

Review

A Brief Review of the Effect of Plutonium on the Human Body

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The Oma nuclear power plant is under construction near the town of Oma and Rokkasho village in Aomori Prefecture. The plant employs a full mixed oxide furnace and includes a plutonium reprocessing plant for the reuse of plutonium. To develop an appropriate medical treatment protocol in case of exposure to radiation from the plant, an understanding of the effects of plutonium on biological systems, in particular of those related to carcinogenicity, is required. Therefore, to examine the influence of plutonium on the human body, we have reviewed existing documents detailing surveys of workers exposed to plutonium radiation at the Manhattan Project in the United States of America and the Mayak facilities in Russia, as well as animal experiments conducted at the National Institute of Radiological Sciences and other facilities.

We found that there is a significant dose-dependent relationship between internal exposure of plutonium and lung, liver, and bone cancers which is influenced by gender, age, and lifestyle habits. In contrast, radiation effects of plutonium on cancers other than those of the lungs, liver, and bone are considered to be extremely low.

Key words: plutonium, biological effect, lung cancer, liver cancer, bone cancer

1. Introduction

Since the Fukushima Daiichi nuclear disaster that occurred as a result of the Great East Japan Earthquake on March 11, 2011, uneasiness and an increased interest have developed regarding radiation exposure, particularly in Japan. In the town of Oma and Rokkasho village in Aomori Prefecture, a nuclear power plant is under construction that employs a full mixed oxide furnace and includes a plutonium reprocessing plant for the reuse of plutonium. The reuse of 47 tons of plutonium currently

stored by Japan is expected at these facilities¹). However, the amount of plutonium radiation emitted from the Fukushima Daiichi plant after the nuclear disaster was marginal; therefore, while the general public is aware and knowledgeable of cesium radiation and the use of iodine, this awareness does not extend to plutonium radiation^{2,3}).

Experimental studies in mice, rats, and dogs as well as autopsy studies in humans have revealed that inhalation of plutonium provides a route for the deposition of plutonium in the lungs, liver, and bone⁴⁻⁷). Because plutonium has a long biological half-life and continues to deliver an alpha dose to these tissues for an extended period, carcinogenesis in the lungs, liver, and bone can be the result^{6,7}).

However, there are few official reports providing details of exposure to plutonium radiation. Among reports of past accidental plutonium radiation exposure,

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the investigation which was conducted under the Manhattan Project during World War II in the United States of America is well known⁸⁻¹¹. This investigation details radiation exposure incidents in plutonium-related facilities and investigated follow-up surveys of plutonium-exposed workers, including periodic medical assessments and autopsies performed at the time of death to measure internal plutonium depositions. Although these follow-up surveys were valuable in understanding the influence of plutonium on the human body, subject numbers were limited and only young men were represented. Furthermore, confounding factors such as age, gender, and lifestyle habits were not considered.

The other experiment related to the Manhattan Project examined the consequences of the injection of citric acid plutonium without informed consent to 21 terminal patients to obtain data regarding the internal metabolism of plutonium, which at that period was unknown¹²⁻¹⁴. This inhumane study had been concealed for several years; however, during recent years, details of the study became public knowledge owing to Eileen Welsome of the Albuquerque Tribune¹³. In the past, therefore, researchers could only surmise the influence of plutonium on the human body from animal experiments using mice, rats, and dogs.

For the purpose of clarifying radiation toxicity by exposure to plutonium, the Pacific Northwest Laboratory and the Inhalation Toxicology Research Institute in the United States of America performed plutonium inhalational experiments using beagles during the 1950s. Thereafter, alpha ray-exposure experiments were conducted using small animals such as rats and mice in European countries during the 1970s. In Japan, the National Institute of Radiological Sciences (NIRS) conducted experiments investigating carcinogenesis related to plutonium exposure using small animals such as rats and mice during the 1990s. Although these experiments at NIRS have now ceased, much knowledge regarding the effects of plutonium exposure to organisms has been collected through them.

In recent years, a follow-up survey of plutonium exposure of workers at the Mayak facilities in Russia was reported. The Mayak Production Association which is located in the southern Urals in the Russian Federation began operations in 1948 to provide plutonium¹⁵⁻¹⁷. Particularly during the early years when the technology was still under development, the workers at Mayak could be exposed to substantial amounts of radiation from external gamma radiation and alpha particles from incorporated plutonium¹⁵. The cohort of workers at Mayak is unique as it incorporates a large number of people (>15,000) including a large number of females^{18, 19}. Furthermore, because gender, lifestyle, and other confounding factors could be considered by comparisons

between males and females, smokers and non-smokers, internal and external exposures, or radiation exposure and chemical substances exposure, this cohort provides an invaluable epidemiologic study. There are numerous reports that investigated the association between plutonium exposure and detrimental human health effects including carcinogenesis^{16, 18, 19, 20-26}.

To develop a medical treatment strategy in response to a plutonium exposure incident in Aomori Prefecture, it is important that an understanding is developed regarding the biological effects of exposure to plutonium radiation, particularly of those related to carcinogenicity. Therefore, in the current study, we investigated the biological effects of plutonium radiation on the human body by examining studies of past accidents and experiments associated with plutonium radiation exposure.

2. Investigation of past incidents of exposure to plutonium radiation

2.1. Exposure to plutonium radiation during the Manhattan Project

Voelz *et al.* conducted a follow-up survey of a group of 26 young males (subject numbers 1–26) who had worked on the Manhattan Project during World War II at Los Alamos in the United States of America during 1944–1945. Among them, internal plutonium depositions exceeded tolerable levels⁸⁻¹¹. These subjects had left Los Alamos prior to 1946, with one person having left in 1948. None of these subjects subsequently worked with plutonium, except for two who were transferred to other atomic energy commission facilities in 1946. Neither of these two subjects was exposed to significant plutonium radiation after leaving Los Alamos. Radiation exposure among subjects mainly occurred through inhalation. However, subject numbers 1, 4, 5, 6, 15, 20, 22, and 24 were potentially contaminated through minor cuts or puncture wounds. Subject numbers 11, 12, and 16 had records of at least one acid burn on the skin with a solution containing plutonium; however, no further details were recorded. The subjects had been medically examined approximately every 5 years since 1952 by Voelz *et al.*⁸⁻¹⁰ Furthermore, Voelz, Lawrence, and Johnson reported a follow-up survey of the 50th year post exposure in 1997¹¹. This report includes the last medical examination that was conducted in 1991 and 1992 at Los Alamos as well as the interview in 1995. In the current review, we mainly interrogated the data within the follow-up survey publication that had occurred during the 50th year by Voelz, Lawrence, and Johnson, with contents of the 50th year of that survey discussed below.

In the results of the 50th-year survey, deposition at the time of the investigation or at the death of a subject ranged from 50 to 3,180 Bq, with effective dose ranging

Table 1. Summary of major medical findings, 1991-1992 examinations (from Voelz, Lawrence, and Johnson, 1997)¹¹⁾

No	Pu(Bq)	Age(1994)	Medical diagnosis
1	1,620	76	<ul style="list-style-type: none"> · Early macular degeneration (vision loss) · Osteoarthritis of hips and spine. · Old inactive granulomatous disease in chest x ray
2	270	73	<ul style="list-style-type: none"> · Hematoma resection, right lung, 1971 · Mild obstructive lung disease, · cholecystectomy, 1984. · Hearing loss at high frequencies.
4	2,200	74	<ul style="list-style-type: none"> · Injured meniscus, right knee, 1989. · Benign colon polyps resected, 1989 · Borderline hypertension. · Osteoarthritis of hips and spine. · Hearing loss. · Moderate obesity
5	1,320	76	<ul style="list-style-type: none"> · Benign colon polyp resection, 1991. · Cataract surgery, 1984 and 1992. · Moderate hypertension. · Conduction defect ECG. · Degenerative joint disease, spine and neck. · Rectal polyps removed, 1979 and 1985 · Hearing loss
6	1,610	74	<ul style="list-style-type: none"> · Skin cancer on back removed by dry ice freezing, 1989 · Rectal polyps removed, 1979 and 1985. · Hearing loss
7	3,180	86	<ul style="list-style-type: none"> · Cataract extraction, 1985 and 1987. · Basal cell carcinoma, forehead. · Benign prostatic hypertrophy. · Hearing loss
8	1,690	71	<ul style="list-style-type: none"> · Glaucoma. · Hypertension · Obesity
9	2,090	79	<ul style="list-style-type: none"> · TRU resection of prostate, 1990. · Benign colon polyps resected, 1992. · Bladder cancer, 1995. · Asymptomatic Paget's Disease in pelvic bones. · Hypertension. · Pleural plaques and fibrosis on chest x ray (pneumonia scars). · Nerve deafness. · left (measles).
11	480	72	<ul style="list-style-type: none"> · Diabetes mellitus since 1975. · TRU resection of prostate, 1991. · Thyroid nodule. · Chronic bronchitis and chronic obstructive pulmonary disease. · Benign prostatic hypertrophy.
12	580	83	<ul style="list-style-type: none"> · Adenocarcinoma, prostate, 1992. · Multiple basal cell and squamous cell carcinoma on face and hands. · Varicose veins in legs. · Kyphoscoliosis. · Degenerative joint disease in hips and lower spine. · Duodenal ulcer, 1954. · Hearing loss, moderate
13	50	77	<ul style="list-style-type: none"> · Malaria, 1985. · Adenocarcinoma, prostate, 1992. · Hypercholesterolemia. · Malignant melanoma on skin of chest, excised 1971. · Hearing loss, moderate.
17	1,330	72	<ul style="list-style-type: none"> · Hearing loss, moderate. · Gout · Raynaud's Disease. · GU bleeding, unknown origin, 1989.
18	1,160	70	<ul style="list-style-type: none"> · Coronary angioplasty, 1985. · Cataract resection, 1991 · Hypertension, mild. · Gout
19	420	70	<ul style="list-style-type: none"> · Abnormal ECG-right bundle branch block. · Hearing loss, moderate.
21	410	69	<ul style="list-style-type: none"> · Arthroscopic knee surgery, 1990. · Benign prostatic hypertrophy. · Obesity

22	260	70	· Hypothyroidism. · Hearing loss
23	320	69	· Recurrent kidney stones, 1953 and 1989. · High frequency hearing loss
24	400	70	· Kidney stones-1965, 1983, 1985. · Adenocarcinoma, prostate; Radical prostatectomy, 1991. · Glaucoma. · Hypertension · Abnormal ECG-right bundle branch block.
26	110	71	· Hypertension · Atherosclerotic artery disease, iliac and femoral arteries. · Hypercholesterolemia

Table 2. Cause of death in 7 of 26 Manhattan Project workers exposed to plutonium in 1944-1945 (from Voelz, Lawrence, and Johnson, 1997)¹¹⁾

ID No.	Age at death	Year of death	Underlying cause of death	Total plutonium deposition (Bq) by	
				Autopsy*	PUQFUA
15	36	1959	Myocardial infarction	No autopsy	380
16	52	1975	Trauma (accident)	620	550
27	62	1982	Pneumonia	246	270
10	71	1985	Lung cancer	No autopsy	740
25	70	1988	Arteriosclerotic heart	98	130
3	66	1989	Prostate cancer	3,300	3,080
20	66	1990	Bone cancer(osteosarcoma)	252	580

*: Autopsy data from the U.S. Transuranium and Uranium Registries, Washington State University, Richland, WA.

from 0.1 to 7.2 Sv. A summary of major medical findings of that study is shown in Table 1. According to the survey by Voelz, Lawrence, and Johnson¹¹⁾ during the 1991–1992 examination, seven malignant tumors were observed in living subjects. These included three cases of prostate cancer, three cases of skin cancer (basal cell carcinoma, squamous cell carcinoma, and malignant melanoma), and one case of bladder cancer. Furthermore, Voelz, Lawrence, and Johnson¹¹⁾ revealed the cause of death in 7 of the 26 Manhattan Project subjects exposed to plutonium (Table 2) by the time of the investigation of 1991–1992. Of the causes of each of the seven deaths, four were not related to cancer. The causes of death in these subjects were myocardial infarction, trauma, pneumonia, and arteriosclerosis, whereas those in the remaining three subjects were lung, prostate, and bone cancers. In contrast, liver cancer, leukemia, and non-neoplastic effects, such as radiation pneumonia and pulmonary fibrosis, were not observed in the subjects. Mortality rate ratios for the Manhattan Project subjects were compared with mortality rates of the 876 unexposed Los Alamos workers, as shown in Table 3. Mortality rate ratio of all causes was 0.77 among the Manhattan Project subjects and was not high compared with unexposed workers; however, a significant difference was not observed. The death rate ratio of all cancers was 1.5, and a significant difference was not observed as only one person developed

Table 3. Mortality rate ratios for the Manhattan Project plutonium workers based on mortality rates of 876 unexposed Los Alamos workers with comparable hire dates (from Voelz, Lawrence, and Johnson, 1997)¹¹⁾

Cause of death	Number	Rate ratio	95% C.I.
All causes	7	0.77	0.36–1.6
All cancers	3	1.5	0.46–4.9
Lung	1	3.31	0.44–25
Prostate	1	7.14	0.36–79
Bone	1	—	1.6 —

lung, prostate, and bone cancers each.

2.2. Study of the cohort of Mayak workers exposed to plutonium radiation

The Mayak Production Association which is located in the southern Urals in the Russian Federation began operations in 1948 to provide plutonium¹⁵⁻¹⁷⁾. Mayak was the first Russian nuclear cycle enterprise during the early years when the technology was still under development. Mayak workers could receive substantial radiation exposure from external gamma exposure and internal exposure to plutonium¹⁵⁾.

During the 1980s and 90s, researchers began active follow-up surveys of workers, including all employers who had ever worked in the Mayak Production

Table 4. Observed and predicted deaths from lung, liver and bone cancer, and estimated excess deaths associated with plutonium and external exposure (from Sokolnikov et al., 2008)¹⁸⁾

	Observed	Predicated by model	Background ¹	Excess	
				Plutonium exposure	External exposure
Lung²					
Plutonium alpha dose					
Estimated as zero ³	139	124.3	114.0 (92)	0.0 (0.0)	10.3 (8.3)
Estimated as positive ⁴	215	222.2	107.9 (49)	91.9 (41)	22.3 (10)
Could not be estimated ⁵	327	334.5	201.9 (60)	106.8 (32)	25.8 (7.7)
Total	681	681	423.9 (62)	198.7 (29)	58.4 (8.6)
Liver⁶					
Plutonium alpha dose					
Estimated as zero ³	14	12.5	11.5 (92)	0.0 (0.0)	1.1 (8.5)
Estimated as positive ⁴	26	28.2	8.9 (32)	17.2 (61)	2.1 (7.4)
Could not be estimated ⁵	35	34.3	21.9 (64)	9.3 (27)	3.1 (9.0)
Total	75	75	42.3 (56)	26.5 (35)	6.3 (8.3)
Bone⁷					
Plutonium alpha dose					
Estimated as zero ³	5	3.8	3.2 (83)	0.0 (0.0)	0.6 (17)
Estimated as positive ⁴	6	6.7	2.8 (42)	3.0 (44)	0.9 (14)
Could not be estimated ⁵	19	19.6	7.0 (36)	11.1 (56)	1.5 (7.6)
Total	30	30	13.0 (43)	14.9 (47)	3.0 (10)
Lung, liver and bone					
Plutonium alpha dose					
Estimated as zero ³	158	140.7	128.6 (91)	0.0 (0.0)	12.0 (8.5)
Estimated as positive ⁴	247	257.0	119.6 (47)	112.1 (44)	25.4 (9.9)
Could not be estimated ⁵	381	388.3	230.9 (60)	127.1 (33)	30.4 (7.8)
Total	786	786	479.1 (61)	239.2 (30)	67.7 (8.6)

Percentages are given in parentheses.

¹Deaths that would have occurred in the absence of external or plutonium radiation exposure. ²Estimated from linear model with modification by gender and attained age. ³Primarily persons who worked only in reactor or auxiliary plants. ⁴Primarily persons who worked in the radiochemical or plutonium plant and were monitored for plutonium. ⁵Worked in radiochemical or plutonium plant and not monitored for plutonium. ⁶Estimated from linear model with modification by gender. ⁷Estimated from pure quadratic model with modification by attained age.

Association¹⁵⁾. Mayak workers of >15,000 people were periodically surveyed for up to > 60 years after exposure and individual radiation doses were estimated. Unique features of the Mayak cohort include the large population of females and the diversity of lifestyle habits represented, such as smoking, as well as the diversity of attained age or age at the time of exposure¹⁸⁾. The cohort has been used to investigate radiation effects on cancer risks, including associations between internal and external exposure doses and cancer at the organs of primary plutonium deposition (lung, liver, and bone surface)^{16, 18, 24, 27)}, other solid cancer organs, and leukemia^{17, 19, 28)} as well as some non-cancer health effects^{29, 30)}.

Sokolnikov *et al.*¹⁸⁾ reported the association between internal exposure of plutonium and cancer mortality in organs of primary plutonium deposition (lungs, liver, and bone) in 2008 (Table 4). Although several reports were published regarding the association between plutonium and these cancers^{16, 18, 20-26)}, Sokolnikov *et al.*'s report was valuable as they analyzed risks of lung, liver, and bone cancers in parallel and adjusted risks by gender, attained age, age at the time of exposure, and time elapsed since

exposure. This study investigated 17,740 workers initially hired at the main plant during 1948–1972. By December 31, 2003, 8,839 of the 17,740 workers had died. Table 4 shows observed and predicted deaths. There were 786 deaths from lung, liver, and bone cancers, including lung cancer (681), liver cancer (75), and bone cancer (30). Among the 786 cancer deaths, 239 (30%) could be caused by plutonium exposure, although 68 (8.6%) cancer deaths could be caused by external exposure.

Lung and liver cancer risks increased in a dose-dependent manner for plutonium doses > 0.2 Gy and > 1.0 Gy, respectively (Table 5)¹⁸⁾. Although bone cancer risk similarly showed a significant dose-dependence, elevated risks were only observed with plutonium dose > 10 Gy (Table 5). The significant dose-dependent relationship was observed in lung, liver, and bone cancers, although levels of plutonium dose that elevated the cancer risk were different.

Total excess deaths which were as a result of plutonium exposure were 239 (30.0%), whereas total excess deaths which were as a result of external gamma exposure were 68 (8.6%). Of the 239 plutonium excess

Table 5. Numbers of person-years, deaths, and relative risks (with 95% CI) for lung, liver and bone cancer mortality by categories of plutonium dose to the cancer site¹ (from Sokolnikov et al., 2008)¹⁸⁾

Plutonium organ dose (Gy)	Lung cancer			Liver cancer			Bone cancer		
	Person-years	Lung cancers	Relative risk (95% CI)	Person-years	Liver cancers	Relative risk (95% CI)	Person-years	Bone cancers	Relative risk (95% CI)
0 ²	144,023	139	1.0	144,022	14	1.0	144,023	5	1.0
>0–0.1	67,980	111	0.98 (<1–1.3)	59,754	9	1.03 ³ (<1–1.8)	34,209	1	
0.1–0.2	6,928	16	1.4 (<1–2.4)	10,319	0		14,406	0	
0.2–0.3	2,864	14	3.3 (1.7–5.8)	4,306	1	1.5 ⁴ (<1–3.2)	7,725	0	0.9 ⁵ (<1–4.3)
0.3–0.5	2,472	14	4.5 (2.4–7.7)	3,656	1		8,599	2	
0.5–1.0	1,972	15	6.4 (3.5–11)	3,078	0		8,643	0	
1.0–2.0	1,129	16	15 (8.1–25)	1,831	2	4.0 ⁵ (1.2–13)	5,171	0	
2.0–3.0	450	8	18 (8.3–35)	599	1		1,839	0	0.0 ⁷ (0.0–8.7)
3.0–5.0	342	7	17 (7.1–35)	518	3	16 (3.3–58)	1,674	0	
5.0–10.0	273	6	27 (10–58)	400	7	43 (12–134)	1,163	0	0.0 (0.0–61)
10.0+	183	8	186 (69–466)	133	2	36 (4.5–196)	1,164	3	82 (17–338)
Total	228,616	354		228,616	40		228,616	11	

Gy, gray; CI, confidence interval.

¹Includes only person-years and cancers for which plutonium doses can be estimated. ²Referent group. ³For dose category > 0.0–0.2 Gy. ⁴For dose category 0.2–1.0 Gy. ⁵For dose category 1.0–3.0 Gy. ⁶For dose category > 0.1–0 Gy. ⁷For dose category 1.0–5.0 Gy.

Table 6. Excess relative risk (ERR) per Gy for plutonium dose by gender, attained age and age at first plutonium dose (from Sokolnikov et al., 2008)¹⁸⁾

	Lung		Liver		Bone	
	No. of deaths ¹	ERR pr Gy (95% CI)	No. of deaths ¹	ERR pr Gy (95% CI)	No. of deaths ¹	ERR pr Gy (95% CI)
By gender ²						
Males	191	7.1 (4.9–10)	14	2.6 (0.7–6.9)	4	0.76 (<0–5.2)
Females	24	15 (7.6–29)	12	29 (9.8–95)	2	3.4 (0.4–20)
<i>P</i> for difference		0.047		<0.001		0.26
By attained age ³						
<55 years	33	10.7 (5.4–20)	6	4.4 (0.8–16)	5	9.2 (2.0–34)
55–64 years	79	6.8 (4.2–10)	9	1.8 (0.3–6.3)	0	
65–74 years	83	3.7 (1.9–6.3)	8	1.8 (0.3–6.7)	1	0.01 ⁵ (<0–1.3)
75+ years	20	4.1 (0.9–10)	3	7.5 (1.0–34)	0	
<i>P</i> trend ⁴		0.002		>0.5		0.011
By age at first plutonium ³ dose						
<20 years	25	10.7 (4.5–20)	4	6.0 (0.6–28)	2	5.7 (0.3–28)
20–24 years	95	8.0 (5.1–12)	12	2.6 (0.6–7.8)	4	
25–30 years	42	4.9 (2.3–8.9)	3	0.5 (<0–4.2)	0	1.1 ⁶ (0.1–5.3)
30+ years	53	3.4 (1.8–5.9)	7	2.9 (0.6–9.3)	0	
<i>P</i> trend ⁴		0.025		0.41		0.22

Gy = gray; CI = confidence interval

¹Number of deaths with positive plutonium doses. ²For lung cancer, ERR estimates are for attained age 60 (based on a model that included attained age). For liver and bone cancers, ERR estimates are for all attained ages. ³For lung and liver cancers, ERR estimates are for males (based on a model that included gender). For bone cancer, ERR estimates are for both genders. ⁴Based on trend over 5-year categories. ⁵For attained age category 55+ years. ⁶For age category 20+ years.

deaths, lung cancer was responsible for the largest number of plutonium excess deaths (199). In contrast, the highest percentage of deaths attributed to plutonium exposure was bone cancer (47%) (Table 4)¹⁸⁾.

In cases of lung and liver cancers, excess relative risk (ERR) per Gy for plutonium dose was higher in females than in males (Table 6)¹⁸⁾. ERR per Gy was higher for younger subjects for lung and bone cancers than for

older subjects. In addition, ERR per Gy was high in workers who were exposed to the radiation at a young age. In Sokolnikov *et al.*'s study¹⁸⁾, baseline rates for male smokers were 9.4 times those for non-smokers for lung cancer. In contrast, these relative risks for females were 4.7.

In the cohort of workers of the Mayak Production Association, the association between internal exposure

to plutonium and cancers, excluding cancers of organs of primary plutonium deposition (lungs, liver, and bone) was investigated. Shilnikova *et al.* reported a smaller but statistically significant influence of internal exposure of plutonium on the risk of death from cancers, excluding those of organs of primary plutonium deposition (lungs, liver, and bone) in the investigation during 1948–1997¹⁷.

Furthermore, Sokolnikov *et al.* examined radiation effects on the risk of mortality from solid cancers other than cancers of the lungs, liver, and bone among 25,757 workers who were employed during 1948–1982¹⁹. In Sokolnikov *et al.*'s study, although 1,825 workers had died from cancers other than those of the lungs, liver, and bone during 1948–2008, no significant association between internal exposure of plutonium and mortality from solid cancers other than lung, liver, and bone cancers was reported.

Furthermore, Shilnikova *et al.* reported no significant association between internal exposure of plutonium and myeloid leukemia¹⁷.

3. Animal experiments

Animal experiments were conducted to estimate the influence of plutonium on the human body, as at that stage, there were not yet documented cases of human exposure. Lung cancer was observed in rats and beagles which had inhaled plutonium aerosols^{31–34}. In contrast, bone cancer was observed in mice injected with plutonium citrate^{35–39}. The association between plutonium and lung or bone cancer risks followed a dose-dependent relationship. Furthermore, it was revealed that the dose–effect relationship follows a sigmoidal model, and exposure had to exceed a threshold dose before lung cancer was observed (Fig. 1)^{33, 34, 40, 41}. In contrast, bone cancer was observed in only a few cases in beagles which had inhaled plutonium aerosols³⁴. Furthermore, liver cancer was not observed for inhalation and injection of plutonium.

The main histological type of lung and bone cancers caused by exposure to plutonium were adenocarcinoma and osteosarcoma^{32, 34, 39}.

Pathological changes in the lungs after inhalation of plutonium include changes in lung cells, the production of inflammatory mediators, and the pathological process that leads to the appearance of pre-neoplastic cells, mutation of the Tp53 tumor suppressor gene, and mutation and expression of epidermal growth factor receptor on tumor cell surfaces^{42–46}. Each of the aforementioned studies focused on individual stages of exposure leading to carcinogenesis; however, the relationship between these stages remains unknown.

While the risk of lung cancer with inhalation of plutonium is dose-dependent, most animals which

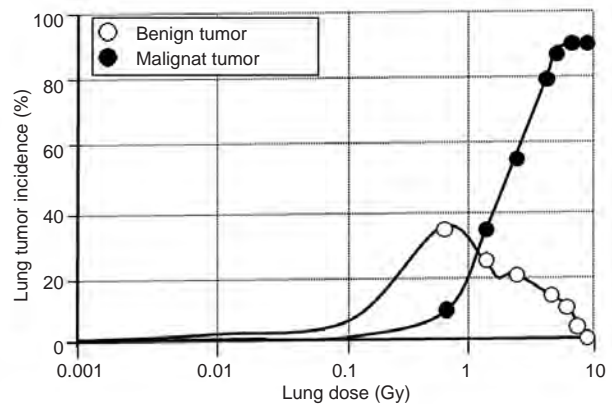


Fig. 1. Association between lung dose and lung tumor incidence (from Oghiso and Yamada, 2013)³⁸.

received extremely high doses of plutonium died early of fatal radiation-related lung diseases, such as radiation pneumonitis and pulmonary fibrosis³⁴.

A few studies found a significant association between plutonium exposure and leukemia. Humphreys *et al.* reported that myeloid leukemia was caused by plutonium injections in a mice experiment⁴⁷. Furthermore, it was reported that plutonium had an affinity for endosteum, accumulated in the adjacent marrow, and could cause myeloid leukemia^{48, 49}. However, the mice which were used in these experiments were of strains which were susceptible to leukemia.

Furthermore, although Oghiso and Yamada reported that B-cell lymphoma occurred in mice in which plutonium was injected, the association with plutonium was unclear because of the considerably low incidence of B-cell lymphoma³⁹.

The comparative risks of other alpha ray-releasing nuclides when the risk of osteosarcoma induced by ²²⁶Ra is standardized to 1 are shown in Table 7^{50, 51}. The risk of osteosarcoma by ²³⁹Pu is 16.6 times that of ²²⁶Ra. Among alpha ray-releasing nuclides, plutonium has the highest carcinogenicity.

4. Controversies

The skin is an effective defense barrier against the alpha rays of plutonium. Therefore, plutonium has a harmful biological effect for the first time when assimilated into the body. From animal experiments using rats and dogs and autopsies of plutonium-exposed human bodies, it was determined that the main intake route of plutonium is through inhalation. After inhalation, plutonium passes through the lungs, and consequently gets deposited in the liver and bone via the bloodstream. The lungs, liver, and bone receive a large quantity of radioactive exposure by

Table 7. Comparison of osteosarcoma induced risk of beagles which were injected to alpha ray-releasing nuclides (from Oghiso, 2013)⁵⁰⁾

alpha ray-releasing nuclides	osteosarcoma induced risk (incidence of per 10 ⁶ beagles)	Risk ratio (ratio for ²²⁶ Ra)
²²⁶ Ra	4.56 ± 0.91	1.0
²⁴¹ Am	24.8 ± 5.60	5.4 ± 1.6
²²⁸ Th	38.6 ± 7.40	8.5 ± 2.3
²³⁹ Pu	75.7 ± 13.8	16.6 ± 4.5

Values are shown as the mean ± standard deviation

alpha rays^{6, 7)}. Therefore, lung, liver, and bone cancers are indicated as the main effects of plutonium exposure.

It was previously found from animal experiments using rats and dogs that inhalation of plutonium could cause lung cancer³¹⁻³⁴⁾. Furthermore, the dose–effect relationship of the sigmoidal model with a threshold dose before lung cancer is observed has been reported^{33, 34, 40, 41)}. In the investigation of plutonium-exposed workers in the Manhattan Project, only one worker had developed lung cancer among 26 people exposed to plutonium¹¹⁾. However, the association with plutonium is unclear as only one worker developed lung cancer, and this individual showed confounding factors such as aging and lifestyle habits. In contrast, in the Mayak worker cohort, several reports showed a significant association between internal exposure of plutonium and the risk of lung cancer^{16, 18, 20-23)}. The relative risk of lung cancer was additionally shown to be dependent on gender, attained age, and age at the first plutonium dose¹⁸⁾. Because smokers have an elevated risk of lung cancer, the overall risk of lung cancer could greatly increase in people exposed to plutonium smoke. In the Mayak worker cohort, a significant dose–response relationship between the exposure dose of plutonium and lung cancer mortality was observed, with the threshold being 0.2 Gy of plutonium organ dose¹⁸⁾. This observed threshold plutonium organ dose that elevated the risks of lung cancer mortality was lower than the threshold dose for liver and bone cancers. Because inhalation is the main exposure route of plutonium and the organ dose for elevated risks of lung cancer mortality is lower than that of other cancers, deaths due to plutonium exposure is considered the highest for lung cancer.

In animal experiments, incidences of bone cancer increased as the exposure dose of plutonium by intravascular increased³⁵⁻³⁹⁾; however, few incidences of bone cancer were observed by plutonium inhalation³⁴⁾. In the investigation of plutonium-exposed workers in the Manhattan Project, only one worker had developed bone cancer among 26 people with plutonium exposure¹¹⁾. This worker had been exposed to plutonium by a wound in addition to inhalational exposure. Despite the possibility that bone cancer developed by this worker was caused

by plutonium exposure, the association is unclear. In the Mayak worker cohort, significant association between internal exposure of plutonium and bone cancer mortality was observed^{18, 26)}. However, the number of cases of bone cancer was less than that of lung and liver cancers¹⁸⁾. Although a significant dose–response relationship was observed between the exposure dose of plutonium and bone cancer mortality, elevated risks were observed only for plutonium doses >10 Gy¹⁸⁾. The incidence of bone cancer death due to plutonium exposure was lower, and the observed threshold dose leading to elevated risks was higher than those for lung and liver cancers. However, the percentage of bone cancer deaths attributed to plutonium exposure was higher than that for lung and liver cancers, whereas plutonium excess deaths were low¹⁸⁾.

In animal experiments using mice, rats, and dogs, no significant association between plutonium exposure and liver cancer was observed for both inhalation and intravascular injection of plutonium. In contrast, a significant dose–response relationship was observed between internal exposure of plutonium and liver cancer in the Mayak worker cohort^{18, 24, 25)}. Furthermore, an elevated risk of liver cancer mortality was observed only for plutonium doses >1.0 Gy¹⁸⁾. In liver cancer, plutonium excess deaths were higher than those for bone cancer, and the percentage of liver cancer deaths attributed to plutonium exposure was higher than that for lung cancer¹⁸⁾. No significant association between plutonium exposure and liver cancer was observed in animal experiments, possibly because of tumorigenic competition between different types of tumors because of the small number of animals used³⁹⁾.

Because one of the organs where plutonium is deposited is the bone, the incidence risk of myeloid leukemia has been noted. In animal experiments and epidemiologic investigations for human exposure, most studies have reported no significant association between internal exposure of plutonium and leukemia. Although a few studies have reported that myeloid leukemia is caused by plutonium injection in mice experiments, the mice which were used in these experiments were strains that were susceptible to leukemia⁴⁷⁻⁴⁹⁾. Because plutonium has an affinity for endosteum and additionally accumulates in the adjacent marrow, myeloid leukemia can occur^{48, 49)}. However, the relationship between plutonium and myeloid leukemia has not been observed in humans.

Radiation effects on malignant tumors other than those of the lungs, liver, and bone have been investigated. Although Oghiso *et al.* reported that B-cell lymphoma occurred in mice after injections of plutonium citrate³⁸⁾, its association with plutonium was unclear because of the low incidence of B-cell lymphoma. In the Mayak worker cohort, Shilnikova *et al.* reported a smaller but

statistically significant influence of internal exposure of plutonium on the risk of death from cancers, excluding those of organs of primary plutonium deposition (lungs, liver, and bone) in the investigation during 1948–1997¹⁷⁾. In contrast, Sokolnikov *et al.* reported no significant association between internal exposure of plutonium and mortality from solid cancers other than lung, liver, and bone cancers in the investigation during 1948–2008¹⁹⁾. Because alpha rays irradiated by plutonium have an extremely short irradiation distance, the risk of death from cancers excluding those of the organs of primary plutonium deposition (lungs, liver, and bone) may not be observed. In contrast, external gamma ray exposure could increase the risk of cancers in all organs because of high transmittance and long irradiation distance^{18,19)}.

5. Conclusion

As inhalation acts as the main route of plutonium assimilation into the body, exposure could result in lung, liver, and bone cancers because plutonium mainly deposits in these organs. Although a dose-dependent relationship is observed between plutonium dose and mortality from cancer of these organs, threshold dose levels leading to elevated risks appear to be dependent on the type of cancer. ERR per Gy for plutonium dose is higher in females than in males. In addition, ERR is higher in people at a young attained age or who were young at the time of exposure. Furthermore, lifestyle habits such as smoking influence the risk of lung and liver cancer. In other word, although internal exposure of plutonium causes lung, liver and bone cancer, the association of plutonium with these cancers has been observed to be influenced by gender, age, and lifestyle habits in addition to plutonium dose. In contrast, radiation effects of plutonium on cancers other than lung, liver, and bone cancers are considered to be extremely low.

6. Suggestion for future studies

Whereas a significant association between internal exposure of plutonium and lung, liver, and bone cancers has been observed, risks of these cancers could be related to threshold doses in the Mayak worker cohort. In other words, it is possible for the exposure dose to exceed a threshold dose before these cancers develop. In many animal experiments, a threshold dose of plutonium before the incidence of lung cancer was pointed out. However, the studies of threshold doses for cancers in humans are still insufficient. It is necessary to detect these threshold doses for cancers in humans using large-scale epidemiologic studies such as the Mayak worker cohort study.

Because plutonium has a long biological half-life and

continues to deliver alpha doses to these tissues over a lifetime, the therapy and convalescence of cancers caused by plutonium exposure may be different compared with those of cancers associated with non-radiation exposure. In the future, a study on the curative effect and convalescence of cancer patients with internal exposure of plutonium is necessary.

Conflict of Interest Disclosure

The authors declare that they have no conflict of interest.

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