ -exposed dogs.

Musculoskeletal Effects. Possible associations between exposure to plutonium and mortality from bone disease (e.g., bone cancer) and other musculoskeletal diseases have been examined in studies of workers at U.S. plutonium production and/or processing facilities (Hanford, Los Alamos, Rocky Flats), as well as facilities in Russia (Mayak) and the United Kingdom (e.g., Sellafield). Collectively, these studies have not found significant associations between mortality rates for bone or musculoskeletal disease, other than cancer, and exposures to plutonium among workers at these facilities. Radiation osteodystrophy, observed in dogs with high intakes of plutonium, would be expected in humans following intake of large amounts of plutonium.

Radiation osteodystrophy, characterized by peritrabecular fibrosis, osteosclerosis, and osteoporosis, was observed on necropsy in dogs exposed to $^{238}\text{PuO}_2$. The incidence and severity was dose-related and was seen at mean initial lung burdens as low as 1.17 kBq/kg; necrotic osteoblasts and empty lacunae near endosteal surfaces were observed at relatively high initial lung burdens. Although osteodystrophy in $^{238}\text{PuO}_2$ exposed dogs was often associated with bone tumors, it also occurred in the absence of bone tumors. Radiation osteodystrophy has also been reported in dogs that inhaled $^{239}\text{Pu}(\text{NO}_3)_4$.

Immunological Effects. Possible associations between exposure to plutonium and mortality from immunological or lymphoreticular diseases have been examined in studies of workers at plutonium production and/or processing facilities in the United States (Rocky Flats) and the United Kingdom (Sellafield). Collectively, these studies have not found statistically significant associations between mortality rates from diseases of the immunological or lymphoreticular systems and exposures to plutonium among workers at these facilities.

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Histopathologic lesions of lymph nodes, particularly tracheobronchial lymph nodes, have been observed following exposure of dogs to aerosols of $^{238}\text{PuO}_2$, $^{239}\text{PuO}_2$, or $^{239}\text{Pu}(\text{NO}_3)_4$. Fibrosis and loss of lung-associated and mediastinal lymph nodes were observed in dogs exposed to $^{238}\text{PuO}_2$ at levels resulting in mean initial lung burdens ≥ 10 kBq/kg. Severity of non-neoplastic lesions was dose-related, progressing from lymphoid atrophy of medullary cords to significant lymph node atrophy with hypocellular scar tissue replacing lymphoid tissue. Similar dose-related atrophy and fibrosis of lung-associated, mediastinal, sternal, and hepatic lymph nodes were observed in dogs exposed to $^{239}\text{PuO}_2$. Sclerotic lymph nodes were observed in the groups of $^{239}\text{Pu}(\text{NO}_3)_4$ -exposed dogs with mean initial lung burdens ≥ 5.91 kBq/kg, but lymph node lesions in these dogs were considered less severe than those observed in $^{238}\text{PuO}_2$ - or $^{239}\text{PuO}_2$ -exposed dogs.

Results of studies on immunological function indicate that inhalation exposure to $^{239}\text{PuO}_2$ impairs T-cell response to antigens, as indicated by decreased response to antigen. One study detected accelerated aging of the T-cell response to mitogenic stimulation in dogs that had been exposed to $^{239}\text{PuO}_2$ 10 years earlier. Other reports of $^{239}\text{PuO}_2$ -induced effects from plutonium exposure include decreases in pulmonary alveolar macrophages in mice and depressed antibody-forming cells in hamsters.

Cardiovascular Effects. Possible associations between exposure to plutonium and cardiovascular disease have been examined in studies of workers at production and/or processing facilities in the United Kingdom (Sellafield). One study compared mortality rates between plutonium workers and other radiation workers within a cohort of Sellafield workers and found the mortality rate ratios were significantly elevated for cerebrovascular disease (1.27, $p < 0.05$) in a cohort of Sellafield workers. The cumulative internal uptakes of plutonium in the cohort were estimated to range from 0 to 12 kBq, with approximately 75% of the cohort having cumulative uptakes ≤ 250 Bq. One study compared mortality rates between plutonium workers and other radiation workers within a cohort of Sellafield workers and found that mortality rate ratios for plutonium workers were significantly elevated for deaths from circulatory disease (2.18, $p < 0.05$) and ischemic heart disease (4.46, $p < 0.01$).

No significant changes in cardiovascular function were seen in dogs exposed to $^{239}\text{PuO}_2$ at initial lung burdens up to and including those resulting in radiation pneumonitis; observed right ventricular hypertrophy was most likely a compensatory response to decreased respiratory function.

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Gastrointestinal Effects. Gastrointestinal effects were observed in rats following oral administration of $^{238}\text{Pu}/\text{kg}$ (as plutonium citrate) by gavage. Effects included mild hypertrophy of the crypts of the small intestine in neonatal rats that received an oral dose of 5,300 kBq $^{238}\text{Pu}/\text{kg}$; total obliteration of epithelial cells and crypts, combined with intestinal hemorrhaging, were noted in rats that received 17,400 kBq $^{238}\text{Pu}/\text{kg}$. Increased neutrophils were noted on the surface epithelium and superficial cellular layers of the large intestine in adult rats given 155 $\mu\text{Ci } ^{238}\text{PuO}_2/\text{kg}$ (5,740 kBq/kg). This effect was noted at 3 (but not 6) days posttreatment.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for plutonium due to the lack of suitable human or animal data regarding health effects following inhalation exposure to plutonium. The strongest evidence for plutonium exposure-response and radiation dose-response relationships in humans is for cancers of the lung, liver, and bone. Although non-neoplastic lesions have been observed in animals exposed to $^{238}\text{PuO}_2$, $^{239}\text{PuO}_2$, and $^{239}\text{Pu}(\text{NO}_3)_4$, these lesions occurred in association with acute exposures that also resulted in fatal cancers.

Oral MRLs

No acute-, intermediate-, or chronic-duration oral MRLs were derived for plutonium due to the lack of suitable human or animal data regarding health effects following oral exposure to plutonium. No data are available on exposure- and radiation dose-response relationships in humans for oral exposures to plutonium. Animal studies of health effects of oral exposures to plutonium have not examined major health outcomes that would be expected to occur from absorbed plutonium (e.g., effects on skeleton, liver, and lymphopoietic systems).