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MORTALITY AMONG PLUTONIUM AND OTHER RADIATION WORKERS AT A PLUTONIUM WEAPONS FACILITY

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Mortality among 5,413 white males who were employed for at least two years at a plutonium weapons facility was investigated to measure risks from exposures to low levels of plutonium and external radiation. When compared with US death rates, fewer deaths than expected were found for all causes of death, all cancers, and lung cancer. No bone cancer was observed. An excess of brain tumors was found for the cohort in general. Elevated rate ratios for all causes of death and all lymphopoietic neoplasms were found when employees with plutonium body burdens ≥2 nCi were compared with those with body burdens <2 nCi, while accounting for age, calendar period, and induction time. Increased rate ratios were also found for esophageal, stomach, colon, and prostate cancers, and for lymphosarcomas and reticulum cell sarcomas. No elevated rate ratios were noted for bone and liver cancers. When employees with cumulative exposures ≥1 rem were compared with those with exposures <1 rem, elevated rate ratios were found for myeloid leukemia, lymphosarcoma and reticulum cell sarcoma, liver neoplasms, and unspecified brain tumors. No overall dose-response relationships were found for plutonium or external radiation exposures. Standardized rate ratios increased, however, as plutonium body burden levels increased for all causes, all cancers, and digestive cancers at five years induction time. Standardized rate ratios also increased as external radiation exposure categories increased for all lymphopoietic cancers and unspecified brain tumors for a two-year induction period. With the exception of analyses of combined categories of death, and perhaps of lung cancer, confidence limits were wide, indicating limited precision. Nevertheless, these findings suggest that increased risks for several types of cancers cannot be ruled out at this time for individuals with plutonium body burdens of ≥2 nCi. Plutonium-burdened individuals should continue to be studied in future years.

environmental exposure; mortality; neoplasms; occupational diseases; plutonium; radiation

Untoward health effects in humans have been discovered for a variety of internal emitters at high levels of exposure. These include lung cancer among uranium miners

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exposed to radon-222 and its daughters (1), liver neoplasms and leukemia experienced by patients who underwent diagnostic procedures that employed thorium-232 (2), leukemia in polycythemia patients treated with phosphorus-32 (3), thyroid tumors among Marshall Islanders who were exposed to iodine-131 fallout from an atmospheric nuclear test (4), osteogenic sarcoma and sinus carcinoma in radium dial painters as a result of exposure to radium-226 (5), and bone sarcomas, leukemia, and liver tumors among ankylosing spondylitis patients who were treated with radium-224 (6).

Investigations of nuclear workers who were exposed to low levels of external forms of ionizing radiation have not produced clear-cut evidence of radiation effects. For instance, Mancuso et al. (7) reported excess mortality for cancers of the lung and pancreas and for multiple myeloma among Hanford workers, but subsequent investigations did not replicate the excess for lung cancer, and the excess for pancreatic cancer was smaller with longer follow-up (8, 9). An excess of leukemia that was reported for Portsmouth Naval Shipyard workers (10) was not replicated in a more thorough study (11). A third investigator has argued, however, that an excess of lung cancer exists for a subgroup of workers exposed to more than 1 rem (12). Finally, excess brain cancers have been reported among workers at a nuclear fuels fabrication plant (13) and at the Oak Ridge Y-12 Plant (14), although these excesses could not be attributed to radiation exposures.

Little is known regarding health effects in humans exposed to plutonium. After 37 years of follow-up, no untoward health effects have been found among 26 former Manhattan Project workers who have the highest known plutonium exposures (15). A follow-up mortality study of 241 Los Alamos National Laboratory workers who had plutonium body burdens of 10 or more nCi in 1974 reported standardized mortality ratios of 200 (95 per cent confidence limits (CL) 3, 1,110) for buccal and 233 (95 per cent CL 3, 1,294) for bladder cancers based on one observed case in each instance (16). Recent studies of melanoma at Los Alamos found no excess incidence among Anglo males. A standardized incidence ratio of 433 (90 per cent CL 22, 1,780, one case observed) was observed for Hispanic males, although no association with radiation exposures was found (17, 18). An investigation of cancer incidence among Los Alamos workers employed from 1969 through 1978 reported standardized incidence ratios of 2.04 (90 per cent CL 0.11, 9.68, one case observed) for bone cancer and 2.49 (90 per cent CL 0.98, 5.23) for lymphosarcoma and reticulum cell sarcoma among males (19). No radiation doses were analyzed in that study. There have been allegations regarding excess mortality from melanoma and from lung and brain cancer among workers at the Rocky Flats Nuclear Weapons Plant, Jefferson County, Colorado (20), and excess cancer among the populace residing in the vicinity of that facility (21), although the latter findings have been questioned (22). In a preliminary study, Voelz et al. (23) reported an excess of benign and unspecified brain tumors for workers at the Rocky Flats Plant, but a deficit for lung cancer.

The purpose of this report is to present results from an in-depth investigation of mortality among workers at the Rocky Flats Plant. To our knowledge, these are the first detailed results for a large cohort of plutonium workers that describe the relationship between exposure to plutonium (and external radiation) and disease by induction time (23, 24).

CHARACTERISTICS OF PLUTONIUM

Several important characteristics regarding the physical and biologic properties of plutonium need to be described. First, plu-

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tonium-239 is characterized by a radioactive half-life estimated to be 24,390 years and an estimated biologic half-life of 100 years for bone depositions in humans (25). The alpha particles emitted by plutonium possess high energies but travel short distances (approximately 50 μm in tissue). As a result, the greatest concern regarding health effects is the damage that may occur once plutonium has been deposited within internal organs. If this occurs, tissues of these organs may be subjected to high-energy alpha particles. Since the skin serves as an effective barrier, inhalation and wounds are the major pathways of exposure.

According to recent autopsy studies of selected tissues from nuclear workers, the greatest concentrations of plutonium are measured in the tracheobronchial lymph nodes, followed, in declining order, by the lungs, liver, and bone where it remains for extended periods of time (26). These studies also show large variations in organ distribution from person to person. Organ dose calculations for an individual using average organ distribution values can result in large errors. In this study, we used an estimate of systemic body burden for selecting plutonium-exposed individuals. This estimate is derived from the amount of plutonium excreted in urine and reflects the concentration of plutonium in the body. Because only those cells that are adjacent to or that migrate near plutonium deposits are irradiated by alpha particles, it makes sense to consider first these organs or cells when attempting to estimate risk.

Much of the concern regarding plutonium is based on knowledge of effects due to radium exposure, especially radium-226 (27). Radium dial painters who were exposed to high levels of radium-226 have experienced excessive rates of osteogenic sarcoma and sinus carcinoma (5). Several interesting differences exist between radium and plutonium, however. Although both are bone-seeking internal alpha emitters, radium is more uniformly distributed throughout the total volume of bone, while plutonium is initially deposited on the periosteal and endosteal surfaces, on surfaces of the trabeculae, and on surfaces of the haversian and Volkmann's canals, with little being found in the cortical bone (28). Over a period of years, plutonium is gradually redistributed to the bone volume. Initially, this may result in higher doses to periosteal or endosteal cells from plutonium than occurs with radium (29). Radium-226 is also readily absorbed through the gastrointestinal tract, whereas plutonium is poorly absorbed.

Another important difference between plutonium and radium is the greater frequency with which significant exposures may occur because of the inhalation of airborne plutonium particles. The internal absorption and redistribution of plutonium is dependent upon particle size and chemical form. Upon inhalation, insoluble plutonium particles are deposited in the lung, where they slowly migrate via the lymphatic system to the tracheobronchial lymph nodes (30). Redistribution from the lung and lymph nodes to other organs, principally the liver and bone, occurs over many months. Radium salts involved in human exposures have usually been more soluble than plutonium, and radium exposures have more often been by ingestion or injection.

Extensive research has been completed on animals exposed to plutonium (31–34). These studies have found excess lung cancers (with inhalation), osteogenic sarcomas, primary liver carcinomas, bile duct tumors, and lymphomas. Although leukemia was not found to be elevated, the bone marrow has been postulated to be a target organ of interest (35).

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Methods

All white males employed at the Rocky Flats Nuclear Weapons Plant from the beginning of operations in 1952 through 1979 were identified from personnel records. Vital status was determined by the Social Security Administration. In addition, a survey of pension and retirement records was conducted. Death certificates were obtained from state health departments, verified, and coded to the Eighth Revision of the *International Classification of Diseases*, following the same procedures used by the National Center for Health Statistics.

Information concerning individual exposures to internal (plutonium) and external (gamma, neutron, beta, and x-rays) forms of ionizing radiation was obtained from health physics records. Exposures to plutonium are estimated from urine bioassays by means of an equation developed by Langham (36). Systemic depositions of less than approximately 2 nCi are not reliably measured by this method. The occupational standard is a maximum permissible body burden of 40 nCi. In this study, workers estimated to have 2 or more nCi of internal plutonium deposition are defined as exposed.

Annual external radiation exposure summaries, based on readings from film and thermoluminescent dosimeter badges, were summed to obtain cumulative exposures through the end-of-study date. For the purpose of this analysis, workers with total cumulative exposures exceeding 1 rem are defined as exposed to external radiation. This is an arbitrary low-dose limit above which we considered a positive occupational radiation dose to be very probable.

A number of procedures were employed to assure data quality. These included editing all coded data and recoding a 10 per cent sample of the edited data. The study cohort was compared with a sequential badge listing to verify completeness of the study population. Individuals for whom vital status was unknown were traced. Sixty (1.1 per cent) of the 5,413 white males who were employed for at least two years could not be located.

Mortality from specific causes of death was evaluated in two ways. First, we calculated standardized mortality ratios, expressed as the ratio of the number of deaths observed among the cohort to the number expected based on US rates × 100 (adjusted for age, sex, and calendar year) (37). Second, we compared exposed with unexposed workers by stratifying on age and calendar period and by computing a stratified maximum likelihood estimate of the rate ratio (38). Ninety per cent Fisher's exact confidence limits were computed for standardized mortality ratios and for the rate ratios when data were sparse. When sufficient data were available, 90 per cent approximate limits for the rate ratios were calculated.

Because transient employees are thought to differ in many respects from permanent workers (8), analyses were restricted to those employed for a minimum of two years. For analyses that did not take exposure into account, person-years were counted beginning two years after date of hire (because of the two-year work restriction) until either date of death, end of study date (December 31, 1979), or termination date (for those lost to follow-up). Various induction times were considered when comparisons of exposed with unexposed employees and dose-response analyses were conducted. The induction time was not begun until a minimum of 2 nCi or 1 rem was accumulated. The time from the date of the first bioassay for plutonium or first badge reading for external radiation until two, five, or 10 years after exposure (depending on the induction period being considered) was treated as unexposed person-time. In these analyses, person-years and deaths that occurred from date of hire until the first bioassay or badge reading were not counted because they are immortal (if analyses are limited to tested subjects, only those who live long enough to be tested should be included in the study). Individuals who were not tested for plutonium or external radiation exposure were not included in comparisons of exposed with nonexposed workers. This allowed us to minimize potential exposure misclassification and to control in a crude manner for other chemical exposures that plutonium-tested workers may have encountered compared with other workers.

Other investigators (8) have demonstrated that both age and calendar time must be accounted for when time-dependent exposures (such as cumulative radiation exposures) are being investigated. Because age and calendar time are associated with both exposure (as one gets older and works longer, the opportunity for exposure becomes greater) and disease, we conducted stratified analyses of cause-specific mortality by age, calendar period, and induction time. Age and calendar time were stratified into five-year strata. We also dichotomized on 2 nCi and 1 rem for reasons previously mentioned. Stratified analyses showed that both age and calendar time were strong confounders for each cause-specific analysis. The confounding sometimes was toward the null value and sometimes away from the null, with no discernible pattern. Therefore, we report maximum likelihood estimates of the rate ratio that account for age and calendar time.

Several methods were used to search for dose-response relationships. Person-years stratified by five-year age and calendar time intervals and deaths were assigned to exposure categories according to the subject's estimated plutonium body burdens (less than 2 nCi (unburdened), 2–4.9 nCi, 5+ nCi). An identical approach was followed for cumulative exposures to external radiation (less than 1 rem (unexposed), 1–4.9 rem, 5+ rem). Mortality rates by exposure category were directly standardized to the age and calendar year distribution (in five-year strata) of the Rocky Flats white male work force who were employed for at least two years (Appendix table 1). Standardized rate ratios by exposure category and induction time were calculated by dividing the directly adjusted rate among the exposed by the directly adjusted rate among the unexposed for each exposure category. Least squares weighted regression and associated 90 per cent exact confidence limits on the slope were employed to estimate whether an overall linear dose-response trend existed for directly adjusted rates by exposure level and by induction time (39–41). The median scores for exposure categories used in the regression analyses were 0.32, 2.96, and 7.20 nCi for plutonium and 0.35, 1.98, and 10.29 rem for external radiation. The weight used for each exposure category was the inverse variance for the rate of that category (39).

To evaluate the effects of using a two-year work restriction, we compared the proportions of deceased and exposed between those employed less than two years with those employed at least two years. Of the 2,196 workers who worked less than two years, 5.4 per cent were deceased, 1.0 per cent had positive plutonium body burdens, and 6.2 per cent were exposed to more than 1 rem of external radiation. Among the 5,413 employed two or more years, 7.6 per cent were deceased, 26.8 per cent had positive plutonium body burdens, and 59.4 per cent were exposed to more than 1 rem. Two deaths occurred among those who were exposed to 2 or more nCi of plutonium who worked less than two years compared with 94 deaths among those exposed to 2 or more nCi who worked at least two years. Three deaths were observed among employees exposed to 1 or more rem who worked less than two years, and 202 deaths were observed among those exposed to 1 or more rem who were employed at least two years.

Three (0.06 per cent) death certificates were not obtained for those who were employed at least two years (two death certificates were not found for those employed less than two years). Since these deaths could not be verified by a death certificate, they were counted among those of unknown vital status. The average length of follow-up was 14.49 years, and the average age at start of employment was 34.85 years.

Approximately 25 per cent of the study population was exposed to both 2 or more nCi and 1 or more rem. The total man rem exposure was 4.13 rem per person, and the total plutonium burden was 1.75 nCi per person.

A total of 118 deaths due to all causes compared with 148.35 expected and of 31 deaths from cancer compared with 28.79 expected were observed for those employed

... compared with 656.17 expected deaths from all causes and 95 observed compared with 134.20 expected deaths from all neoplasms were found.

RESULTS

Standardized mortality ratios are presented in table 1. The expected numbers of deaths were obtained by indirect age adjustment to US death rates. Fewer deaths than expected are observed for most specific causes including all causes, all cancers, ... tem, and deaths from accidents, poisonings, and violence. No bone cancer is observed, and observed deaths are also less than expected for digestive system neoplasms, cancers of the buccal cavity, kidney and unspecified urinary organs, and lymphopoietic cancers.

An excess is present for benign and unspecified neoplasms. A review of death certificates revealed these neoplasms to be intracranial tumors. Standardized mortality ratios are elevated for cancers of the liver and gallbladder, prostate, brain, and thyroid; however, the confidence intervals

TABLE 1

Standardized mortality ratios (SMRs) for selected causes of death among white males employed at least two years,† Rocky Flats Nuclear Weapons Plant, Jefferson County, CO*

Cause of death (ICD‡)	Observed	Expected	SMR	90% Fisher's exact confidence limits
All causes (001–998)	409	656.21	62	57, 68
All cancers (140–209)	95	134.21	71	59, 84
Buccal cavity and pharynx (140–149)	1	4.58	22	1, 104
Digestive organs and peritoneum (150–159)	25	34.42	73	51, 101
Esophagus (150)	3	3.19	94	26, 243
Stomach (151)	5	5.93	84	33, 177
Colon (153)	7	11.17	63	29, 118
Rectum (154)	2	3.79	53	1, 166
Liver and gallbladder (155, 156)	3	2.16	139	38, 359
Pancreas (157)	4	7.28	55	19, 126
Respiratory system (160–163)	32	49.12	65	47, 88
Larynx (161)	2	2.08	96	17, 303
Lung (162, 163)	30	46.57	64	46, 87
Bone (170)	0	0.67		447
Skin (172, 173)	3	2.94	102	28, 264
Prostate (185)	8	5.63	142	71, 256
Bladder (188)	3	3.23	93	25, 240
Kidney and unspecified urinary organs (189)	2	3.60	56	10, 175
Brain and other central nervous system (191, 192)	6	5.02	119	52, 236
Thyroid (193)	1	0.27	370	19, 1,757
All lymphopoietic (200–209)	9	14.14	64	33, 111
Lymphosarcoma and reticulum cell sarcoma (200)	2	3.21	62	11, 196
All leukemia (204–207)	4	5.35	75	26, 171
Other lymphatic (202, 203, 208)	3	3.34	90	25, 232
Benign and unspecified neoplasms (210–239)	7	1.86	376	177, 707
Other cancers§	5	9.41	53	21, 112
Diseases of the circulatory system (390–458)	193	315.02	61	54, 69
Accidents, poisonings, and violence (800–998)	55	85.11	65	51, 81

* Standardized mortality ratios were calculated using a lifetable program developed by Monson (37). Fisher's exact 90 per cent confidence limits were computed using an adaptation of program 14 in Rothman and Boice (38).

† Person-years and deaths were not counted for the first two years of employment.

‡ ICD, *International Classification of Diseases*, Eighth Revision.

§ This category consisted of two secondary neoplasms (ICD 197) and three cancers, site unspecified (ICD 199).

a deficit cannot be ruled out.

Comparisons of employee cohorts with the general populace are subject to a form of selection bias often referred to as the healthy worker effect. To circumvent this problem, we compared mortality rates of exposed with unexposed workers using person-year denominators. Tables 2–4 present age- and calendar period-adjusted maximum likelihood estimates of the rate ratio by induction time for employees with systemic plutonium depositions of 2 or more nCi compared with those with systemic depositions of less than 2 nCi.

tion period of two years. A minimum induction time of two years is usually accepted for leukemia and bone cancer. As previously mentioned, no bone cancer is observed and no thyroid cancers occurred among workers tested for plutonium. Especially interesting is the high risk estimate that is present for the lymphopoietic neoplasms. A rate ratio of 7.69 (90 per cent exact CL 0.99, 72.93) is observed for all lymphopoietic neoplasms. The rate ratio for lymphosarcoma and reticulum cell sarcoma is 2.01 (90 per cent exact CL 0.10, 31.48). Rate ratios of 3.26 (90 per cent exact

TABLE 2

Maximum likelihood estimates of the rate ratio for workers† with plutonium body burdens of ≥2 nCi compared with those with body burdens <2 nCi for a two-year induction time, while controlling for age and calendar period, Rocky Flats Nuclear Weapons Plant, Jefferson County, CO*

Cause of death (ICD‡)	Deaths: Exposed (14,702.9 person-years)	Deaths: Unexposed (38,068.6 person-years)	RR_{ML}§	90% Fisher's exact confidence limits
All causes (001–998)	84	164	1.14	0.91, 1.43‖
All cancers (140–209)	17	33	1.01	0.62, 1.66‖
Digestive organs and peritoneum (150–159)	6	8	1.31	0.45, 3.64
Esophagus (150)	2	1	3.26	0.25, 36.81
Stomach (151)	2	2	1.84	0.20, 14.40
Colon (153)	1	2	0.97	0.07, 10.88
Liver (155)	1	2	0.80	0.06, 9.03
Pancreas (157)	0	1		50.00
Lung (162, 163)	4	13	0.67	0.20, 1.89
Skin (172, 173)	0	2		9.01
Prostate (185)	2	1	3.74	0.29, 42.31
Bladder (188)	0	1		50.00
Kidney and unspecified urinary organs (189)	0	1		50.00
All brain tumors (191, 192, 225, 238)	1	9	0.22	0.02, 1.27
Malignant brain and other central nervous system (191, 192)	0	4		2.89
Benign brain and other central nervous system (225)	0	1		50.00
Unspecified brain and other central nervous system (238)	1	4	0.44	0.04, 3.40
All lymphopoietic (200–209)	4	1	7.69	0.99, 72.93
Lymphosarcoma and reticulum cell sarcoma (200)	1	1	2.01	0.10, 31.48
Non-Hodgkin's lymphoma (202)	1	0		0.14
Multiple myeloma (203)	1	0		0.14
Myeloid leukemia (205)	1	0		0.14

* Maximum likelihood estimates were calculated using an adaptation of programs 6 and 7 in Rothman and Boice (38).

† The period of exposure-related risk was defined as beginning two years after one's cumulative systemic burden reached 2 nCi of plutonium. Unexposed person-years and events were counted from two years after date of hire or first bioassay, whichever occurred later.

‡ ICD, *International Classification of Diseases*, Eighth Revision.

§ Maximum likelihood estimate of the rate ratio.

‖ Ninety per cent approximate confidence limits were calculated in place of Fisher's exact limits using a method described by Rothman (40, p. 212).

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CL 0.25, 36.81), 1.84 (90 per cent exact CL 0.20, 14.40), and 3.74 (90 per cent exact CL 0.29, 42.31) are observed for esophageal, gastric, and prostatic cancers, respectively. On the other hand, rate ratios are low for lung cancer, liver cancer, all brain tumors combined, and unspecified brain tumors. No exposed cases are observed for pancreatic, bladder, kidney, skin, malignant brain cancers, and benign brain tumors. No unexposed cases are present for non-Hodgkin's lymphoma, multiple myeloma, and myeloid leukemia.

Table 3 presents results for those cancer sites that require at least five years induction time, such as brain and thyroid tumors (42), as well as blood, lymph, and other solid tumors. A rate ratio of 9.86 (90 per cent exact CL 1.26, 94.03) is observed for all lymphopoietic tumors. A 33 per cent excess is present for all causes of death, and almost a fivefold excess is found for cancer of the prostate (RR_{ML} = 4.90, 90 per cent exact CL 0.38, 55.84). Rate ratios of 3.68 (90 per cent exact CL 0.29, 41.56) for esophageal cancer, 2.50 (90 per cent exact CL 0.12, 39.57) for lymphosarcoma and reticulum cell sarcoma, 2.18 (90 per cent exact CL 0.23, 17.11) for stomach cancer, 1.68 (90 per cent exact CL 0.58, 4.71) for all

TABLE 3

Maximum likelihood estimates of the rate ratio for workers† with plutonium body burdens of ≥2 nCi compared with those with body burdens <2 nCi for a five-year induction time, while controlling for age and calendar period, Rocky Flats Nuclear Weapons Plant, Jefferson County, CO*

Cause of death (ICD‡)	Deaths: Exposed (10,521.2 person-years)	Deaths: Unexposed (42,250.3 person-years)	RR_{ML}§	90% Fisher's exact confidence limits
All causes (001–998)	74	174	1.33	1.05, 1.68‖
All cancers (140–209)	16	34	1.24	0.75, 2.07‖
Digestive organs and peritoneum (150–159)	6	8	1.68	0.58, 4.71
Esophagus (150)	2	1	3.68	0.29, 41.56
Stomach (151)	2	2	2.18	0.23, 17.11
Colon (153)	1	2	1.62	0.11, 18.27
Liver (155)	1	2	0.91	0.07, 10.30
Pancreas (157)	0	1		76.92
Lung (162, 163)	3	14	0.61	0.15, 1.91
Skin (172, 173)	0	2		13.89
Prostate (185)	2	1	4.90	0.38, 55.84
Bladder (188)	0	1		76.92
Kidney and unspecified urinary organs (189)	0	1		76.92
All brain tumors (191, 192, 225, 238)	1	9	0.35	0.03, 2.10
Malignant brain and other central nervous system (191, 192)	0	4		4.48
Benign brain and other central nervous system (225)	0	1		76.92
Unspecified brain and other central nervous system (238)	1	4	0.71	0.06, 5.63
All lymphopoietic (200–209)	4	1	9.86	1.26, 94.03
Lymphosarcoma and reticulum cell sarcoma (200)	1	1	2.50	0.12, 39.57
Non-Hodgkin's lymphoma (202)	1	0		0.21
Multiple myeloma (203)	1	0		0.21
Myeloid leukemia (205)	1	0		0.21

* Maximum likelihood estimates were calculated using an adaptation of programs 6 and 7 in Rothman and Boice (38).

† The period of exposure-related risk was defined as beginning five years after one's cumulative systemic burden reached 2 nCi of plutonium. Unexposed person-years and events were counted from two years after date of hire or first bioassay, whichever occurred later.

‡ ICD, *International Classification of Diseases*, Eighth Revision.

§ Maximum likelihood estimate of the rate ratio.

‖ ... confidence limits were calculated in place of Fisher's exact limits using a method described

plutonium need to be described ... account. No

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digestive cancers combined, and 1.62 (90 per cent exact CL 0.11, 18.27) for cancer of the colon are also observed. Low risk estimates are present for liver, unspecified brain, lung, and all brain tumors combined.

An induction period of 10 years is employed in the analyses presented in table 4. With the exception of bone, thyroid, brain, and lymphopoietic neoplasms, an induction time of at least 10 years is usually accepted as the minimum for radiogenic solid tumors to appear after exposure. The rate ratio for all lymphopoietic tumors declined to 5.22 (90 per cent exact CL 0.57, 38.80). A small excess for all causes of death (RR_{ML} = 1.39, 90 per cent CL 1.04, 1.87) continues to be observed. A higher risk estimate for all cancers (RR_{ML} = 1.61, 90 per cent CL 0.88, 2.93) than was previously seen is also observed. Risk estimates of 10.62 (90 per cent exact CL 0.76, 127.15) for prostate cancer, 5.70 (90 per cent exact CL 0.38, 65.21) for cancer of the colon, and 4.82 (90 per cent exact CL 0.51, 38.18) for stomach cancer are present. It is interesting to note that the rate ratio for lung cancer is 1.43 (90 per cent exact CL 0.33, 4.65), whereas deficits in the risk estimates were observed for in-

TABLE 4

Maximum likelihood estimates of the rate ratio for workers† with plutonium body burdens of ≥2 nCi compared with those with body burdens <2 nCi for a 10-year induction time, while controlling for age and calendar period, Rocky Flats Nuclear Weapons Plant, Jefferson County, CO*

Cause of death (ICD‡)	Deaths: Exposed (4,438.5 person-years)	Deaths: Unexposed (48,333.0 person-years)	RR_{ML}§	90% Fisher's exact confidence limits
All causes (001–998)	40	208	1.39	1.04, 1.87‖
All cancers (140–209)	10	40	1.61	0.88, 2.93‖
Digestive organs and peritoneum (150–159)	3	11	1.46	0.34, 4.77
Esophagus (150)	0	3		18.52
Stomach (151)	2	2	4.82	0.51, 38.18
Colon (153)	1	2	5.70	0.38, 65.21
Liver (155)	0	3		18.52
Pancreas (157)	0	1		200.00
Lung (162, 163)	3	14	1.43	0.33, 4.65
Skin (172, 173)	0	2		38.46
Prostate (185)	2	1	10.62	0.76, 127.15
Bladder (188)	0	1		200.00
Kidney and unspecified urinary organs (189)	0	1		200.00
All brain tumors (191, 192, 225, 238)	0	10		3.80
Malignant brain and other central nervous system (191, 192)	0	4		12.20
Benign brain and other central nervous system (225)	0	1		200.00
Unspecified brain and other central nervous system (238)	0	5		8.93
All lymphopoietic (200–209)	2	3	5.22	0.57, 38.80
Lymphosarcoma and reticulum cell sarcoma (200)	0	2		38.46
Non-Hodgkin's lymphoma (202)	0	1		200.00
Multiple myeloma (203)	1	0		0.57
Myeloid leukemia (205)	1	0		0.57

* Maximum likelihood estimates were calculated using an adaptation of programs 6 and 7 in Rothman and Boice (38).

† The period of exposure-related risk was defined as beginning 10 years after one's cumulative systemic burden reached 2 nCi of plutonium. Unexposed person-years and events were counted from two years after date of hire or first bioassay, whichever occurred later.

‡ ICD, *International Classification of Diseases*, Eighth Revision.

§ Maximum likelihood estimate of the rate ratio.

‖ Ninety per cent approximate confidence limits were calculated in place of Fisher's exact limits using a method described [illegible]

‖ Ninety per cent approximate confidence limits were calculated in place of Fisher's exact limits using a method described

duction periods of two and five years. No exposed deaths are found for esophageal, liver, pancreatic, skin, bladder, kidney, and all brain tumors, or for lymphosarcoma and reticulum cell sarcoma, and non-Hodgkin's lymphoma. No unexposed deaths are observed for multiple myeloma and myeloid leukemia.

For most of the results just mentioned, the precision of our point estimates is limited as demonstrated by the wide confidence intervals. The exceptions are those analyses that compare combined categories of cause-specific deaths such as all causes, all cancers, cancers of the digestive organs, or more common types of neoplasms such as lung cancer.

A similar analysis was conducted for employees whose cumulative whole body exposures equaled or exceeded 1 rem of external radiation compared with workers with lower or no cumulative exposures. When an induction time of two years is employed (see Appendix table 2), the rate ratio for unspecified brain tumors is 3.46 (90 per cent exact CL 0.45, 32.78). For all lymphopoietic cancers, a rate ratio of 1.49 (90 per cent exact CL 0.36, 7.25) is observed. For lymphosarcoma and reticulum cell sarcoma and for myeloid leukemia, two exposed deaths but no unexposed deaths are observed. Three exposed but no unexposed deaths are found for esophageal and liver cancers. No exposed deaths are observed for oral, laryngeal, skin, and thyroid cancers, and for benign brain tumors.

Use of a five-year induction period (Appendix table 3) results in risk estimates of 1.73 (90 per cent exact CL 0.27, 11.69) for unspecified brain neoplasms and of 1.69 (90 per cent exact CL 0.13, 18.96) and 1.66 (90 per cent exact CL 0.34, 9.01) for liver and prostatic cancers, respectively.

Table 5 presents results when a 10-year induction period is used. A fourfold excess is observed for unspecified brain tumors (RR_{ML} = 3.96, 90 per cent exact CL 0.60, 27.16). Rate ratios of 3.00 (90 per cent exact CL 0.12, 58.16) for lymphosarcoma and reticulum cell sarcoma, 3.02 (90 per cent exact CL 0.15, 46.42) for myeloid leukemia, 2.77 (90 per cent exact CL 0.22, 31.19) for liver cancer, and 1.71 (90 per cent exact CL 0.45, 5.89) for all brain tumors are also observed. A deficit is present for all cancers (RR_{ML} = 0.65, 90 per cent CL 0.42, 0.99).

Although the number of observations for specific causes of death are sometimes small, we searched for the presence of dose-response relationships when there were at least as many exposed deaths as exposure categories. Table 6 presents results for plutonium body burdens of less than 2 nCi, 2–4.9 nCi, and 5 or more nCi by induction time. No overall linear dose-response trends were found. When standardized rate ratios are considered, however, increases with increasing body burden levels are observed for all causes of death for five- and 10-year induction periods, for all cancers for a five-year induction period, and for all digestive cancers for a five-year induction period. Standardized rate ratios for all lymphopoietic neoplasms with two years of induction time also increase with increasing body burden level, but in a nonlinear manner.

Table 7 presents dose-response analyses for cumulative exposures to external radiation of less than 1 rem, 1–4.9 rem, and 5 or more rem by induction time. No overall linear dose-response trends are observed. Standardized rate ratios increase, however, as exposure categories increase for all lymphopoietic neoplasms for a two-year induction time and for unspecified brain tumors for induction times of two and five years.

Discussion

To our knowledge, these comprise the first epidemiologic findings that suggest an association between exposure to plutonium and untoward health effects in humans. Elevated risk estimates are present for all lymphopoietic neoplasms combined and for all causes of death. Possible excesses are also present for digestive system cancers (especially esophageal and stomach) and for prostatic cancers when appropriate induction times are taken into account. No

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bone or thyroid tumors are observed among employees with plutonium body burdens greater than or equal to 2 nCi. It is interesting that risk estimates for some organ sites where plutonium is known to concentrate, such as the bone and liver, are not elevated among the plutonium-burdened. A small increase in lung cancer is observed for a 10-year induction time. The absence of smoking data, however, makes further interpretation of this finding difficult. When external radiation exposures are considered, rate ratios are elevated for brain tumors (especially unspecified brain tumors), liver cancer, lymphosarcoma and reticulum cell sarcoma, and myeloid leukemia.

The manner in which rate ratio estimates vary by induction time is noteworthy. Because appropriate induction times for can-

TABLE 5

Maximum likelihood estimates of the rate ratio for workers† exposed to ≥1 rem of external radiation compared with workers exposed to <1 rem for a 10-year induction time, while controlling for age and calendar period, Rocky Flats Nuclear Weapons Plant, Jefferson County, CO*

Cause of death (ICD‡)	Deaths: Exposed (13,172.5 person-years)	Deaths: Unexposed (64,608.9 person-years)	RR_{ML}§	90% Fisher's exact confidence limits
All causes (001–998)	99	307	0.96	0.78, 1.17‖
All cancers (140–209)	20	73	0.65	0.42, 0.99‖
Buccal cavity and pharynx (140–149)	0	1		90.91
Digestive organs and peritoneum (150–159)	6	18	0.59	0.27, 1.30‖
Esophagus (150)	1	2	0.65	0.05, 7.34
Stomach (151)	0	5		4.03
Colon (153)	1	5	0.55	0.05, 3.94
Rectum (154)	1	1	1.42	0.07, 21.82
Liver (155)	2	2	2.77	0.22, 31.19
Pancreas (157)	0	4		5.46
Respiratory system (160–163)	8	24	0.89	0.43, 1.84‖
Larynx (161)	0	2		16.95
Lung (162, 163)	8	22	0.91	0.44, 1.89‖
Skin (172, 173)	0	3		8.40
Bladder (188)	0	3		8.40
Kidney and unspecified urinary organs (189)	0	2		16.95
Prostate (185)	2	6	0.79	0.11, 3.98
All brain tumors (191, 192, 225, 238)	4	8	1.71	0.45, 5.89
Malignant brain and other central nervous system (191, 192)	1	5	0.65	0.05, 5.08
Benign brain and other central nervous system (225)	0	1		90.91
Unspecified brain and other central nervous system (238)	3	2	3.96	0.60, 27.16
Thyroid (193)	0	1		90.91
All lymphopoietic (200–209)	2	6	0.84	0.12, 3.95
Lymphosarcoma and reticulum cell sarcoma (200)	1	1	3.00	0.12, 58.16
Non-Hodgkin's lymphoma (202)	0	2		16.95
All leukemia (204–207)	1	3	1.01	0.80, 9.12
Myeloid leukemia (205)	1	1	3.02	0.15, 46.42

* Maximum likelihood estimates were calculated using an adaptation of programs 6 and 7 in Rothman and Boice (38).

† The period of exposure-related risk was defined as beginning 10 years after one's cumulative external radiation exposure reached 1 rem. Unexposed person-years and events were counted from two years after date of hire or first badge reading, whichever occurred later.

‡ ICD, *International Classification of Diseases*, Eighth Revision.

§ Maximum likelihood estimate of the rate ratio.

‖ Ninety per cent approximate confidence limits were calculated in place of Fisher's exact limits using a method described ... rates per 10[illegible] person-years.

[redacted]'ement records was

cers that may be putatively associated with plutonium are unknown, we employed three induction periods that are analogous to those of external radiation-induced cancers. Rate ratios increase monotonically across all induction times for all causes of death, all cancers, and stomach and colon cancers, thus suggesting minimum induction times of 10 years for these organ sites. On the other hand, lymphopoietic and esophageal cancers peaked at an induction period of five years. None of the causes of death that were investigated peaked at a two-year induction period.

Most of these relationships, however, are characterized by low precision. Oftentimes, comparisons between exposed and unexposed subjects were based on few cases. This made evaluation of dose-response relationships difficult. Additional follow-up is necessary to acquire more deaths and added person-time experience.

TABLE 6

Directly adjusted rates (DAR), standardized rate ratios (SRR), and weighted least squares regression coefficients for white males, by plutonium body burden level and induction time, Rocky Flats Nuclear Weapons Plant, Jefferson County, CO*

Cause of death (ICD†)	Induction time (years)		Plutonium body burden levels <2 nCi	2-4.9 nCi	5+ nCi	β	90% exact confidence limits on slope
All causes (001-998)	2	DAR‡	484.5	459.7	918.5	2.95	−43.02, 48.92
		SRR	1.00	0.95	1.90		
	5	DAR	467.2	517.0	963.2	31.71	−22.71, 86.13
		SRR	1.00	1.11	2.06		
	10	DAR	480.2	738.7	1,684.5	107.54	−2.70, 217.77
		SRR	1.00	1.54	3.51		
All cancers (140-209)	2	DAR	92.2	70.6	106.9	0.25	−9.27, 9.77
		SRR	1.00	0.77	1.16		
	5	DAR	86.1	89.2	106.7	2.70	−7.32, 12.73
		SRR	1.00	1.04	1.24		
	10	DAR	84.3	193.9	109.6	5.63	−8.07, 19.33
		SRR	1.00	2.30	1.30		
All digestive cancers (150-159)	2	DAR	21.4	21.2	43.0	2.15	−3.40, 7.70
		SRR	1.00	0.99	2.01		
	5	DAR	19.3	23.3	49.3	3.34	−2.70, 9.37
		SRR	1.00	1.21	2.55		
	10	DAR	22.0	65.5	24.7	0.84	−5.25, 6.94
		SRR	1.00	2.98	1.12		
Lung cancer (162, 163)	2	DAR	37.2	27.9	10.1	−3.95	−7.39, −0.52
		SRR	1.00	0.75	0.27		
	5	DAR	36.8	26.6	11.2	−3.72	−7.33, −0.11
		SRR	1.00	0.72	0.30		
	10	DAR	31.6	61.5	19.9	−1.47	−6.69, 3.76
		SRR	1.00	1.95	0.63		
Prostatic cancer (185)	2	DAR	2.6	0.0	29.4	−0.70	−2.27, 0.88
		SRR	1.00	0.0	11.31		
	5	DAR	2	0.0	36.3	−0.69	−2.20, 0.82
		SRR	1.00	0.0	15.13		
	10	DAR	2.0	0.0	65.1	−0.67	−1.98, 0.63
		SRR	1.00	0.0	32.55		
All lymphopoietic cancers (200-209)	2	DAR	2.6	21.5	15.6	2.83	−0.63, 6.28
		SRR	1.00	8.27	6.00		
	5	DAR	2.4	39.3	0.0	−0.37	−1.15, 0.40
		SRR	1.00	16.38	0.0		
	10	DAR	5.4	66.8	0.0	−0.79	−1.94, 0.37
		SRR	1.00	12.37	0.0		
Unspecified brain tumors (238)	2	DAR	11.2	7.6	0.0	−1.66	−2.87, −0.44
		SRR	1.00	0.68	0.0		
	5	DAR	9.4	8.0	0.0	−1.42	−2.61, −0.23
		SRR	1.00	0.85	0.0		
	10	DAR	10.1	0.0	0.0	−0.80	−2.08, −0.48
		SRR	1.00	0.0	0.0		

* Mortality rates were directly adjusted to the age and calendar year distribution of white males who worked two or more years at Rocky Flats Nuclear Weapons Plant between 1952 and 1979.

† ICD, *International Classification of Diseases*, Eighth Revision.

‡ Directly adjusted rates per 10^5 person-years.

In these data, considerable confounding exists with age at death and calendar period. Both are strongly associated with the occurrence of cancer and exposure. We have accounted for confounding by stratifying on age and calendar period and by calculating pooled estimates of the rate ratio by means of the maximum likelihood approach. For dose-response analyses, we directly adjusted person-years and deaths to the age and calendar period distribution of person-years for the Rocky Flats Nuclear Weapons Plant work force. The possibility still exists that risk estimates for the plutonium-burdened are confounded by external radiation exposure. Plutonium workers are often exposed to whole body external radiation, primarily neutrons and gamma rays, depending upon the operation in which they are engaged. Equally plausible, however, is the possibility of interaction between plutonium and external radiation.

TABLE 7

Directly adjusted rates (DAR) and standardized rate ratios (SRR) for white males, by exposure level to external radiation and induction time, Rocky Flats Nuclear Weapons Plant, Jefferson County, CO*

Cause of death (ICD†)	Induction time (years)		Cumulative external radiation exposure			β	90% exact confidence limits on slope
			<1 rem	1–4.9 rem	5+ rem		
All causes (001–998)	2	DAR‡	524.5	442.0	467.6	−4.14	−15.02, 6.74
		SRR	1.00	0.84	0.89		
	5	DAR	516.0	459.2	486.9	−2.79	−16.10, 10.52
		SRR	1.00	0.89	0.94		
	10	DAR	526.0	386.8	438.0	−9.60	−23.74, 4.55
		SRR	1.00	0.74	0.83		
All cancers (140–209)	2	DAR	129.6	99.8	91.5	−3.13	−8.00, 1.73
		SRR	1.00	0.77	0.71		
	5	DAR	128.1	100.5	79.9	−4.84	−9.18, 0.12
		SRR	1.00	0.78	0.62		
	10	DAR	133.4	67.0	115.8	−3.65	−12.02, 4.71
		SRR	1.00	0.50	0.87		
All digestive cancers (150–159)	2	DAR	31.5	28.8	29.6	−0.13	−2.80, 2.55
		SRR	1.00	0.91	0.94		
	5	DAR	30.3	32.8	29.2	−0.15	−3.00, 2.70
		SRR	1.00	1.08	0.96		
	10	DAR	36.1	24.6	21.7	−1.53	−5.39, 2.34
		SRR	1.00	0.68	0.60		
Lung cancer (162, 163)	2	DAR	45.8	36.2	18.9	−2.53	−4.99, −0.07
		SRR	1.00	0.79	0.41		
	5	DAR	43.8	28.8	21.1	−1.93	−4.49, 0.63
		SRR	1.00	0.66	0.48		
	10	DAR	39.8	26.0	38.4	−0.41	−4.80, 3.98
		SRR	1.00	0.65	0.96		
Prostatic cancer (185)	2	DAR	8.6	3.1	18.6	0.96	−0.99, 2.91
		SRR	1.00	0.36	2.16		
	5	DAR	7.9	12.5	7.3	−0.10	−1.49, 1.29
		SRR	1.00	1.58	0.92		
	10	DAR	11.2	11.3	0.0	−1.17	−1.94, −0.40
		SRR	1.00	1.01	0.0		
All lymphopoietic cancers (200–209)	2	DAR	7.3	8.1	18.0	1.07	−0.81, 2.95
		SRR	1.00	1.11	2.47		
	5	DAR	9.0	8.5	13.9	0.49	−1.35, 2.33
		SRR	1.00	0.94	1.54		
	10	DAR	10.6	0.0	28.7	−1.66	−4.82, 1.49
		SRR	1.00	0.0	2.71		
Unspecified brain tumors (238)	2	DAR	2.6	8.4	10.8	0.87	−0.46, 2.20
		SRR	1.00	3.23	4.15		
	5	DAR	4.7	4.8	12.4	0.76	−0.80, 2.32
		SRR	1.00	1.02	2.64		
	10	DAR	3.4	14.7	8.4	0.57	−0.91, 2.05
		SRR	1.00	4.32	2.47		

* Mortality rates were directly adjusted to the age and calendar year distribution of white males who worked two or more years at Rocky Flats Nuclear Weapons Plant between 1952 and 1979.

† ICD, *International Classification of Diseases*, Eighth Revision.

‡ Directly adjusted rates per 10^5 person-years.

... The presence ... tinue to be observed years after initial ex-

In addition, plutonium workers may be exposed to potentially hazardous chemicals. Possible confounding due to chemical exposures was not investigated. Limiting the analyses of exposed and unexposed workers to only those who were tested for plutonium, however, may control in a crude fashion for such confounding. On the basis of an examination of the plant site by several of the investigators, and an assessment by an industrial hygienist, likely exposures to hazardous quantities of chemicals during current operations were not obvious. These interesting possibilities warrant further investigation.

Consideration was given to the possibility of nondifferential misclassification that existed because of the presence of untested persons among the unexposed and unburdened subcohorts. Since these individuals contribute person-years and deaths only to the unexposed, if misclassification does occur, it is in the form of misclassifying exposed individuals as unexposed, thereby leading to an underestimate of the true effect. To account for potential misclassification, we limited our comparisons of exposed with unexposed to those who were tested for either plutonium or external radiation exposure. This increases the validity, but decreases the precision, of our estimates. Employees who were not tested for plutonium or who were not issued radiation badges were included only in standardized mortality ratio (SMR) analyses of the entire cohort.

We have attempted to deal with the type of selection bias common to studies of occupational cohorts (healthy worker effect) by directly comparing exposed with unexposed subcohorts. The low standardized mortality ratios for all causes of death (SMR = 62) and circulatory diseases (SMR = 61) are evidence that such selection bias is present within this cohort. By contrast, the rate ratios for all causes of death are somewhat elevated among plutonium-exposed compared with unexposed workers.

The elevated risks associated with plutonium exposure that we have discovered appear plausible for some cancers. Preliminary results from autopsy studies of plutonium depositions in tissues from whole body donations show higher concentrations in the esophagus, stomach, red marrow, and prostate than in muscle tissues. The highest plutonium levels, however, are still found in organs such as the lung, lymph nodes, bone, and liver (43).

A large body of literature exists demonstrating the association between the blood and lymph cancers and exposure to ionizing radiation (44–46). In occupational settings, radiologists (47, 48) and uranium mill workers (49) have been found to experience elevated risks for leukemia and non-Hodgkin's lymphoma. Especially pertinent, however, are the excess leukemias (primarily myeloid) and blood dyscrasias that have been found in studies of thorotrast and radium-224 patients (2, 6, 50–52).

The high rate ratios for esophageal and gastric cancers are also supported by the literature. In an international cooperative study of women irradiated for cervical cancer, Boice et al. (53) report significant excesses for esophageal but not for stomach cancers. Studies of atomic bomb survivors show small increases in risks for both of these digestive system cancers (46, 54), as do investigations of British ankylosing spondylitis patients (44, 55). Esophageal cancer after irradiation for breast cancer (56) has been reported, as have increased risks for gastric cancer among US (57) and Swedish (58) uranium miners. In most of the examples just mentioned, however, exposures were to external radiation, and most of these exposures were much higher than those experienced by the plutonium workers in this study. Furthermore, esophageal and stomach tissues have not been considered to be heavily irradiated from plutonium. Passage of plutonium through the gastrointestinal tract in a bolus of food is not thought to result in high exposures because of the short range of alpha particles. Given the preliminary results from the whole body autopsy studies cited above, additional research to improve our understanding of the distribution of plutonium throughout the human body is clearly needed.

The elevated rate ratios that we found for prostatic cancer are unanticipated. The BEIR III report classified the prostate as a site for which evidence of radiation induction is lacking (59). Nevertheless, slight excesses for this site have been reported among radiologists (60), uranium miners (57), and nuclear workers (61), although associations with radiation exposure were not demonstrated. In addition, a recent study of British nuclear workers has reported an excess of prostatic cancers among the subcohort of workers who were monitored for radiation exposures (62).

Several studies of clinical populations have discovered associations between radiation exposures and brain cancer. Although two investigations suggest that excess tumors occur at less than 100 rads (45, 63), most studies report excesses at more than 100 rads of cumulative exposure (64–67). Among nuclear workers, three studies demonstrate an excess of brain tumors (13, 14, 23), and three do not (8, 9, 68). When excesses have been demonstrated among these occupational cohorts, no associations have been found with radiation or other job-related exposures. Although a number of reports of brain cancer excesses among workers from a variety of industries exist (69), with the exception of vinyl chloride (70), specific exposures have not been identified.

Results of this investigation suggest that plutonium-burdened individuals may experience increased risks from lymphopoietic neoplasms. The high rate ratios for certain digestive system and prostatic cancers need further consideration before a plutonium exposure effect can be accepted. We also found elevated rate ratios for unspecified brain tumors, myeloid leukemia, and lymphosarcoma and reticulum cell sarcoma among workers exposed to external radiation. In all of these instances, however, the confidence intervals are wide, and a deficit cannot be ruled out. The presence of suggestive dose-response trends for all causes of death, digestive system cancers, and lymphopoietic neoplasms among the plutonium-burdened, and for lymphopoietic cancers and unspecified brain tumors among those exposed to external radiation, lends some credence to these findings.

The results from autopsy studies of selected human tissues and from animal studies suggest that the bone, liver, lung, and perhaps lymph nodes should be the organs of greatest concern among plutonium-burdened workers. However, we found no association between mortality from bone or liver cancer and exposure to plutonium. The lack of information about smoking makes interpretation of the lung cancer risk ratios difficult. The higher rate ratio that is observed for a 10-year induction period compared with shorter induction times, however, is consistent with our present knowledge of the time required for the induction of lung cancer in humans. Still to be resolved are the lack of dose-response for many of the elevated rate ratios that we found, the limited precision with which we were able to measure exposure-disease relationships, the question of plutonium exposure being confounded by external radiation or other exposures, and the possibility of interaction between plutonium and external radiation. Additional results from whole body autopsy studies are required to understand better the distribution of plutonium throughout the human body and to determine thereby if the high rate ratios we found for digestive and prostatic cancers are biologically plausible. The increased risk with increasing plutonium burden that was found for all causes of death warrants further investigation of nonneoplastic disease. Furthermore, these findings need to be replicated in another plutonium-exposed population before they can be accepted as strong evidence of causation. Given the experience of the atomic bomb survivors (46) and thorotrast studies (51) in which solid tumors and leukemia, respectively, continue to be observed years after initial exposures, it would be prudent to continue to evaluate the mortality experienced by these plutonium workers.

References

1. Archer VE, Lundin FE, Wagoner JK. Lung cancer among uranium miners in the United States. Health Phys 1973;25:351–71.
2. Van Kaick G, Lieberman D, Lorenz D, et al. Recent results of the German thorotrast study—epidemiological results and dose-effect relationships in thorotrast patients. Health Phys 1983;44(Suppl 1):299–306.
3. Modan B, Lilienfeld AM. Polycythemia vera and leukemia—the role of radiation treatment: a study of 1222 patients. Medicine 1965;44:305–44.
4. Larsen PR, Conrad RA. Thyroid hypofunction appearing as a delayed manifestation of accidental exposure to radioactive fallout in a Marshallese population. BNL-24104. Upton, NY: Brookhaven National Laboratory, 1978.
5. Rowland RE, Steheny AF, Lucas HF. Dose-response relationships for female radium dial workers. Radiat Res 1978;76:368–83.
6. Mays CW, Speiss H. Epidemiological studies of German patients injected with ^{224}Ra. In: Proceedings of the 16th midyear topical meeting of the Health Physics Society, Albuquerque, NM, January 10-13, 1983. CONF-830101, UC-41. Washington, DC: National Technical Information Service, 1983:159–66.
7. Mancuso FT, Stewart A, Kneale G. Radiation exposures of Hanford workers dying from cancer and other causes. Health Phys 1977;33:369–85.
8. Gilbert ES, Marks S. An analysis of the mortality of workers in a nuclear facility. Radiat Res 1979;79:122–48.
9. Tolley HD, Marks S, Buchanan JA, et al. A further update on Hanford workers. Radiat Res 1983;95:211–13.
10. Najarian T, Colton T. Mortality from leukemia and cancer in shipyard nuclear workers. Lancet 1978;1:1018–20.
11. Rinsky RA, Zumwalde RD, Waxweiler RJ, et al. Cancer mortality at a naval nuclear shipyard. Lancet 1981;1:231–5.
12. Bross IDJ, Driscoll DL. Direct estimates of low-level radiation risks of lung cancer at two NRC-compliant nuclear installations: why are the new risk estimates 20 to 200 times the old official estimates? Yale J Biol Med 1981;54:317–28.
13. Hadjimichael OC, Ostfeld AM, D'Atri DA, et al. Mortality and cancer incidence experience of employees in a nuclear fuels fabrication plant. J Occup Med 1983;25:48–61.
14. Lushbaugh CC. The development and present state of the DOE health and mortality studies. Proceedings of the DOE radiation contractors workshop, April, 1982:1–36.
15. Voelz GL, Grier RS, Hempelmann LH. A 37-year medical followup of Manhattan project plutonium workers. Health Phys 1985;48:249–59.
16. Voelz GL, Wilkinson GS, Healy JW, et al. Mortality study of Los Alamos workers with high 16th midyear topical meeting of the Health Physics Society, Albuquerque, NM, January 10-13, 1983. CONF-830101, UC-41. Washington, DC: National Technical Information Service, 1983:318–27.
17. Acquavella JF, Tietjen GL, Wilkinson GS. Malignant melanoma incidence at the Los Alamos National Laboratory. Lancet 1982;1:883–4.
18. Acquavella JF, Wilkinson GS, Tietjen GL, et al. A melanoma case-control study at the Los Alamos National Laboratory. Health Phys 1983;45:587–92.
19. Acquavella JF, Wilkinson GS, Wiggs LD, et al. An evaluation of cancer incidence among employees at the Los Alamos National Laboratory. In: Proceedings of the 16th midyear topical meeting of the Health Physics Society, Albuquerque, NM, January 10–13, 1983. CONF-830101, UC-41. Washington, DC: National Technical Information Service, 1983:338–45.
20. Johnson CJ. A preliminary evaluation of brain cancer, melanoma, and respiratory cancer of employees of the Rocky Flats Nuclear Weapons Plant in Jefferson County, Colorado. Annual Meeting of the American Public Health Association, Epidemiology Exchange Section. Detroit, MI, 1980.
21. Johnson CJ. Cancer incidence in an area contaminated with radionuclides near a nuclear installation. Ambio 1981;1:176–82.
22. Dreyer NA, Laughlin JE, Fahey FH, et al. The feasibility of epidemiological studies of cancer in residents near the Rocky Flats Plant site. Health Phys 1982;42:65–8.
23. Voelz GL, Wilkinson GS, Acquavella JF, et al. An update of epidemiologic studies of plutonium workers. In: Proceedings of the international meeting on the radiobiology of radium and the actinides in man, Lake Geneva, Wisconsin, October 11–16, 1981. Health Phys 1983;44(Suppl 1):493–503.
24. Wilkinson GS, Voelz GL, Acquavella JF, et al. Mortality among plutonium and other workers at a nuclear facility. In: Proceedings of the 16th midyear topical meeting of the Health Physics Society, Albuquerque, NM, January 10–13, 1983. CONF-830101, UC-41. Washington, DC: National Technical Information Service, 1983:328–37.
25. International Commission on Radiological Protection. The metabolism of compounds of plutonium and other actinides. Publication no. 19. Oxford, England: Pergamon Press, 1972.
26. McInroy JF. The Los Alamos Scientific Laboratory's human autopsy tissue analysis study. In: Jee WSS, ed. The health effects of plutonium and radium. Salt Lake City, UT: JW Press, 1976:247–70.
27. Langham WH, Healy J. Maximum permissible body burdens and concentrations of plutonium: biological basis and history of development. In: Hodge HC, Stannard JM, Jursh JB, eds. Handbook of experimental pharmacology. New York: Springer-Verlag, 1973:569–72.
28. Marshall JH. The retention of radionuclides in bone. In: Mays CW, [illegible]

Salt Lake City, UT: University of Utah Press, 1969:9.
29. Mays CW, Speiss H, Taylor GN, et al. Estimated risk to bone from ^{239}Pu. In: Jee WSS, ed. The health effects of plutonium and radium. Salt Lake City, UT: JW Press, 1976:343–62.
30. Huth GC, Dugas DJ. The relationship of lung cancer induction to inhalation of submicron particles—either stable or radioactive. In: Jee WSS, ed. The health effects of plutonium and radium. Salt Lake City, UT: JW Press, 1976:729–50.
31. Bair WJ, Ballou JE, Park JF, et al. Plutonium in soft tissues with emphasis on the respiratory tract. In: Hodge HC, Stannard JN, Hursh JB, eds. Uranium, plutonium, transplutonic elements. Chap 11. New York: Springer-Verlag, 1974.
32. Jee WS, ed. The health effects of plutonium and radium. Salt Lake City, UT: JW Press, 1976.
33. Wrenn MW, ed. Actinides in man and animals. Salt Lake City, UT: RD Press, 1981.
34. International Commission on Radiological Protection. The metabolism of compounds of plutonium and other actinides. ICRP publication 19. Oxford: Pergamon Press, 1972.
35. Vaughan J. Plutonium—a possible leukaemic risk. In: Jee WSS, ed. The health effects of plutonium and radium. Salt Lake City, UT: JW Press, 1976:691–705.
36. Langham WH, Bassett SH, Harris PS, et al. Distribution and excretion of plutonium administered intravenously to man. Health Phys 1980;38:1031–60.
37. Monson RR. Analysis of relative survival and proportional mortality. Comput Biomed Res 1974;7:325–32.
38. Rothman KJ, Boice JD. Epidemiologic analysis with a programmable calculator. (US DHHS (PHS, NIH) NIH publication no. 79-1649). Washington, DC: US GPO, 1979.
39. Kleinbaum DG, Kupper LL. Applied regression analysis and other multivariable methods. Boston, MA: Duxbury Press, 1978.
40. Rothman KJ. Modern epidemiology. Boston, MA: Little Brown and Company, 1986.
41. Rothman KJ. Induction and latent periods. Am J Epidemiol 1981;114:253–9.
42. Shore RE, Woodard E, Hildreth N, et al. Thyroid tumors following thymus irradiation. JNCI 1985;74:1177–84.
43. McInroy J. Distribution of ^{239}Pu and ^{241}Am in whole body donations from nuclear workers. In: Voelz G, ed. Occupational health and environmental research 1985. Health, Safety, and Environment Division. (unpublished).
44. Smith P. Late effects of x-ray treatment of ankylosing spondylitis. In: Boice JD Jr, Fraumeni JF Jr, eds. Radiation carcinogenesis: epidemiology and biological significance. New York: Raven Press, 1984:107–18.
45. Bithell JF, Stewart A. Prenatal irradiation and childhood malignancy: a review of British data from the Oxford survey. Br J Cancer 1975;31:271–87.
46. Kato A, Schull WJ. Cancer mortality among atomic bomb survivors. Part 1. RERF TR 12-80.
47. Matanoski GM, Seltser R, Sartwell PE, et al. The current mortality rates of radiologists and other physician specialists: specific causes of death. Am J Epidemiol 1975;101:199–210.
48. Lewis EB. Leukemia, multiple myeloma, and aplastic anemia in American radiologists. Science 1963;147:1492–4.
49. Archer VE, Wagoner JK, Lundin FE. Cancer mortality among uranium mill workers. J Occup Med 1973;15:11–14.
50. Wick RR, Gossner W. Followup study of late effects in ^{224}Ra-treated ankylosing spondylitis patients. Health Phys 1983;44(Suppl 1):187–95.
51. Van Kaick G, Muth H, Kaul A, et al. Results of the German thorotrast study. In: Boice JD Jr, Fraumeni JF Jr, eds. Radiation carcinogenesis: epidemiology and biological significance. New York: Raven Press, 1984:253–61.
52. Mole RH. The radiobiological significance of the studies with ^{224}Ra and thorotrast. Health Phys 1978;35:167–74.
53. Boice JD Jr, Day ME, Andersen A, et al. Cancer risk following radiotherapy of cervical cancer: a preliminary report. In: Boice JD Jr, Fraumeni JF Jr, eds. Radiation carcinogenesis: epidemiology and biological significance. New York: Raven Press, 1984:161–79.
54. Wakabayashi T, Kato H, Ikeda T, et al. Studies of the mortality of a-bomb survivors, report 7, part III. Radiat Res 1983;93:112–46.
55. Court Brown WM, Doll R. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. Br Med J 1965;2:1327–32.
56. Goffman TE, McKeen EA, Curtis RE, et al. Esophageal carcinoma following irradiation for breast cancer. Cancer 1983;52:1808–9.
57. Waxweiler RJ, Roscoe RJ, Archer VE, et al. Mortality followup through 1977 of the white underground uranium miners cohort examined by the United States Public Health Service. In: Gomez M, ed. Radiation hazards in mining. Kingsport, TN: Kingsport Press, Inc, 1981:823–30.
58. Radford EP, Renard KG. Lung cancer in Swedish iron miners exposed to low doses of radon daughters. N Engl J Med 1984;310:1485–94.
59. Committee on the Biological Effects of Ionizing Radiation. The effects on populations of exposure to low levels of ionizing radiation. Washington, DC: National Academy Press, 1980:266–7.
60. Matanoski GM, Sartwell PE, Elliott E, et al. Cancer risks in radiologists and radiation workers. In: Boice JD Jr, Fraumeni JF Jr, eds. Radiation carcinogenesis: epidemiology and biological significance. New York: Raven Press, 1984:83–96.
61. Checkoway H, Mathew RM, Wolf SH, et al. Mortality among workers at the Oak Ridge National Laboratory. In: Proceedings of the 16th midyear topical meeting of the Health Physics Society, Albuquerque, NM, January 10–13, 1983. CONF-830101, UC-41. Washington, DC: National Technical Information Service, 1983:90–104.
62. Beral V, Inskip H, Fraser P, et al. Mortality of employees of the United Kingdom Atomic Energy Authority, 1946–1979. Br Med J 1985;291:440–7.
63. Sandler DP, Comstock GW, Matanoski GM, N...

a deficit cannot be ruled out. The presence tinue to be observed years after initial ex-

64. Modan B, Baidatz D, Mart H, et al. Radiation-induced head and neck tumors. Lancet 1974;1:277-9.
65. Shore RE, Albert RE, Pasternak BS. Follow-up study of patients treated by x-ray epilation for tinea capitis. Arch Environ Health 1976;31:17-24.
66. Colman M, Kirsch M, Creditor M. Tumors associated with medical x-ray exposure in childhood. In: Late biological effects of ionizing radiation. Vol 1. Vienna: International Atomic Energy Agency, 1978.
67. Seyama S, Ishimaru T, Iijima S, et al. Primary intracranial tumors among atomic bomb survivors and controls, Hiroshima and Nagasaki, 1961-1975. Radiation Effects Research Foundation Report. RERFTR 15-79, 1979.
68. Reyes M, Wilkinson G, Tietjen G, et al. Brain tumors at a nuclear facility. J Occup Med 1984;26:721-4.
69. Selikoff IJ, Hammond EC, eds. Brain tumors in the chemical industry. Ann NY Acad Sci 1982;381.
70. Waxweiler RJ, Stringer W, Wagoner JK, et al. Neoplastic risk among workers exposed to vinyl chloride. Ann NY Acad Sci 1976;271:40-8.

Appendix table 1

Person-years and weights for computing directly adjusted rates for all white males employed for two or more years at Rocky Flats Nuclear Weapons Plant, Jefferson County, CO

Age	Calendar year						
	1950	1955	1960	1965	1970	1975	Sum
15	0.0*	0.0	0.0	0.7	0.0	0.0	0.7
	0.0000000†	0.0000000	0.0000000	0.0000089	0.0000000	0.0000000	
20	14.6	173.4	229.1	387.9	579.5	248.2	1,632.7
	0.0001861	0.0022102	0.0029201	0.0049442	0.0073863	0.0031636	
25	71.3	753.7	1,008.9	1,652.8	1,822.5	1,390.6	6,699.8
	0.0009088	0.0096067	0.0128595	0.0210666	0.0232296	0.0177246	
30	75.7	1,221.8	1,653.8	2,408.9	2,875.1	2,533.2	10,768.5
	0.0009649	0.0155731	0.0210794	0.0307039	0.0366461	0.0322882	
35	53.4	1,130.5	2,054.6	2,605.6	3,070.3	3,204.5	12,118.9
	0.0006806	0.0144094	0.0261880	0.0332110	0.0391341	0.0408446	
40	50.6	834.0	1,968.5	2,859.9	3,114.1	3,281.8	12,108.9
	0.0006449	0.0106302	0.0250905	0.0364523	0.0396924	0.0418299	
45	29.7	645.2	1,438.1	2,648.8	3,283.1	3,285.0	11,329.9
	0.0003786	0.0082237	0.0183300	0.0337616	0.0418464	0.0418707	
50	13.2	406.3	998.7	1,843.4	2,931.8	3,360.4	9,553.8
	0.0001682	0.0051787	0.0127294	0.0234960	0.0373688	0.0428317	
55	2.7	180.5	612.6	1,170.3	2,000.6	2,959.1	6,925.8
	0.0000344	0.0023007	0.0078082	0.0149167	0.0254997	0.0377167	
60	3.7	117.0	272.6	663.4	1,150.3	1,948.5	4,155.5
	0.0000472	0.0014913	0.0034746	0.0084557	0.0146617	0.0248356	
65	0.0	32.9	122.2	253.3	571.4	1,018.7	1,998.5
	0.0000000	0.0004193	0.0015576	0.0032286	0.0072831	0.0129844	
70	0.0	0.0	32.9	101.1	220.1	491.5	845.6
	0.0000000	0.0000000	0.0004193	0.0012886	0.0028054	0.0062647	
75	0.0	0.0	0.0	22.9	77.6	159.7	260.2
	0.0000000	0.0000000	0.0000000	0.0002919	0.0009891	0.0020355	
80	0.0	0.0	0.0	0.0	12.4	38.4	50.8
	0.0000000	0.0000000	0.0000000	0.0000000	0.0001581	0.0004894	
85	0.0	0.0	0.0	0.0	0.0	6.3	6.3
	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000803	
Sum	314.9	5,495.3	10,392.0	16,619.0	21,708.8	23,925.9	78,455.9

* Person-years.
† Weights.

APPENDIX TABLE 2

Maximum likelihood estimates of the rate ratio for workers† exposed to ≥1 rem of external radiation compared with workers exposed to <1 rem for a two-year induction time, while controlling for age and calendar period, Rocky Flats Nuclear Weapons Plant, Jefferson County, CO*

Cause of death (ICD‡)	Deaths: Exposed (35,088.1 person-years)	Deaths: Unexposed (42,693.4 person-years)	RR$_{ML}$§	90% Fisher's exact confidence limits
All causes (001-998)	186	220	0.95	0.80, 1.12∥
All cancers (140–209)	41	52	0.79	0.55, 1.14∥
Buccal cavity and pharynx (140–149)	0	1		23.26
Digestive organs and peritoneum (150–159)	13	11	0.91	0.46, 1.81
Esophagus (150)	3	0		0.71
Stomach (151)	2	3	0.54	0.06, 3.50
Colon (153)	2	4	0.54	0.07, 3.12
Rectum (154)	1	1	0.58	0.03, 8.87
Liver (155)	3	0		0.71
Pancreas (157)	1	3	0.24	0.02, 2.25
Respiratory system (160–163)	12	20	0.67	0.36, 1.28∥
Larynx (161)	0	2		4.22
Lung (162, 163)	12	18	0.68	0.36, 1.30∥
Skin (172, 173)	0	3		2.09
Prostate (185)	4	4	1.33	0.27, 7.40
Bladder (188)	1	2	0.71	0.05, 8.65
Kidney and unspecified urinary organs (189)	1	1	0.91	0.05, 13.90
All brain tumors (191, 192, 225, 238)	6	6	0.98	0.31, 3.08
Malignant brain and other central nervous system (191, 192)	2	4	0.52	0.06, 2.91
Benign brain and other central nervous system (225)	0	1		23.26
Unspecified brain and other central nervous system (238)	4	1	3.46	0.45, 32.78
Thyroid (193)	0	1		23.26
All lymphopoietic (200–209)	5	3	1.49	0.36, 7.25
Lymphosarcoma and reticulum cell sarcoma (200)	2	0		0.35
Non-Hodgkin's lymphoma (202)	1	1	0.92	0.04, 15.01
All leukemia (204–207)	2	2	1.00	0.11, 7.77
Myeloid leukemia (205)	2	0		0.35

* Maximum likelihood estimates were calculated using an adaptation of programs 6 and 7 in Rothman and Boice (38).

† The period of exposure-related risk was defined as beginning 10 years after one's cumulative external radiation exposure reached 1 rem. Unexposed person-years and events were counted from two years after date of hire or first badge reading, whichever occurred later.

‡ ICD, *International Classification of Diseases*, Eighth Revision.

§ Maximum likelihood estimate of the rate ratio.

∥ Ninety per cent approximate confidence limits were calculated in place of Fisher's exact limits using a method described by Rothman (40, p. 212).

APPENDIX TABLE 3

Maximum likelihood estimates of the rate ratio for workers† exposed to ≥1 rem of external radiation compared with workers exposed to <1 rem for a five-year induction time, while controlling for age and calendar period, Rocky Flats Nuclear Weapons Plant, Jefferson County, CO*

Cause of death (ICD‡)	Deaths: Exposed (25,753.0 person-years)	Deaths: Unexposed (52,028.5 person-years)	RR_{ML}§	90% Fisher's exact confidence limits
All causes (001–998)	159	247	1.00	0.84, 1.20‖
All cancers (140–209)	35	58	0.80	0.55, 1.16‖
Buccal cavity and pharynx (140–149)	0	1		38.46
Digestive organs and peritoneum (150–159)	12	12	1.02	0.52, 2.01
Esophagus (150)	3	0	∞	1.18
Stomach (151)	2	3	0.67	0.08, 4.36
Colon (153)	2	4	0.71	0.09, 4.00
Rectum (154)	1	1	0.85	0.04, 13.02
Liver (155)	2	1	1.69	0.13, 18.96
Pancreas (157)	1	3	0.33	0.05, 2.99
Respiratory system (160–163)	10	22	0.68	0.35, 1.33‖
Larynx (161)	0	2		6.99
Lung (162, 163)	10	20	0.69	0.36, 1.36‖
Skin (172, 173)	0	3		3.46
Prostate (185)	4	4	1.66	0.34, 9.01
Bladder (188)	1	2	1.13	0.07, 15.33
Kidney and unspecified urinary organs (189)	1	1	1.23	0.06, 18.93
All brain tumors (191, 192, 225, 238)	4	8	0.70	0.19, 2.27
Malignant brain and other central nervous system (191, 192)	1	5	0.29	0.05, 2.14
Benign brain and other central nervous system (225)	0	1		38.46
Unspecified brain and other central nervous system (238)	3	2	1.73	0.27, 11.69
Thyroid (193)	0	1		38.46
All lymphopoietic (200-209)	4	4	1.18	0.28, 5.00
Lymphosarcoma and reticulum cell sarcoma (200)	2	0		0.58
Non-Hodgkin's lymphoma (202)	1	1	1.11	0.06, 17.48
All leukemia (204–207)	1	3	0.44	0.04, 3.96
Myeloid leukemia (205)	1	1	1.31	0.07, 20.15

* Maximum likelihood estimates were calculated using an adaptation of programs 6 and 7 in Rothman and Boice (38).

† The period of exposure-related risk was defined as beginning 10 years after one's cumulative external radiation exposure reached 1 rem. Unexposed person-years and events were counted from two years after date of hire or first badge reading, whichever occurred later.

‡ ICD, *International Classification of Diseases*, Eighth Revision.

§ Maximum likelihood estimate of the rate ratio.

‖ Ninety per cent approximate confidence limits were calculated in place of Fisher's exact limits using a method described by Rothman (40, p. 212).