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International Plutonium Workers' Study: Considerations and Preliminary Results

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THE NATIONAL PLUTONIUM WORKERS' STUDY: CONSIDERATIONS AND PRELIMINARY RESULTS*

by

John F. Acquavella and Gregg S. Wilkinson

ABSTRACT

The National Plutonium Workers' Study developed from the clinical follow-up of workers with body burdens in excess of 10 nCi. The importance of plutonium to energy and weapons development and the uncertainty about its biological effects motivated the formation of an epidemiologic study of more than 125 000 workers at six Department of Energy facilities. This report reviews recent results from The National Plutonium Workers' Study, including an analysis of cancer mortality among workers at the Rocky Flats Plant and a study of malignant melanoma among employees at Los Alamos National Laboratory. The problems inherent in large-scale epidemiologic studies, as well as the future directions for the study, are discussed.

I. INTRODUCTION

This report concentrates on our efforts at Los Alamos to study plutonium-related health effects within the context of the Department of Energy (DOE)-sponsored National Study of Workers in the Nuclear Industry. This study includes more than 125 000 former and present workers at six DOE facilities, including Los Alamos National Laboratory, Oak Ridge National Laboratory, Mound Facility, and the Rocky Flats, Savannah River, and Hanford Plants. At Los Alamos, we are primarily interested in investigating potential plutonium-related health effects, with particular emphasis on cancers of the lung, bone, and liver (the anatomical sites that accumulate plutonium). Similar epidemiology programs at the Oak Ridge National Laboratory and the Hanford Environmental Health Foundation concentrate on health effects related to low-level external penetrating radiation. Because plutonium workers also are exposed to external penetrating forms of radiation, there is extensive collaboration among the three epidemiology programs.

Plutonium was first produced in significant quantities during the latter days of the Manhattan Project. The ^{239}Pu isotope, which is much more fissile than uranium, has become an integral part of any expansion plans for the nuclear power and weapons industries. Consequently, the results of this study are extremely important to people who favor or disapprove of nuclear development.

Plutonium is an alpha-emitting radionuclide, which is a form of high linear energy transfer (LET) radiation. This designation refers to the higher ionization density produced by alpha particles in solution as compared to low LET forms of radiation (for example, gamma rays). Because high LET particles disperse their energy over extremely short distances, they must be near target tissue to produce an effect. In general, high LET radiation is more damaging per unit dose than is low LET radiation. This comparative property is usually expressed by the

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relative biological effectiveness (RBE) of a particular dose with reference to the same dose of gamma rays. For alpha particles, the RBE is usually considered to be 10. Therefore, 10 rad of alpha-particle radiation should produce an equivalent biological effect of 100 rad of gamma radiation. However, the RBE is dose dependent and may be as high as 40 at low radiation doses.[1]

Animal research into the physiologic properties of plutonium began soon after Glenn Seaborg discovered it in 1943. Seaborg was aware of the similar radioactive properties of plutonium and radium and of the latter's ability to cause bone cancers in humans. He gave J. G. Hamilton of the Crocker Radiation Laboratory in Berkeley, California, 10 mg from the first 500 mg of plutonium for metabolic studies with animals. Hamilton's purpose was to determine if plutonium could be handled safely by workers. His report summarizes what we know today about the physiologic properties of plutonium. "Oral absorption of all valence states is less than 0.05%; lung retention high; absorbed material predominantly in the skeleton; excretion very small in urine and feces."[2] Consequently, early in plutonium-related research and production, plutonium was known to accumulate in the lung, liver, and bone. However, in contrast to radium, it was poorly absorbed by the digestive system. Since that time, extensive research has demonstrated plutonium-related cancer of the lung, liver, and bone among experimental animals.[3] Therefore, we are concerned about these cancers among plutonium workers.

Before the beginning of The National Plutonium Workers' Study in 1976, there had been no epidemiologic study of humans exposed to plutonium. A clinical examination of 26 Manhattan Project workers with the highest plutonium exposures (ranging between 7 and 230 nCi) found these former employees in exceptionally good health.[4] Since that time, a mortality analysis has been published of an additional 241 workers (224 males) with body burdens in excess of 10 nCi. These people represent roughly one-third of the US workers with body burdens exceeding 25% of the current standard. Mortality in this group was less than expected based on US death rates. Specifically, for the anatomical sites that accumulate plutonium, we detected one lung cancer (versus 3.6 expected) and no cancers of the liver or bone.[5]

We derive most of our expectations about the potential consequences of plutonium exposure from animal studies and studies of workers exposed to ^{226}Ra. In fact, the current occupational standard of 40 nCi plutonium for human body burden is based on the existing standard for radium of 100 nCi divided by 2.5—a quality factor representing plutonium's greater capability to induce bone tumors in rodents. The 40-nCi limit for plutonium was based on three considerations: (1) comparison with the 100-nCi limit for radium is acceptable as a standard; (2) bone, the critical organ for radium, is also the critical organ for plutonium; and (3) comparative effects of plutonium and radium in animal systems can be extrapolated meaningfully to man.[3] Comparison of plutonium with radium is less appropriate when considering organs other than bone.

Some researchers assert that the plutonium standard is too high and that the process of setting the standard neglects some important differences between plutonium and radium exposure. Paramount among these differences are the much longer physical and biological half-life of plutonium and its tendency to concentrate on the bone surface rather than in the bone matrix.[3] Plutonium accumulation on bone surface is considered more dangerous because of its proximity to rapidly dividing endosteal cells, which are more susceptible than bone matrix to alpha-radiation-induced carcinogenesis.[6] Plutonium also accumulates in the tracheobronchial lymph nodes, lung, and liver.

Fortunately, occupational exposures to plutonium have been kept quite low. [See Table I where the population at risk at all six facilities is listed by percentage of maximum permissible body burden (%MPBB) through 1977.] Relatively few workers have plutonium body burdens approaching the standard; in fact, over 75% are not tested for plutonium exposure because they do not work in plutonium-related areas. We consider them to be unexposed.

This lack of high exposures limits what we may learn about plutonium-related health effects. Based on current risk estimates, we expect few related effects at these low exposure levels. However, these risk estimates were based on extrapolations from populations exposed at high levels to substances other than plutonium. As such, they may not be appropriate for low-level occupational plutonium exposure and may in fact under- or overestimate effects considerably.

In a recent article in *Science,* Land addressed the power controversy and enumerated the huge sample sizes necessary to detect health effects resulting from low-level radiation exposures.[7] He also pointed out that we know more about radiation carcinogenesis than about most, if not all, other carcinogens; yet scientists disagree by two orders of magnitude about associated

TABLE I. Nuclear Industry Worker Populations by Plutonium Exposure and DOE Site

nCi	%MPBB	Hanford[a]	Los Alamos[a]	Mound[a] Facility	Oak Ridge[a]	Savannah River[a]	Rocky Flats[a]	Total[a]
≥20	≥50	15	63	34	1	3	25	141
≥4 - <20	≥10 - <50	44	323	100	14	50	354	885
≥1 - <4	≥2.5 - <10	147	680	230	46	122	2 500	3 725
≥0 - <1	≥0 - <2.5	6 732	5 393	1 000	89	6 900	4 100	24 200
Not tested	Not tested	30 728	32 000	4 700	20 000	10 000	1 500	98 900
Total population		37 666	38 500	6 100	20 150	17 000	8 500	127 900
Currently employed (1977)		8 000	7 540	1 600	5 500	5 450	2 650	30 750

[a]These are estimates of the number of persons in each exposure category.

risks. For plutonium, the political reality is that influential parties disagree about risks by over six orders of magnitude. In view of the potential importance of plutonium, a direct estimate of excess human risk is desirable. Although this estimate will certainly not provide an absolute answer about the adequacy of current standards for plutonium, it will provide an interval estimate of excess risk for responsible decision making. Also, follow-up of the most highly exposed workers should be continued until a complete survival analysis is possible.

II. PROBLEMS IN OCCUPATIONAL RADIATION HEALTH EFFECTS STUDIES

Before describing our specific research efforts, we will consider some of the uncertainties in the study of low-level occupational radiation-related health effects and suggest solutions for some of the problems.

A. Enumeration of the Population at Risk

A major problem in historical prospective studies is enumerating the population at risk. Those familiar with the studies of military participants in nuclear weapons tests will appreciate the difficulty involved in reconstructing a cohort many years after a common exposure.[8] Cohort enumeration has occupied the majority of our group's efforts since the beginning of the study in 1976. Verification of study rosters using independent sources of personnel listings is necessary to assure complete enumeration.[9] For example, personnel department records can be compared with health physics records and payroll listings. This study is unusual in that security clearance lists provide an additional resource.

B. Ascertainment of Vital Status

The related problem of ascertaining vital status for cohort members is usually accomplished by submitting a roster of employees to the Social Security Administration (SSA) and obtaining death certificates for those deceased. Follow-up of workers through SSA is usually 80 to 97% complete. The remaining workers are considered lost to follow-up (LTF).[10,11] We examined the completeness of SSA reporting of deaths for the Los Alamos working population by submitting a list of known deaths to SSA.[12] The initial submission resulted in identification of 77% of 684 deaths (Table II). The SSA reported 82% of male deaths, which was significantly better than the 66% of female deaths.

County of residence or cause of death did not affect SSA ascertainment; however, age at death did. The SSA correctly identified 88% of deaths occurring after age 65 compared with only 70% of deaths occurring before age 65. A second submission to SSA of deaths that were not identified on the first submission improved male reporting to 91% and female reporting to 80% (Table III).

From this point more extensive tracing efforts are usually required. We suggest a second submission to SSA as the most efficient first step to reduce the number of workers LTF. Of course, no matter how much effort is devoted to tracing, some cohort members will remain LTF. In Sec. III.E, we discuss a statistical technique we used to adjust for potential LTF bias in our recently reported mortality analysis at Rocky Flats. This technique can be used to estimate comparative mortality for the cohort at different simulated levels of LTF mortality and provides an indication when tracing efforts are no longer necessary for valid statistical estimates.

TABLE II. First Submission: Percentages of Known Deaths Correctly Identified by the SSA

Study File	Total	Male	Female	<65 Years	≥65 Years
Los Alamos resident Los Alamos occupation Noncancer deaths	71.3	76.6	60.0	65.4	84.0
Los Alamos resident Los Alamos occupation Cancer deaths	71.6	81.6	60.9	67.2	82.1
Los Alamos resident Los Alamos occupation All deaths	68.0	90.0	53.3	57.9	100.0
Los Alamos resident Los Alamos occupation All deaths	83.2	86.9	75.9	81.0	85.4
Rio Arriba County resident Rio Arriba occupation All deaths	75.0	85.3	59.9	64.3	85.7
Santa Fe County resident Santa Fe occupation All deaths	81.8	83.8	76.3	68.6	94.5
Plutonium workers	80.0	84.8	0.0[a]	72.0	90.0
Total	77.2	82.3	66.2	70.0	87.7

[a]Two females total.

C. Accuracy of Death Certificate Diagnoses

Another potential source of error is the accuracy of death certificate diagnoses for certain types of cancer. For example, in Gilbert's study of radiation workers at Hanford, the existence of a dose-response relationship for pancreatic cancer hinged on whether an assumed case in the highest exposure category had pancreatic or stomach cancer.[13] Clearly, this type of inaccuracy casts considerable doubt on any resulting biological or mathematical models. We are fortunate to have available a population-based tumor registry in New Mexico that routinely achieves 85 to 90% histological confirmation of cancer diagnoses. This registry, which has operated since 1969, participates in the Surveillance Epidemiology and End Results (SEER) program. Incidence data from this source can be used to check results from the analysis of death certificates and are also useful for the study of less fatal cancers.

D. Exposure Assessment

Another problem in occupational health studies is exposure assessment. This problem is a lesser difficulty in our study because we have individual radiation exposure estimates for cohort members. Individual measurements are superior to estimates based on area monitors or reconstructed work histories. Yet, considerable problems in exposure assessment still exist. Cohort members have been exposed to several forms of radiation, including beta, gamma, and neutron external radiation and internal accumulation of plutonium. Film badges and more recently thermoluminescent dosimeters

TABLE III. First and Second Submissions: Percentages of Known Deaths Correctly Identified by the SSA

Study File	Male		Female	
	1	1 and 2	1	1 and 2
Los Alamos resident Los Alamos occupation Noncancer deaths	76.6	90.6	60.0	80.0
Los Alamos resident Los Alamos occupation Cancer deaths	81.6	91.8	60.9	82.6
Los Alamos resident Los Alamos occupation All deaths	90.0	90.0	53.3	86.6
Los Alamos resident Los Alamos occupation All deaths	86.9	93.9	75.9	79.3
Rio Arriba County resident Rio Arriba occupation All deaths	85.3	88.2	59.1	72.7
Santa Fe County resident Santa Fe occupation All deaths	83.8	90.5	76.3	81.6
Plutonium workers	84.8	90.0	0.0[a]	50.0

[a]Two females total.

routinely measure external radiation exposure. Film badges have improved over the years, making comparability of recent and previous measurements tenuous. For example, neutron exposures at Los Alamos were not measured before 1952. Also, cumulative measurements based on several low-level exposures will probably differ from the same dose received in a single exposure.

Assessment of plutonium exposure, usually accomplished by urinalysis of exposed workers, is even more problematic. The limited autopsy work done on occupationally exposed workers suggests that estimates of body burdens based on urinalysis are two to three times too high.[14] Further, the discrepancy may be greater when estimating burdens in specific organ systems. Our autopsy program at Los Alamos is working to improve the prediction of body burdens based on urine assay by correlating worker body burdens at autopsy with measurements taken during their working lifetimes.

Experience in the nuclear industry has shown that inhaling insoluble PuO_2 is the most prevalent route of exposure.[15] Plutonium retention occurs, but the amount retained is governed by several complex processes. The Langham power function used to estimate total plutonium in the body and in specific organs is based on intravenous injection of plutonium. Several attempts have been made to modify this equation to allow for the physical and chemical characteristics of inhaled material.[16] For these reasons, urinary excretion is only a qualitative index of plutonium exposure. However, it is considered an accurate measure of systemic plutonium (that is, plutonium in the liver and skeleton). Urine assay results from persons subjected to multiple exposures by inhalation are particularly difficult to interpret; unfortunately, this is the most common type of exposure.

To learn more about estimating plutonium in specific tissues, the Epidemiology Group has a subsection that analyzes volunteered autopsy specimens from former workers. The variation of the plutonium distribution in the bodies of former workers suggests that each exposure situation is unique. Autopsy specimens usually include the lung, tracheobronchial lymph nodes, liver, kidney, and bone. Plutonium alpha activity is measured by alpha-pulse-height analysis that can distinguish the different energies of the various plutonium isotopes. The lower limit of detection is 0.02 dis/min/kg.

Plutonium concentrations in exposed workers are highest in the tracheobronchial lymph nodes, followed by the lung, liver, bone, and kidney, which suggests that inhalation is the most frequent route of exposure (Table IV).[17] It is also important to note that plutonium may reside in the lung for long periods. In many recorded cases, the only documented exposures were 20 to 30 years before analysis.

Estimating plutonium in the skeleton is very difficult because of the relatively small samples obtainable for autopsy and the observed variability of plutonium distribution in the bone. Wide variations in plutonium concentrations have been measured in different bones and different parts of the same bone. Liver concentrations tend to be 2 to 10 times the average concentration in the skeleton.

Table V gives the percentage of plutonium body burden found in each tissue.[17] This distribution, which reflects the size of the affected tissue and the nonuniform distribution of plutonium within these tissues, is quite different from relative tissue concentrations. The skeleton has the highest percentage of body burden—almost 48% of the total. The lung contained 28%, the liver 18%, the tracheobronchial lymph nodes 5%, and the kidney less than 1%.

TABLE IV. Average Plutonium Concentration in Autopsy Tissues of Former Workers

Tissue	(dpm/kg)	Range of Pu Concentrations
Tracheobronchial lymph nodes	56 376	0-787 949
Lung	3 390	1- 69 955
Liver	789	1- 9 836
Bone	407	0- 3 550
Kidney	21	0- 294

TABLE V. Average Percentage of Plutonium Body Burden in Specific Tissues of Former Workers

Tissue	% Body Burden	Range of Pu Body Burdens
Skeleton	47.5	11-98%
Lung	28.2	1-77%
Liver	18.1	1-54%
Tracheobronchial lymph node	4.7	1-17%
Kidney	0.5	1- 4%
Other	6.9	1-20%

E. Statistical Analysis

Available methods of statistical analysis have limitations. Comparing the ratio of observed-to-expected deaths [that is, the standardized mortality ratio (SMR)] with the number of observed deaths assumed to be distributed as a Poisson variate is a relatively insensitive technique. SMR analysis may be augmented by considering only a restricted segment of the population (for example, those with high exposures).[18] However, restricting the analysis requires an arbitrary selection criterion, which may be devoid of any biological significance. SMR analysis can also be improved by allowing for the induction period of cancer. In this instance, each worker would be entered into the analysis at a time after initial exposure that corresponds to the time necessary for cancer induction. This technique is complicated by the arbitrary choice of an appropriate cancer induction period after a meaningful exposure has occurred. Its strength is that observed and expected deaths occurring too soon after initial exposure are not counted, lending more specificity to the analysis. Related problems include the choice of an appropriate standard population and interpretation of results, as employed populations have lower mortality rates than does the general population (that is, the healthy worker effect). Calculation of expected numbers of deaths based on unexposed workers at the same facility circumvents this problem, but the resulting comparison rates are usually highly variable and may be based on a much younger population or one with strikingly different demographic characteristics. Clearly, we need to develop more powerful analytical

methods. In this regard, Gilbert suggested a variation of the Cox proportional hazards model in which dose is the single time-dependent regression variable and other variables are controlled through stratification.[18] Gilbert described the application of this model to the Hanford occupational mortality analysis as resulting in a moderate increase in power.[18]

III. EPIDEMIOLOGIC STUDIES OF PLUTONIUM-EXPOSED WORKERS

A. Clinical Follow-up of Workers with Highest Plutonium Exposures

More than 30 years ago, during and shortly after the Manhattan Project at Los Alamos, most of the highest plutonium exposures occurred among workers. Active clinical follow-up of the 241 workers with the highest plutonium body burdens failed to demonstrate any adverse health effects that are attributable to plutonium exposure. In fact, these workers manifest extremely good health and have fewer deaths than expected based on US death rates.[5] Quinquennial surveillance of these workers will continue as part of the general epidemiologic study of plutonium workers.

B. Analyses of Worker Populations at Various DOE Facilities

Although clinical studies of the most highly exposed workers yield valuable information, they have limited statistical power to associate health effects with plutonium exposure. Accordingly, a much larger effort has been initiated that considers all employees at each facility as the population at risk from plutonium exposure. Studies of disease incidence and mortality among these populations are progressing. At the present time, Rocky Flats is the only facility whose personnel and health records have been sufficiently processed to report a preliminary mortality analysis.[19] A special study of malignant melanoma incidence among current workers at Los Alamos has also been published.[20] Data from the remaining facilities are being processed and will be analyzed in the near future. Eventually, data from several facilities will be combined to yield the most precise estimates of risk associated with plutonium exposure.

C. Rocky Flats Mortality Analysis

The Rocky Flats Plant in Golden, Colorado, has produced components for nuclear weapons since its inception in 1952. Workers may be exposed while recovering plutonium and while assembling plutonium-containing systems. Exposures also may occur from external penetrating radiation, uranium, and other metals.

Results from Rocky Flats are extremely important to the assessment of plutonium- and radiation-related human health effects for several reasons. (1) This work force has the largest number of employees with measured positive plutonium body burdens. (2) The Rocky Flats analysis marks the initial epidemiologic results. (3) Rocky Flats is similar to the Hanford facility, whose work force has been the subject of many mortality analyses and much controversy.[13,18,21,22] Despite the controversy, the Hanford studies all found a correlation between radiation exposure and death from pancreatic cancer and multiple myeloma. Therefore, the analysis at Rocky Flats may attest to or detract from the generalizability of the Hanford findings.

Table VI characterizes the work force at Rocky Flats with respect to date of birth, date of hire, radiation exposure, and vital status through 1978. The distribution of birth dates indicates that the work force is still relatively young; over 50% of the workers were born after 1930 and are therefore at lower risk of death from chronic disease. The lower risk is manifest by the low mortality among cohort members (6.4%) during the study period (1951-1978). This high survival rate at Rocky Flats was not totally unexpected because the healthy worker effect is greater at younger ages and tends to diminish as the cohort ages.[23,24] However, a large healthy worker effect must be considered in interpreting this analysis. We were unable to ascertain vital status for 8% of the cohort members. Our treatment of these LTF workers and the statistical method we used to quantitate the resulting bias in this analysis are discussed in Sec. III.E.

Initial employment occurred before 1969 for more than 80% of the cohort, allowing an average of 14 years follow-up for cohort members. The distribution of cohort members by radiation exposure shows that approximately half have had a positive test for plutonium; a more detailed characterization by plutonium body burden is not available at this time. Occupational exposure to external penetrating radiation has been

TABLE VI. Selected Characteristics of Rocky Flats White Male Workers 1951-1978

Characteristic		No.	%
Date of birth	1890-1909	417	6.2
	1910-1929	2805	41.4
	1930-1949	3233	47.7
	1950+	323	4.8
	Total	6778	100.1
Vital status	Alive	5779	85.3
	Dead	431	6.4
	Unknown	568	8.4
Date of hire	1951-1959	2201	32.5
	1960-1969	3414	50.4
	1970-1978	1163	17.2
Plutonium exposure	Any	3157	46.6
	None	3621	53.4
External radiation (rem)	0	888	13.1
	0-1	2715	40.1
	1-5	1937	28.6
	5-10	579	8.5
	10+	659	9.7
	Mean		3.4

recorded for 86.2% of the cohort, with most of these exposures at very low levels; only 17.5% exceeds 5 rem.

Table VII characterizes those workers employed at least 2 years and those employed less than 2 years. Longer term workers are older, as evidenced by the higher percentage born before 1930. Differences in radiation exposure are even more striking: more than 67% of longer term workers and only 16% of shorter term workers have had positive plutonium tests. Similarly, for external radiation exposure, 45% of longer term workers have had at least 1 rem of cumulative exposure, whereas only 7.5% of shorter term workers have reached this exposure level. Mean external radiation exposures for the two groups are 4.46 rem and 0.28 rem, respectively.

These differences between workers based on a 2-year length of employment criterion provide a rationale for separating them in the analysis. Gilbert cited similar differences and the improbability of shorter term workers receiving meaningful exposures as reasons for restricting her analysis at Hanford to longer term workers.[13] Transient workers also have higher mortality than do more stable employees, as poor health is often related to transiency. We considered this possiblility among Rocky Flats workers by comparing directly age-adjusted mortality rates from all causes of death for longer versus shorter term workers. Data in Table VIII show that age-adjusted mortality was significantly higher among shorter term workers. Examination of age-specific rates reveals that this difference was especially marked in the two age groups from 45 to 49 and from 50 to 54. For these reasons, we restricted further analysis to workers with at least 2 years of continuous employment.

In evaluating employee mortality at Rocky Flats, we have tried to adhere to an underlying biological model consistent with the known physiologic properties of plutonium. This model directs our attention to diseases in anatomical sites that accumulate plutonium or have been related previously to external radiation exposure. Use of a biological model limits chance associations of non-causally associated variables. However, at Rocky Flats a previous, unpublished report of excess brain cancers among workers caused concern, so we included brain cancers and benign tumors of the central nervous system (CNS) in our analysis.

Tabulation of observed and expected deaths from particular causes and statistical analysis of their ratio (that is, the SMR) were accomplished by the Monson program.[25] In Table IX, the numbers of deaths from all cases, all malignant neoplasms, and lung cancer are significantly fewer than expected. Deaths from cancer of the liver, brain, pancreas, and leukemia do not differ significantly from the expected; no deaths were due to bone cancer. We did find a statistical excess of benign CNS tumors; 6 deaths were observed, whereas only 1.5 were expected. The combined category of brain cancer and benign CNS neoplasms has an associated SMR of 217, which is significantly elevated [95% Confidence Interval (CI) 112-380].

Table X gives the SMRs for the same causes of death, allowing 5, 10, and 15 years from initial employment for cancer induction. These time intervals allow comparative mortality evaluation without relating observed and expected events occurring too soon after employment to be related to workplace exposure. If a causal relationship exists between a particular cancer and an occupational exposure, the highest SMR should result at the modal

TABLE VII. Selected Characteristics of Rocky Flats White Male Workers by Length of Employment

Characteristic		Length of Employment			
		<2 years		≥2 years	
		No.	%	No.	%
Date of birth	1890-1909	74	4.0	343	7.0
	1910-1929	548	29.5	2257	45.9
	1930-1949	1040	55.9	2193	44.6
	1950-1969	197	10.6	126	2.5
Vital status	Alive	1532	82.4	4253	86.5
	Dead	94	5.1	331	6.7
	Unknown	233	12.5	335	6.8
Date of hire	1951-1959	313	16.8	1888	38.4
	1960-1969	974	52.4	2440	49.6
	1970-1978	572	30.8	591	12.0
Plutonium exposure	Any	298	16.0	3323	67.6
	None	1561	84.0	1596	32.4
External radiation (rem)	0	673	36.2	215	4.4
	0-1	1049	56.4	1666	33.9
	1-5	130	7.0	1807	36.7
	5-10	5	0.3	574	11.7
	10+	2	0.1	657	13.4
	Mean		0.3		4.7

value for the cancer induction period.[26] However, if no relationship exists, the highest SMR will occur at the modal time from first employment till death from that particular cause.

The results of this analysis are consistent with our previous results: mortality from all causes is significantly less frequent than expected for all three induction periods, as is lung cancer mortality for the first two periods. The SMR for benign CNS tumors is significantly elevated for the 10- and 15-year periods, whereas the aggregate category for brain cancer and CNS tumors is elevated for all three periods (95% CIs 101-387, 124-515, 150-771, respectively). SMRs for the remaining causes of death are not significantly elevated and tend to increase slightly with a longer allowance for cancer induction. These slight increases are typical in analyses that allow for cancer induction because as the interval increases an older segment of the cohort is sampled and the survival advantage of working populations (that is, the healthy worker effect) decreases with age.[23,24]

We have been processing yearly radiation exposure data for Rocky Flats workers to enable analysis by radiation dose. These data will soon be available. In our preliminary report on Rocky Flats workers' mortality, we used cumulative exposure history as a measure to dichotomize the cohort for plutonium at 1 μCi/day and at 100 mrem for external radiation. Results from this analysis are pertinent to assessing the cancer risk at Rocky Flats associated with occupational radiation exposure.

SMRs for workers with plutonium exposure exceeding 1 μCi/day through 1978 are shown in Table XI. The number of observed deaths is significantly low for all causes of death, all malignant neoplasms, and lung cancer. There were no cancers of the pancreas, bone, brain, or thyroid and only one liver cancer (versus 0.79

TABLE VIII. All Causes Mortality Rates per 1000 Person Years for White Males by Length of Employment

Age	Length of Employment <2 years Rate	≥2 years Rate	Rate Ratio
20-24	0.62	0.00	---
25-29	0.76	1.10	0.69
30-34	1.10	0.80	1.38
35-39	2.67	1.52	1.76
40-44	1.69	2.00	0.85
45-49	8.55	3.50	2.44
50-54	9.70	5.90	1.64
55-59	11.95	10.23	1.17
60-64	22.32	18.91	1.18
65-69	41.09	26.42	1.56
70-74	26.98	44.09	0.61
75+	63.69	111.54	0.57
Age-adjusted rate	6.57	4.92	1.33
Standard error	0.67	0.26	

expected). Mortality from benign and unspecified neoplasms was not statistically more frequent than expected. Overall, plutonium exposure does not seem an important cancer risk factor for workers at this time.

Comparative mortality among workers with cumulative external radiation exposure exceeding 100 mrem is analyzed in Table XII. Again, deaths were significantly fewer than expected from all causes, all malignant neoplasms, and lung cancer. Observed deaths for the other types of cancer were consistent with the expected; only benign and unspecified neoplasms caused significantly more deaths than expected. The SMR for brain cancers and benign neoplasms combined was also significantly elevated (95% CI 125-424). More detailed analyses are necessary to determine if this excess is causally related to external radiation exposure.

D. Evaluation of Brain Cancer Cases and Controls

To evaluate occupational and personal factors that may be associated with the excess of benign CNS tumors and possibly brain cancer, we initiated a case control study. We are particularly interested in examining the radiation exposure history of study subjects and possible exposure to certain solvents known to cause brain cancer. Preliminary analyses indicate that cancer cases have not had higher exposure to plutonium or external penetrating radiation. Also, no unusual clustering seems to occur within a specific time period for diagnosis or hire date. We are continuing to analyze these data with particular attention to specific occupations and related nonradiation exposures. However, the cases are well distributed among occupational groups, a fact that argues against a common etiologic exposure.

TABLE IX. SMRs for Selected Causes for White Males Employed at Least 2 Years

Cause (ICD)[a]	Observed	Expected	SMR	95% CI
All causes (1-998)	334	522.44	64	57-71
All malignant neoplasms (140-209)	79	105.02	75	60-94
Lung cancer (162,163)	22	35.90	61	38-93
Liver cancer (155,156)	3	1.75	171	34-500
Bone cancer (196)	0	0.54	0	0-674
Brain cancer (191,192)	6	4.04	149	54-324
Benign CNS neoplasms (210-235)	6	1.49	405	148-881
Pancreatic cancer (157)	4	5.73	70	19-179
Leukemia (204-207)	5	4.26	117	9-286

[a]According to the eighth revision of the International Classification of Diseases (ICD).

TABLE X. SMRs for White Males Employed at Least 2 Years by Different Induction Periods

Cause (ICD)	5 Years			10 Years			15 Years		
	Observed	SMR	95% CI	Observed	SMR	95% CI	Observed	SMR	95% CI
All causes (1-998)	311	67	60-75	256	74	65-84	155	74	63-87
All malignant neoplasms (140-209)	76	80	63-100	64	87	67-111	45	97	71-130
Lung cancer (162,163)	20	60	37-93	15	57	32-94	9	54	24-102
Liver cancer (155,156)	3	192	39-560	3	259	52-757	2	289	32-1044
Brain cancer (191,192)	6	172	63-375	5	206	66-481	4	293	79-751
Benign CNS neoplasms (210-239)	4	316	85-809	4	451	121-1156	3	585	118-1708
Leukemia (204-207)	5	135	44-315	5	187	60-436	4	249	67-638
Pancreatic cancer (157)	4	76	21-195	3	74	15-215	2	78	9-281

E. Assessment of LTF Bias in Rocky Flats Preliminary Analysis

One unanswered question in most occupational mortality studies is whether the results would have differed if vital status were known for workers LTF. Particularly, when the cause of death under study is a rare disease like cancer, a few missed cancers among the LTF may change study results.

Workers LTF are commonly treated in one of two ways. All can be considered alive at the end of the study period, which underestimates mortality if any missing cohort members are dead. A more common technique removes these workers from the analysis as soon as they become lost (typically employment termination date). The effect of this treatment is less certain because the LTF group may have a more or less favorable mortality experience than the remaining work force. However, this treatment does allow an unbiased estimate of comparative mortality for those of known vital status. We propose a third alternative that tries to obtain a valid result for the entire cohort. This method involves sampling the LTF to obtain an estimate of cumulative mortality. Confidence limits can be placed around the LTF mortality estimate, as best and worst case estimates. Mortality can then be simulated at these levels for the remaining LTF and combined with the life-table analysis for the entire cohort.

We applied these three techniques to our preliminary analysis at Rocky Flats to illustrate the effect of simulated LTF mortality. We estimated mortality among the LTF workers (N = 727) by tracing a 25% random

TABLE XI. SMRs for Rocky Flats White Males Employed 2 or More Years and Exposed to ≥1 μCi/Day Cumulative Plutonium

Cause (ICD)	Observed	Expected	SMR	95% CI
All causes (1-998)	75	197.08	38	30-48
All malignant neoplasms (140-209)	14	39.45	35	19-60
Liver cancer (155,156)	1	0.60	167	2-929
Pancreatic cancer (157)	0	2.11	0	0-174
Lung cancer (162,163)	1	13.83	7	0-40
Bone cancer (196)	0	0.21	0	0-1735
Brain cancer (191,192)	0	1.73	0	0-212
Thyroid cancer (193)	0	0.08	0	0-4356
Leukemia (204-207)	1	1.63	61	1-340
Benign and unspecified neoplasms (210-239)	1	0.60	167	2-931

TABLE XII. SMRs for Rocky Flats White Males Employed 2 or More Years and Exposed to ≥100 mrem External Radiation

Cause (ICD)	Observed	Expected	SMR	95% CI
All causes (1-998)	257	456.29	56	50-64
All malignant neoplasms (140-209)	61	91.93	66	51-85
Liver cancer (155,156)	3	1.50	200	40-584
Pancreatic cancer (157)	3	4.99	60	12-175
Lung cancer (162,163)	19	31.69	60	36-94
Bone cancer (196)	0	0.48	0	0-767
Brain cancer (191,192)	6	3.63	165	60-360
Thyroid cancer (193)	0	0.19	0	0-1898
Leukemia (204-207)	4	3.73	107	29-275
Benign and unspecified neoplasms (210-239)	6	1.31	458	167-996

sample (N = 187) to determine their vital status. A total of 159 workers (85%) was located, among whom 7 or 4.4% (95% CI 2.1—8.8%) were dead. The upper 95% CI of 8.8% was considered the worst case estimate of LTF mortality.

We created a study file of all remaining LTF workers. Those successfully traced as part of the sample were combined with the file of employees of known vital status. The time between the individual LTF employee termination date and the end-of-study date was considered the period at risk of death. LTF individuals were randomly selected to be dead by generating a random number between 0.00 and 1.00. If the random number was less than the percentage of LTF assumed dead, the individual worker was considered to have died. The specific cause of death was similarly randomly assigned according to the percentage distribution of deaths in the total cohort. We randomly assigned a death date for these cases that was equally probable from employment termination date to the end of the study date. In this way, all LTF members were designated alive or dead, and those considered dead were assigned a specific cause of death and a death date. This file was then combined with the total cohort file.

We tabulated the numbers of observed and expected deaths (based on national death rates), SMRs, and approximate 95% CIs with the Monson program.[26] The conditions imposed on the LTF group were varied from all living to 100% dying subsequent to their employment termination.

The LTF subcohort is described in Table XIII. The 568 white males in this group had an average age at hire of 29, which is 4 years younger than the total cohort. The mean age at employment termination was 34, compared with 42 for the total cohort. This information indicates that many of those LTF worked at Rocky Flats for a short period early in their lives. Their young average age at termination suggests that this employment will not be their primary lifetime occupation. Their mean year at entry was similar to the total cohort, and they contribute roughly 10% of total employee time. However, if we simulate 100% mortality among LTF workers (as some suggest), this will more than double the number of deaths reported for the entire cohort. Clearly then, the most relevant comparisons involve simulated LTF mortality in the range of 0 through 10%.

Table XIV compares mortality for selected causes of death for the entire cohort when mortality among LTF

TABLE XIII. Selected Characteristics of LTF Employees 1951-1978

LTF	568
Mean age at entry	29
Mean year of entry	1963
Mean age employment termination	34
Total person years	9429
Person years (5 years after employment)	6599
Person years (10 years after employment)	3769

TABLE XIV. Rocky Flats White Males—Mortality From Selected Causes Assuming Various Percentages (LTF) Dead 1951-1978

Cause of Death (ICD)	% LTF[a]	Observed	Exposed	SMR	95% CI
All causes (1-998)	0[b]	425	692.94	61	56-67
	0[c]	425	666.56	64	58-70
	5	449	667.00	67	61-74
	10	483	667.69	72	66-79
	25	549	669.06	82	75-89
	50	695	671.44	104	96-111
	75	838	673.97	124	116-133
	100	987	677.28	146	137-155
All cancer (140-209)	0[b]	101	136.05	74	60-90
	0[c]	101	131.24	77	63-94
	5	107	131.31	81	67-98
	10	116	131.42	88	73-106
	25	133	131.65	101	85-120
	50	169	132.03	128	109-149
	75	204	132.42	154	134-177
	100	234	133.00	176	154-200
Lung cancer (161,162)	0[b]	30	45.90	65	44-93
	0[c]	30	44.28	68	46-97
	5	32	44.30	72	49-102
	10	35	44.33	79	55-110
	25	38	44.40	86	61-117
	50	43	44.51	97	70-130
	75	56	44.63	125	95-163
	100	61	44.81	136	104-175
Brain cancer (191,192)	0[b]	8	5.53	145	62-285
	0[c]	8	5.26	152	65-299
	5	8	5.27	152	65-299
	10	8	5.28	152	65-299
	25	11	5.29	208	104-372
	50	15	5.31	282	158-466
	75	17	5.34	318	185-510
	100	20	5.37	372	227-575
Leukemia, aleukemia (204-207)	0[b]	6	5.78	104	38-226
	0[c]	6	5.54	108	40-236
	5	6	5.54	108	40-236
	10	7	5.55	126	51-260
	25	7	5.56	126	50-259
	50	10	5.59	179	86-329
	75	12	5.61	214	110-374
	100	18	5.64	319	189-504

[a]Per cent of LTF simulated to have died.
[b]LTF considered alive at the end of the study.
[c]LTF dropped from analysis at employment termination.

employees is simulated at several levels between 0 and 100%. Comparing the first two rows illustrates the difference between treating LTF as living or as lost at employment termination. The respective SMRs will always be lower in the former instance because those LTF are effectively "immortal" starting at their employment termination date. This difference is trivial if the SMR is based on many deaths or if those LTF are a small percentage of the total cohort. For example, the all causes mortality SMR of 61 increases slightly to 64 when LTF workers are considered lost at employment termination. There is also an accompanying shift in the 95% CI. Small increments of the SMRs and 95% CIs also occur for all malignant neoplasms and lung cancer. Slightly larger changes are affected for the less frequent causes of death, brain cancer and leukemia. However, the extent of these differences would not change any conclusions that were based on the assumption that all those LTF were living at the end of the study date.

The 5% row in Table XIV corresponds closely to our point estimate of LFT cumulative mortality (that is, 4.4%). The results of this simulation for all causes of death, all malignant neoplasms, lung cancer, brain cancer, and leukemia are remarkably consistent with the estimates generated by counting those LTF as lost at their employment termination. Accordingly, comparative mortality estimates in rows 1 and 2 appear relatively unbiased by LTF for these cause of death categories.

The data in Table XIV are presented graphically in Figs. 1-5, illustrating the effect of mortality simulated beyond our worst case assumption (that is, exceeding 8.8% cumulative LTF mortality). There are two possible frameworks for considering these data. First, we can determine the approximate LTF mortality necessary to change our basic conclusions from rows 1 or 2 of either lesser or no greater mortality than expected. Alternatively, these data also indicate the extent of mortality in excess of that worst case estimate necessary to reverse our conclusions.

For the all causes of death category, our conclusion of fewer than expected deaths is supported until nearly 40 of the LTF are simulated to have died, which is more than four times our worst case estimate. LTF mortality of approximately 50% supports the conclusion that mortality among the total cohort is not different from the expected mortality. More than 60% of the LTF need to be dead for our original conclusion to be untenable.

Estimates of comparative mortality for the remaining cause of death categories are more sensitive to mortality among LTF employees. Our conclusion of fewer than expected deaths from malignant neoplasms appears valid in the range of our worst case estimate. LTF mortality simulated between 25 and 40% would not suggest mortality in excess of that expected. Mortality in excess of 40% would support the conclusion of more deaths than expected from malignant neoplasms.

Our conclusion of fewer lung cancer deaths than expected would change if more than 4.4% (our point estimate) of those LTF were dead. A conclusion of mortality not different than expected is supported by simulations between 5 and 85%. Nearly 100% of the LTF must have died to reverse our original conclusion.

Our simulations for brain cancer and the leukemias support our earlier conclusion of mortality consistent with that expected. For brain cancer, LTF mortality three times our worst case assumption is necessary to change our conclusion. Our conclusion for the leukemias appears even more stable; mortality exceeding seven times our worst case estimate is required to reverse it.

These results suggest that LTF mortality is unlikely to be a meaningful bias in this analysis. This conclusion appears justified even in the event of extremely high mortality among LTF workers. However, this analysis does not suggest that mortality among workers LTF is not an important potential bias in occupational mortality studies. Rather, it indicates for this cohort, characterized by young average age and fewer deaths than expected for most causes, that even extreme mortality among those LTF does not noticeably affect estimates of cohort mortality.

This technique should prove useful for evaluating potential LTF bias in other occupational cohorts, especially in preliminary analyses when the number of workers LTF may be high. Considerable time and money can be saved by tracing a random sample of those LTF and simulating mortality for the remaining LTF group based on their experience. Concurrence between this analysis and those based on the entire cohort would suggest that LTF mortality would not change study results appreciably. However, disagreement would indicate the importance of more intensive tracing of workers LTF before final results are reported.

F. Malignant Melanoma Incidence at Los Alamos National Laboratory

As part of our continuing study of Los Alamos workers, we recently published a study of malignant melanoma incidence among workers employed between

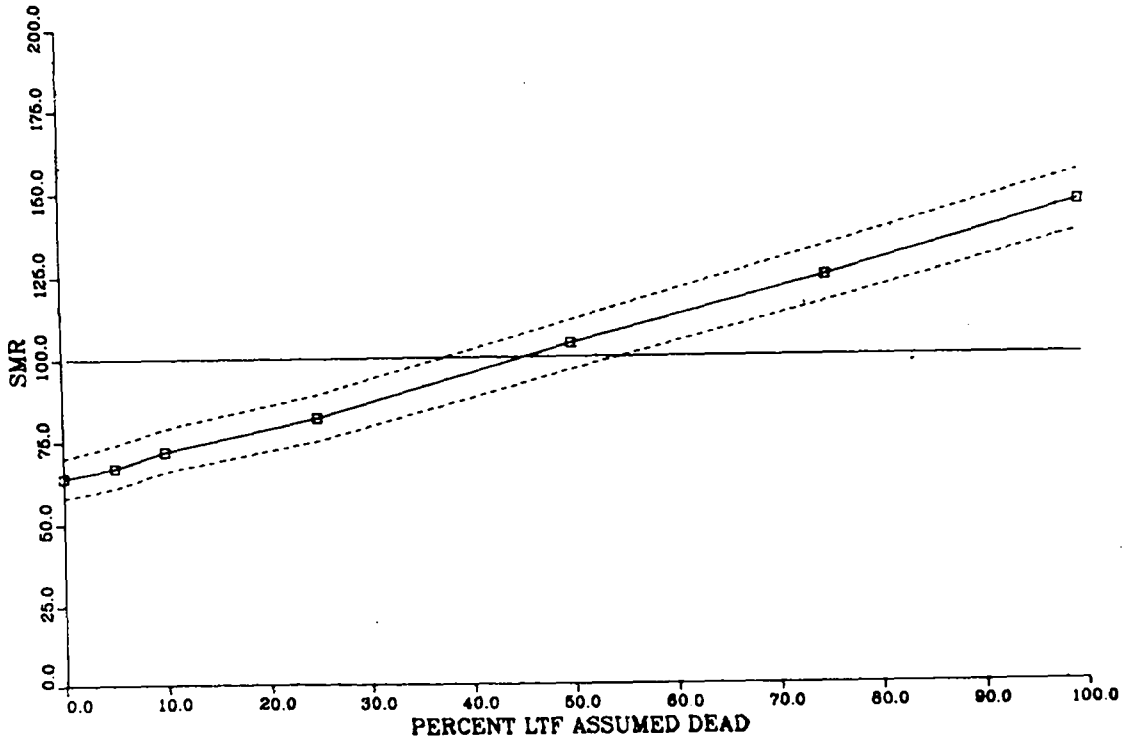

Fig. 1. SMRs and 95% CIs for all causes of death.

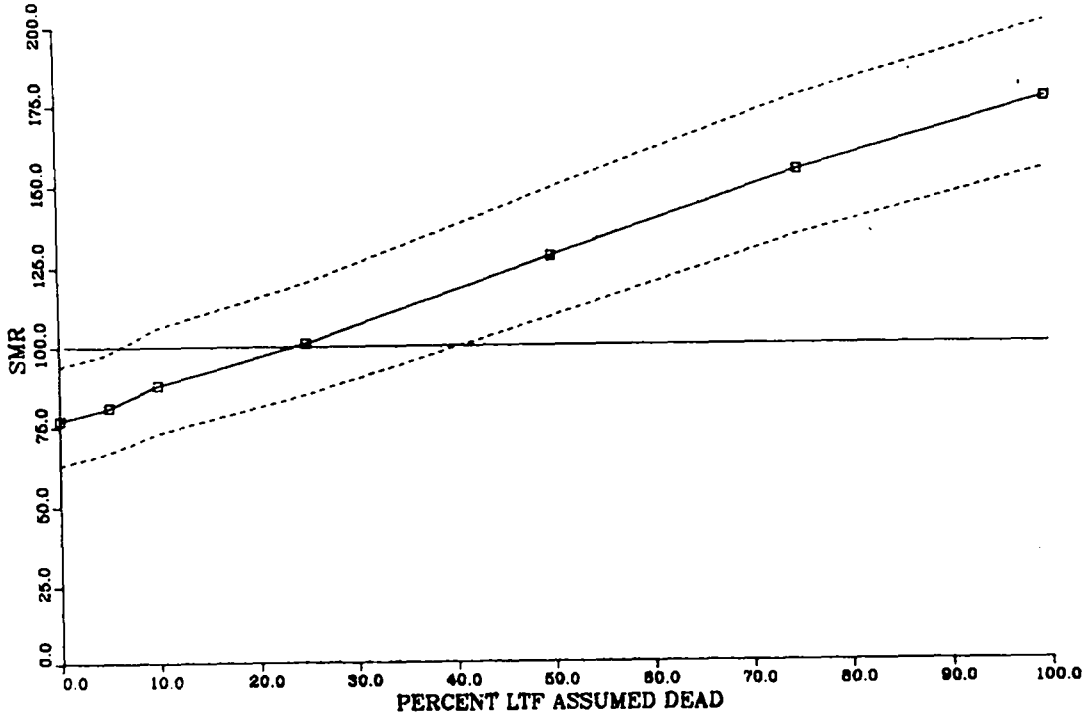

Fig. 2. SMRs and 95% CIs for all cancers.

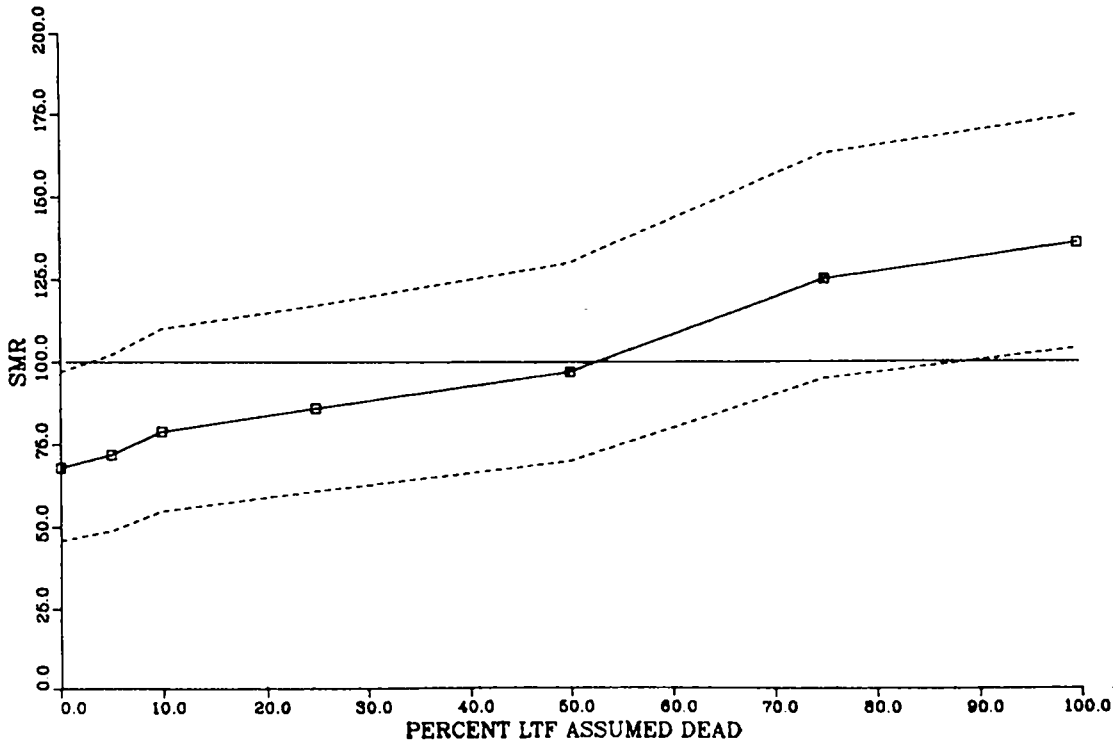

Fig. 3. SMRs and 95% CIs for lung cancer.

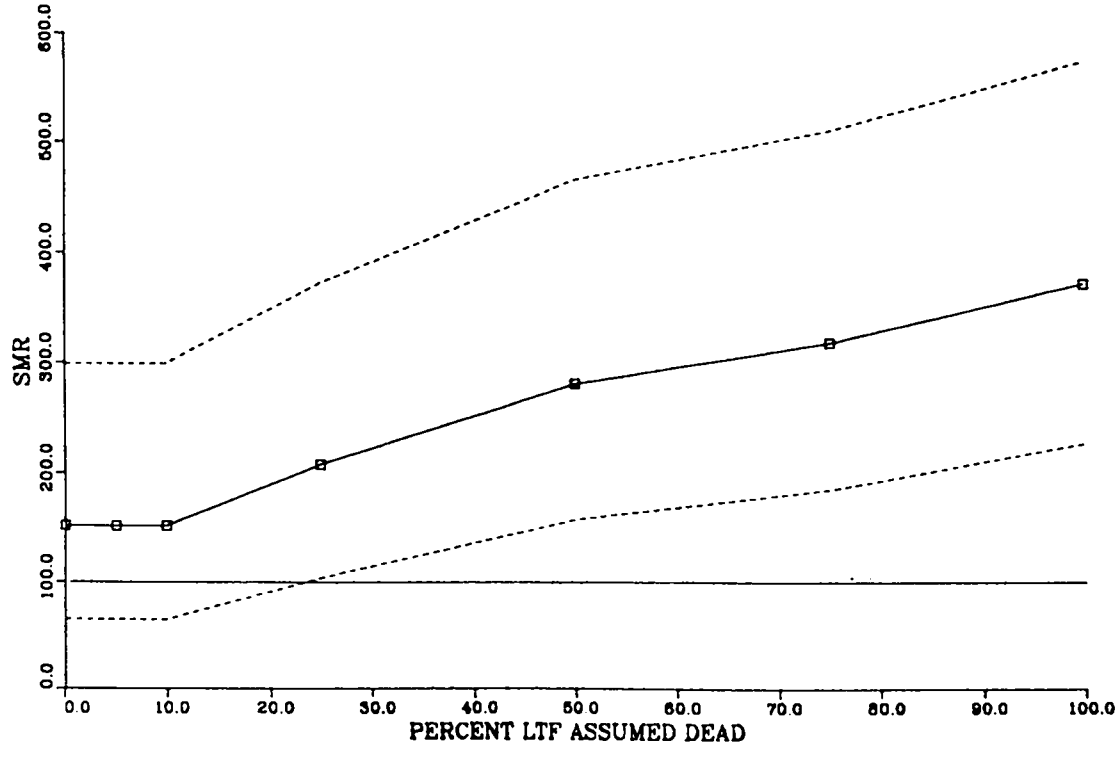

Fig. 4. SMRs and 95% CIs for brain cancer.

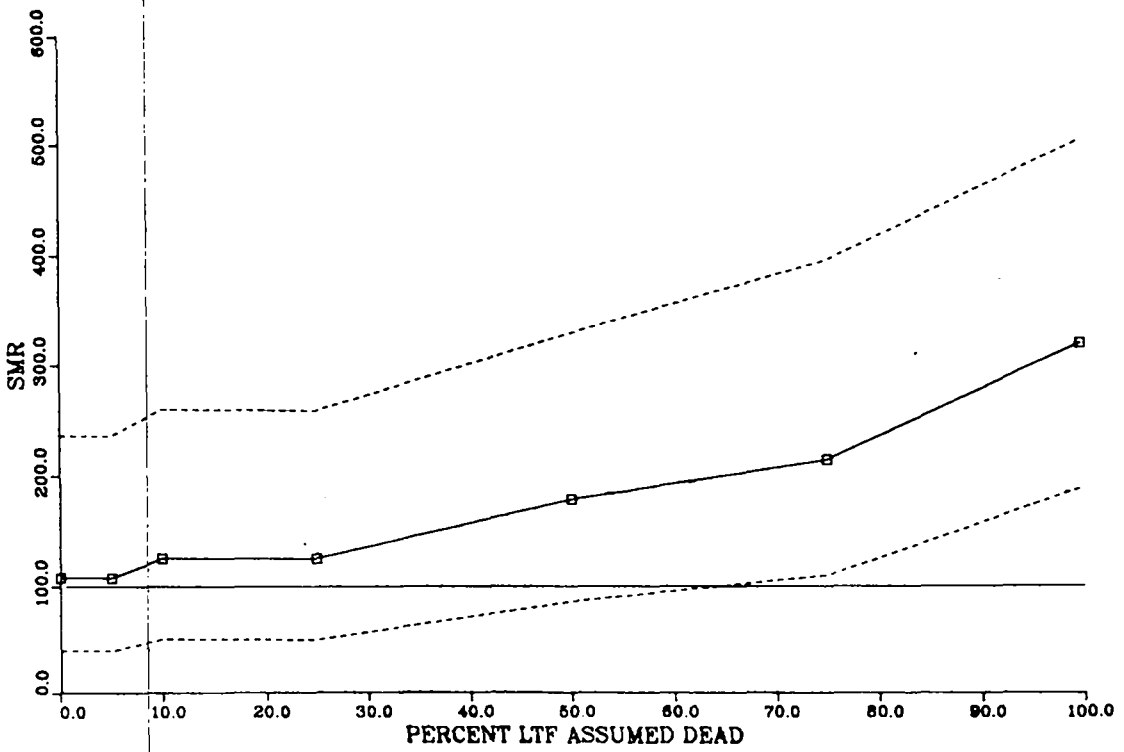

Fig. 5. SMRs and 95% CIs for leukemia, aleukemia.

1969 and 1978.[20] This study was prompted by a reported threefold excess of melanoma incidence at the Lawrence Livermore National Laboratory (LLNL).[27] At LLNL 19 cases of melanoma occurred between 1972 and 1977; only 6.14 were expected (SIR = 297; 95% CI 179-464). A case control analysis suggested that significantly more melanoma occurred among chemists than occurred among workers in other employment categories. However, monitored radiation exposure was not associated with these melanoma cases.

Our study of melanoma incidence found six cases between 1969 and 1978. This finding was similar to the 5.68 cases expected, resulting in a standardized incidence ratio (SIR) of 105. The associated 90% CI ranged from 51 to 198 and does not suggest either a deficit or an excess of malignant melanoma in this cohort.

Table XV summarizes the distribution of person years and the observed and expected cases for the total cohort, which is further broken down into four subgroups, specific for sex and ethnicity (non-Hispanic or Hispanic).

TABLE XV. Distribution of Observed and Expected Incident Cases of Malignant Melanoma 1969-1978

	Observed Cases	Expected Cases	SIR	Exact 90% CI	Exact 1-Sided p-Value
Non-Hispanic men	3	4.39	68	23-163	0.27
Non-Hispanic women	2	1.00	200	49-569	0.17
Hispanic men	1	0.23	433	22-1780	0.12
Hispanic women	0	0.07	0	0-4219	0.47
Total	6	5.69	105	51-198	0.42

The largest subgroup, non-Hispanic males, had 3 cases versus the 4.39 expected. The SIR of 68 and the 90% CI (23-163) give no indication that melanoma incidence is different from that expected. Less data were available to evaluate melanoma incidence in the remaining subgroups. Accordingly, statistical estimates of comparative incidence vary too much to allow any conclusions. However, there were few cases in these groups, which gave no hint of unusually frequent melanoma incidence. Comparison of directly age-adjusted melanoma incidence rates with rates for New Mexico (Table XVI) gave similar results for the total cohort and all four subgroups.

Table XVII details the year of diagnosis, age at diagnosis, occupation, and histological characteristics of the six melanoma cases. Interestingly, the three non-Hispanic male cases were professional researchers, both non-Hispanic females were secretaries, and the Hispanic male case was a truck driver. This employment pattern is consistent with the predominant occupations for these subgroups at Los Alamos over the study period. This distribution of cases by age, anatomical site, and invasive character is not unusual and is consistent with the LLNL report.[27]

Although these results do not suggest an association between melanoma incidence and employment at Los Alamos, some of the cases identified possibly may be related to occupational risk factors. Evidence from LLNL that cases were more frequently employed as chemists than were controls supported this possibility. We evaluated this and other risk factors by conducting a case control study of all known present and former Los Alamos employees who had been diagnosed as having malignant melanoma.[28] This investigation's goal was to identify potential occupational factors that might induce melanoma, including exposure to plutonium, external radiation, chemicals, and ultraviolet light. We also considered personal characteristics that could be obtained from personnel records.

We identified 15 male and 5 female cases who had worked at least one continuous year at Los Alamos. Four controls were matched to each case by sex, ethnicity, birth date, and date of first employment at Los Alamos. We obtained personnel and health physics records for all study subjects and abstracted data on primary job title, personal factors, and radiation exposure history. The last included plutonium body burden and exposure to beta, gamma, and neutron forms of external radiation.

We did not find any differences between male cases and controls for any type of radiation exposure as indicated by t-tests for beta ($t_{14} = -1.34$, $p = 0.20$), gamma ($t_{14} = 0.16$, $p = 0.88$), or neutron exposures ($t_{14} = -0.12$, $p = 0.91$), and plutonium body burden ($t_{14} = -0.41$, $p = 0.65$). Table XVIII presents the median value for cases and controls exposed to more than 0.10 rem cumulative external radiation or 2 nCi plutonium and the related tests for association. These data illustrate the absence of exposure among all female and most male subjects. Accordingly, our investigation indicated no association between malignant melanoma and any monitored form of radiation exposure.

Contingency table analyses for personal characteristics, summarized in Table XIX, show that male cases had college educations or graduate degrees more often than did controls. There was no similar

TABLE XVI. Age-Adjusted Malignant Melanoma Incidence Rates (Per 100 000 Person Years) for Los Alamos National Laboratory Employees and New Mexico 1969-1978

	Los Alamos			New Mexico		
	No.	Rate	SE[a]	No.	Rate	SE[a]
Non-Hispanic men	3	5.96	3.44	93	10.72	0.76
Non-Hispanic women	2	16.17	11.68	87	11.39	0.77
Hispanic men	1	4.99	4.98	5	0.86	0.29
Hispanic women	0	0.00	0.00	9	0.21	0.35
Total	6	7.20	2.95	192	7.53	0.35

[a]Standard error of the age-adjusted rate.

TABLE XVII. Malignant Melanoma Cases at Los Alamos National Laboratory 1969-1978

Subgroup	Year	Age	Occupation	Site	Invasive
Non-Hispanic male	1969	56	Physicist	Trunk	Yes
Non-Hispanic male	1972	35	Chemist	Trunk	Yes
Non-Hispanic male	1976	43	Engineer	Arm	Yes
Non-Hispanic female	1977	40	Secretary	Leg	No
Non-Hispanic female	1978	53	Secretary	Trunk	No
Hispanic male	1972	45	Truck driver	Trunk	Yes

association among females. Male cases were also more likely to be employed in a professional capacity, a finding consistent with having advanced educations. No significant association with employment as a chemist or a physicist existed for either males or females.

To further evaluate the suggestive association for education, we used the Mantel-extension test for linear trend to determine whether melanoma risk increased with increasing educational level (Table XX).[29] We found that standardized rate ratios (SRRs) increased with increasing educational attainment. College graduates had a SRR of 2.11, and those with graduate degrees had the highest SRR of 3.11. The Mantel-extension probability ($p = 0.038$) suggests a significant association with increasing educational attainment.

These results indicate that occupational factors are not related to melanoma incidence at the Los Alamos National Laboratory. Particularly, we did not uncover an association with specific job titles nor with any monitored form of radiation. The association between melanoma and increasing educational attainment points to personal factors, common to highly educated persons, as likely etiologic agents for malignant melanoma at Los Alamos.

TABLE XVIII. Analysis of Radiation Exposures for Melanoma Cases and Controls

Cumulative Radiation	Median Exposed Cases[a]	No. Exposed	Median Exposed Controls	No. Exposed	t_{14}	Odds Ratio	95% CI[b]
			MALES				
Beta	0.97	4	0.89	15	–1.34	1.09	0.30-3.98
Gamma	3.17	4	0.66	18	0.16	0.85	0.24-3.05
Neutron	---	0	0.40	2	–0.12	0.00	---
Total external radiation	1.25	6	1.81	21	–0.19	1.24	0.39-2.98
Plutonium	---	0	6.52	2	–0.41	0.00	---
			FEMALES				
Total external radiation	---	0	0.16	1	---	0.00	---
Plutonium	---	0	---	0	---	0.00	---

[a]Exposed is defined as 0.10 rem cumulative exposure for beta, gamma, or neutron radiation and 2 nCi for plutonium.

[b]Test-based confidence interval for the odds ratio.

TABLE XIX. Analysis of Occupational and Personal Characteristics of Male Cases

Variable	No. of Cases	Odds Ratio	95% CI
Job title			
Chemist	1	1.00	[b]
Physicist	3	1.42	0.33-6.07
Education[a]			
College degree	8	2.82	0.87-9.16
Graduate degree	6	2.75	0.81-9.23

[a]Education unknown for one case and four controls.
[b]Test-based CI could not be calculated.

IV. FUTURE EFFORTS

Future efforts will be directed toward reporting mortality analyses from Rocky Flats, Mound Facility, Savannah River, and Los Alamos. Radiation exposure will be considered in detail at each facility and at all facilities collectively. Nested case control studies will be used to evaluate significant elevations of specific diseases at individual facilities and for the total study population. This approach is being employed, a priori, to study the possible association between plutonium body burden and lung cancer at Rocky Flats, Savannah River, and Los Alamos. More than 300 cases will be included, and next-of-kin interviews will be conducted for cases and controls to determine their smoking and employment histories. Plutonium body burden, external radiation exposure, and smoking history will be considered individually and simultaneously to determine if plutonium exposure is a risk factor for cases. The possibility of a synergistic relationship between plutonium, external radiation, and smoking will be evaluated. Occupational categories and related nonradiation exposures will also be considered.

Concurrently, we will launch a study of disease incidence among the 5 000 most highly exposed plutonium workers and a sample of 20 000 unexposed cohort members. This study will supplement the occupational mortality studies and allow investigation of plutonium as a cause of less fatal cancers and other health effects. It will also allow collection of information on important disease covariates. We now are waiting for Office of Management and Budget (OMB) clearance for a telephone interview schedule that will be used in this study. Interviewing will begin after OMB approval and will continue for several years.

These efforts should increase our understanding of the human biological effects of plutonium. In view of the increasing importance of plutonium as a power source for energy and weapons development, this evaluation takes on added importance. Further, we believe these studies will provide important information for assessing the human cancer risk associated with low-level radiation exposures.

TABLE XX. Standardized Risk Ratios (SRRs) and Mantel-Extension Trend Test for Education

Education Level	Cases	Controls	SRRs
College degree	6	38	1.00
College degree	2	6	2.11
Graduate degree	6	12	3.17
Total[a]	14	56	
Mantel Linear Trend test, p = 0.038			

[a]Education unknown for one case and four controls.

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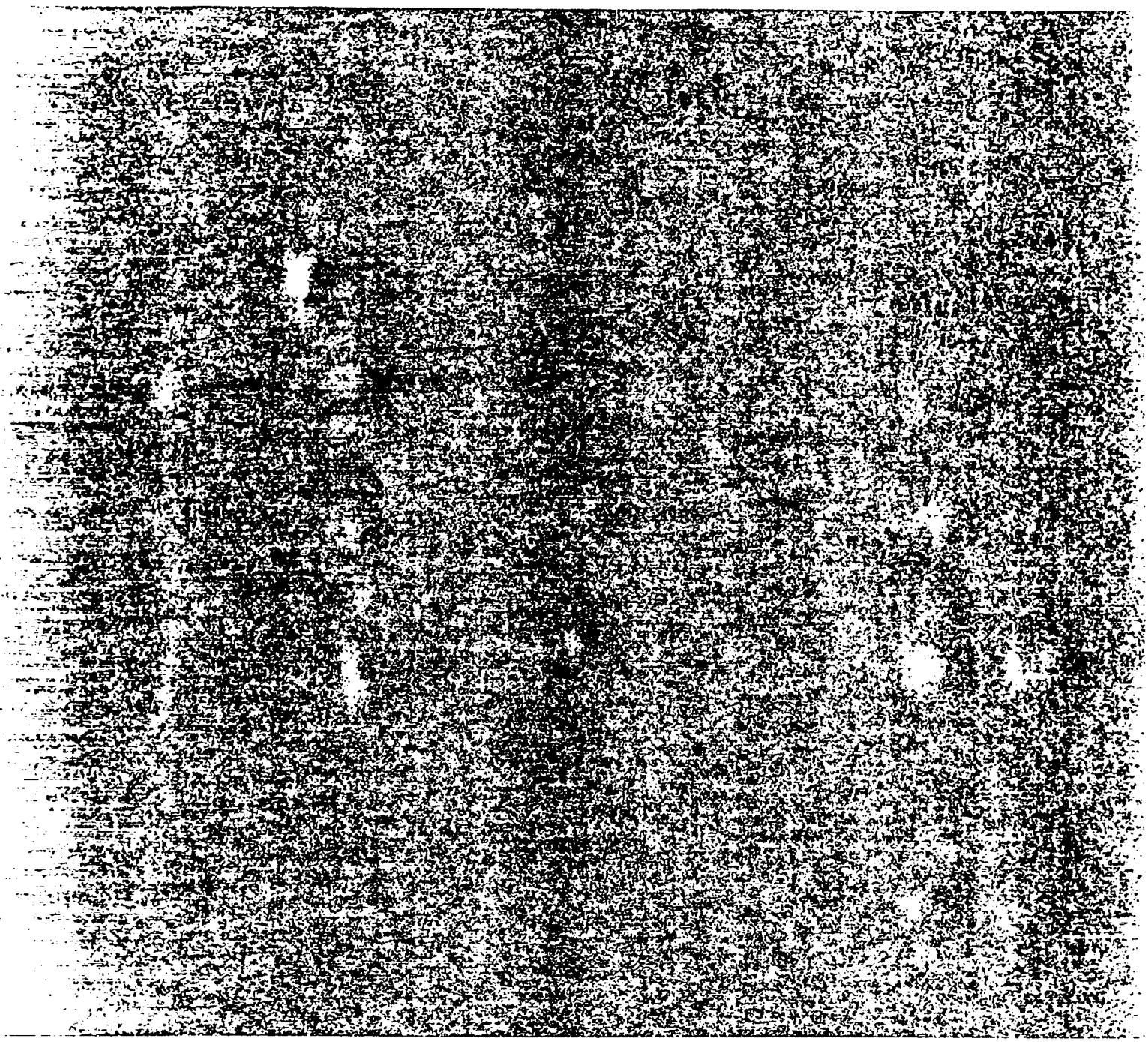

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