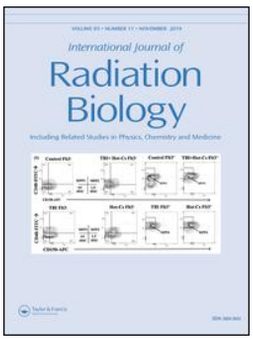

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ORIGINAL ARTICLE

Mortality among workers at the Los Alamos National Laboratory, 1943–2017

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ABSTRACT

Background: During World War II (WWII), the Manhattan Engineering District established a secret laboratory in the mountains of northern New Mexico. The mission was to design, construct and test the first atomic weapon, nicknamed 'The Gadget' that was detonated at the TRINITY site in Alamogordo, NM. After WWII, nuclear weapons research continued, and the laboratory became the Los Alamos National Laboratory (LANL).

Materials and methods: The mortality experience of 26,328 workers first employed between 1943 and 1980 at LANL was determined through 2017. Included were 6157 contract workers employed by the ZIA Company. Organ dose estimates for each worker considered all sources of exposure, notably photons, neutrons, tritium, ^{238}Pu and ^{239}Pu. Vital status determination included searches within the National Death Index, Social Security Administration and New Mexico State Mortality Files. Standardized Mortality Ratios (SMR) and Cox regression models were used in the analyses.

Results: Most workers (55%) were hired before 1960, 38% had a college degree, 25% were female, 81% white, 13% Hispanic and 60% had died. Vital status was complete, with only 0.1% lost to follow-up. The mean dose to the lung for the 17,053 workers monitored for radiation was 28.6 weighted-mGy (maximum 16.8 weighted-Gy) assuming a Dose Weighting Factor of 20 for alpha particle dose to lung. The Excess Relative Risk (ERR) at 100 weighted-mGy was 0.01 (95%CI −0.02, 0.03; $n = 839$) for lung cancer. The ERR at 100 mGy was −0.43 (95%CI −1.11, 0.24; $n = 160$) for leukemia other than chronic lymphocytic leukemia (CLL), −0.06 (95%CI −0.16, 0.04; $n = 3043$) for ischemic heart disease (IHD), and 0.29 (95%CI 0.02, 0.55; $n = 106$) for esophageal cancer. Among the 6499 workers with measurable intakes of plutonium, an increase in bone cancer (SMR 2.44; 95%CI 0.98, 5.03; $n = 7$) was related to dose. The SMR for berylliosis was significantly high, based on 4 deaths. SMRs for Hispanic workers were significantly high for cancers of the stomach and liver, cirrhosis of the liver, nonmalignant kidney disease and diabetes, but the excesses were not related to radiation dose.

Conclusions: There was little evidence that radiation increased the risk of lung cancer or leukemia. Esophageal cancer was associated with radiation, and plutonium intakes were linked to an increase of bone cancer. IHD was not associated with radiation dose. More precise evaluations will await the pooled analysis of workers with similar exposures such as at Rocky Flats, Savannah River and Hanford.

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Million Person Study; Los Alamos National Laboratory; plutonium; radiation epidemiology; dosimetry

Introduction

The Million Person Study (MPS) of low-level radiation exposure was designed to evaluate the level of health effects when exposure is gradual over time and not delivered briefly. Over a million healthy American workers and veterans are being studied to evaluate cancer and non-cancer mortality following low-level low-LET as well as high-LET exposure (Boice, Cohen, et al. 2019; Boice, Quinn, et al. 2021). The large study size also enables the evaluation of radiation associations for rare cancers, intakes of radioactive elements, and differences between men and women. A major component of the MPS is the U.S. Department of Energy (DOE) workers employed during and after the Manhattan Project (Boice, Cohen, et al. 2006; Boice et al. 2011, 2014; Ellis, Boice, et al. 2018; Ellis, Girardi, et al. 2018; Boice, Cohen, et al. 2019; Golden et al. 2019), including workers at the Los Alamos National Laboratory (LANL).

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During World War II (WWII), the Manhattan Engineering District established a secret laboratory in the mountains of northern New Mexico. Named Project Y, the mission was to design, construct, and test the first atomic weapon, nicknamed 'The Gadget', with the detonation code name of TRINITY. The plutonium device was successfully tested on 16 July 1945 in Alamogordo, New Mexico. After WWII, the laboratory continued with nuclear weapons research and design and became known as the Los Alamos Scientific Laboratory and eventually as LANL. Over the years, mortality studies were conducted of the early LANL workers exposed to external gamma-rays and intakes of plutonium (Hempelmann et al. 1973; Wiggs 1987; Wilkinson et al. 1987; Galke et al. 1992; Wiggs et al. 1994; Voelz et al. 1997; Daniels et al. 2006). The current investigation expands upon the previous work, extends the follow-up an additional 27 years, includes women for the first time, includes workers at Zia, a maintenance contractor (Galke et al. 1992; Ellis, Girardi, et al. 2018), and uses comprehensive dose reconstruction techniques to estimate organ-specific doses for each worker from photons, neutrons, tritium, ^{238}Pu, and ^{239}Pu.

Materials and methods

Human subjects research approval was received from the Oak Ridge Site-wide Institutional Review Board and the Vanderbilt University Institutional Review Board.

Study population

The LANL worker population was assembled from three previously studied cohorts: male LANL workers employed 1943 through 1977 (Wiggs et al.1994); female LANL workers employed 1943 through 1977 (Wiggs 1987); and male and female workers employed 1946 through 1977 by the Zia Company, a support services contractor to LANL (Galke et al. 1992; History Associates Incorporated 1997; Ellis, Girardi, et al. 2018). The Zia Company employed 14,326 workers but only the 6157 employees who were monitored for external and/or internal radiation while working at LANL are included. Throughout the paper, 'LANL workers' is used to refer to all LANL and ZIA employees who worked at LANL. The combined LANL population cohort initially consisted of 27,497 workers. After excluding 780 workers with insufficient or incorrect identifying information, 58 workers with missing or insufficient occupational data, and 331 workers employed for fewer than 30 days, 26,328 workers remained eligible for the study (Table 1, Figure 1). Worker information including demographics and employment dates were obtained from rosters utilized in the previous studies (Voelz and Hempelmann 1975; History Associates Incorporated 1997; Ellis, Girardi, et al. 2018). Educational attainment was available for 24,826 workers (94%) and was classified as less than high school, some high school, high school graduate, associate degree, college degree, or graduate degree. For 1116 workers (4.2%), education was imputed using residential address and Census data as described in Cohen et al. (2018). For $n = 387$ workers (1.5%), where an address history could not be obtained, the education level was assigned to be high school.

Table 1. Descriptive characteristics of the 26,328 LANL workers first employed 1943–1980 and followed through 2017.

Characteristic	*n*	%
Employer		
LANL	20,171	76.6
ZIA	4,237	16.1
Both LANL and ZIA	1,920	7.3
Sex		
Male	19,804	75.2
Female	6,524	24.8
Education		
<High school, some high school	3,823	14.5
High school graduate	2,097	8.0
Associates degree	10,364	39.4
College degree	5,750	21.8
Graduate degree	4,294	16.3
Race/ethnicity		
Asian	29	0.1
Black	102	0.4
Hispanic[a]	3,357	12.8
Native American	197	0.1
White	21,252	80.7
Unknown	1,391	5.3
Year of Birth		
Prior to 1900	934	3.6
1900–1919	6,143	23.3
1920–1939	11,818	44.9
1940–1962	7,433	28.2
Year of Hire		
1943–1949	8,368	31.8
1950–1959	6,180	23.5
1960–1969	5,188	19.7
1970–1980	6,592	25.0
Age at First Hire (years)		
16–19	3,079	11.7
20–24	6,738	25.6
25–29	6,146	23.3
30–39	6,641	25.2
40+	3,724	14.1
Age at End of Follow-up (Dec. 31, 2017) (years)		
<40	406	1.5
40–49	717	2.7
50–59	1,655	6.3
60–69	5,786	22.0
70–79	7,985	30.3
80–89	7,154	27.2
90–95+	2,625	10.0
Vital status as of Dec. 31, 2017		
Confirmed dead	15,737	59.8
Confirmed alive	10,517	40.0
Died outside U.S.	42	0.2
Lost to follow-up	32	0.1

[a]While Hispanic is an ethnicity rather than a race category, we chose to tabulate them separately.

Vital status and outcome determination

Vital status and cause of death for LANL workers as of 31 December 2017, was determined from linkages with the National Death Index (NDI); state mortality files; the Social Security Administration (SSA) Death Master File; the SSA Service to Epidemiological Researchers (which confirms alive status); and credit reporting agencies (Mumma et al. 2018). The Centers for Disease Control and Prevention LinkPlus program, which incorporates a probabilistic scoring system that does not require exact matches on all variables, was used for in-house matches (Campbell 2008). The ability to

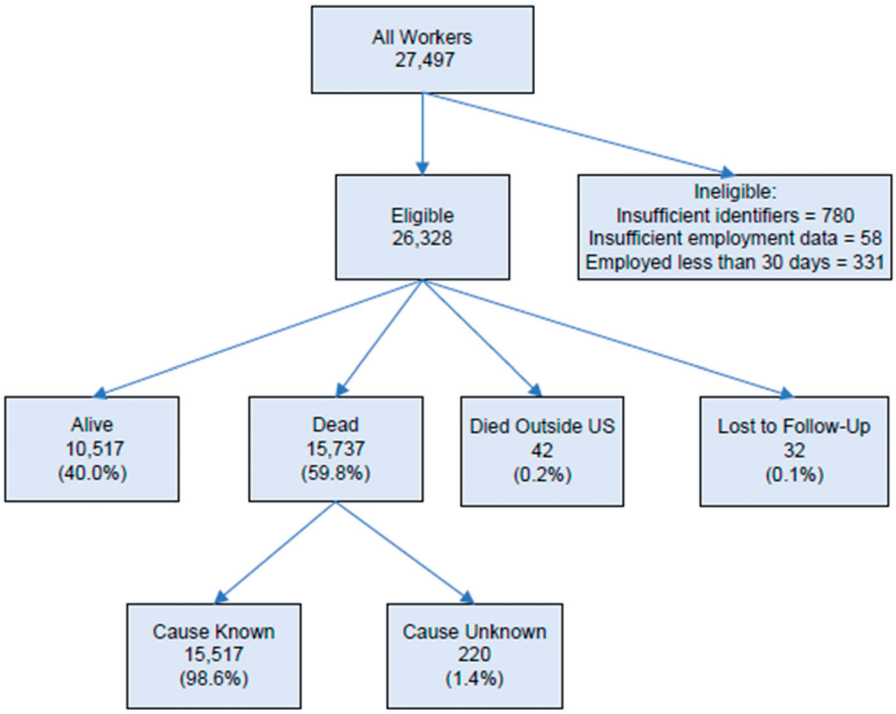

Figure 1. Schematic of the selection and vital status tracing results for the 26,328 workers at the Los Alamos National Laboratory (LANL) first employed between 1943 and 1980 and followed through 2017.

match worker rosters to state mortality data, including data from the New Mexico Department of Vital Status, was especially valuable in identifying deaths that occurred before 1979 when the NDI began.

SSA vital status files and other sources confirmed that 10,517 workers (40.0%) were alive in 2017 (Figure 1). The cause of death was determined for all but 220 (1.4%) of the 15,737 workers who had died. Workers without a match in SSA, a state mortality file, NDI, or if a credit header record could not be located ($n = 32$, 0.1%) were assumed alive until their date of last employment at LANL. Workers with serious renal disease were identified by linkage with the U.S. Renal Data System (1975–2018), which includes persons who received kidney dialysis or transplant (U.S. Renal Data System 2020), and their causes of death determined.

Radiation dose reconstructions for external sources of radiation and tritium

Measurements of gamma, neutron, and tritium exposures were obtained from data files submitted to the Department of Energy's Comprehensive Epidemiologic Data Resource (CEDR) (Department of Energy 2021) from previous studies (Wiggs 1987; Galke et al. 1992; Wiggs et al. 1994). Pocket chambers or film dosimeters were used for personnel monitoring from 1944 through 1980 when they were replaced with thermoluminescent dosimeters.

The weighted absorbed dose to the tissues of the body was estimated assuming an irradiation geometry and energy spectrum of incident photons and neutrons on the body. The irradiation geometry assumed half the radiation was incident of the body in an anterior-posterior (AP) manner and half in a rotational (ROT) manner as recommended in NCRP Report 178 (National Council on Radiation Protection and Measurements 2018b). The dose coefficients for such geometries are tabulated in ICRP Publication 116 (International Commission on Radiological Protection 2010). The recorded photon annual personal dose equivalent, Hp(10), was assumed to be associated with down-scattered photon energy spectra associated with ^{137}Cs. The distribution of the tissue doses is shown in Figure 2.

Annual personal dose equivalent values also were recorded for thermal, fast, and other neutron exposures. The fast neutron values were interpreted assuming the Watt spontaneous-fission spectra, while the thermal neutron values assume energy of 0.025 eV. The other neutron exposures assume a degraded fast neutron energy spectrum. The tissue equivalent annual doses for the neutron exposures assume a radiation weighting factor of 2.5 for the thermal neutrons (International Commission on Radiological Protection 2007, Figure 1). A radiation weighting factor of 16 for non-thermal neutrons, both fast neutrons and fission neutrons, was assumed based on the fast neutron spectrum-weighted average over the ICRP Publication 103 (International Commission on Radiological Protection 2007, Figure 1) continuous neutron radiation weighting factor function. The distribution of tissue doses for the fast neutrons is shown in Figure 2.

Tritium intakes were monitored by measurements of activity within the urine. The measurements were recorded without information on the exposure period. The pre-1968 analytical methods involved Geiger–Müller detectors which were replaced by liquid scintillation procedures in later years. The pre-1968 medium detectable tritium concentration was 1 μCi/L, and it was 0.1 μCi/L in later years. Considerable uncertainties exist in the estimated annual doses; however, these dose contributions are rather minor –

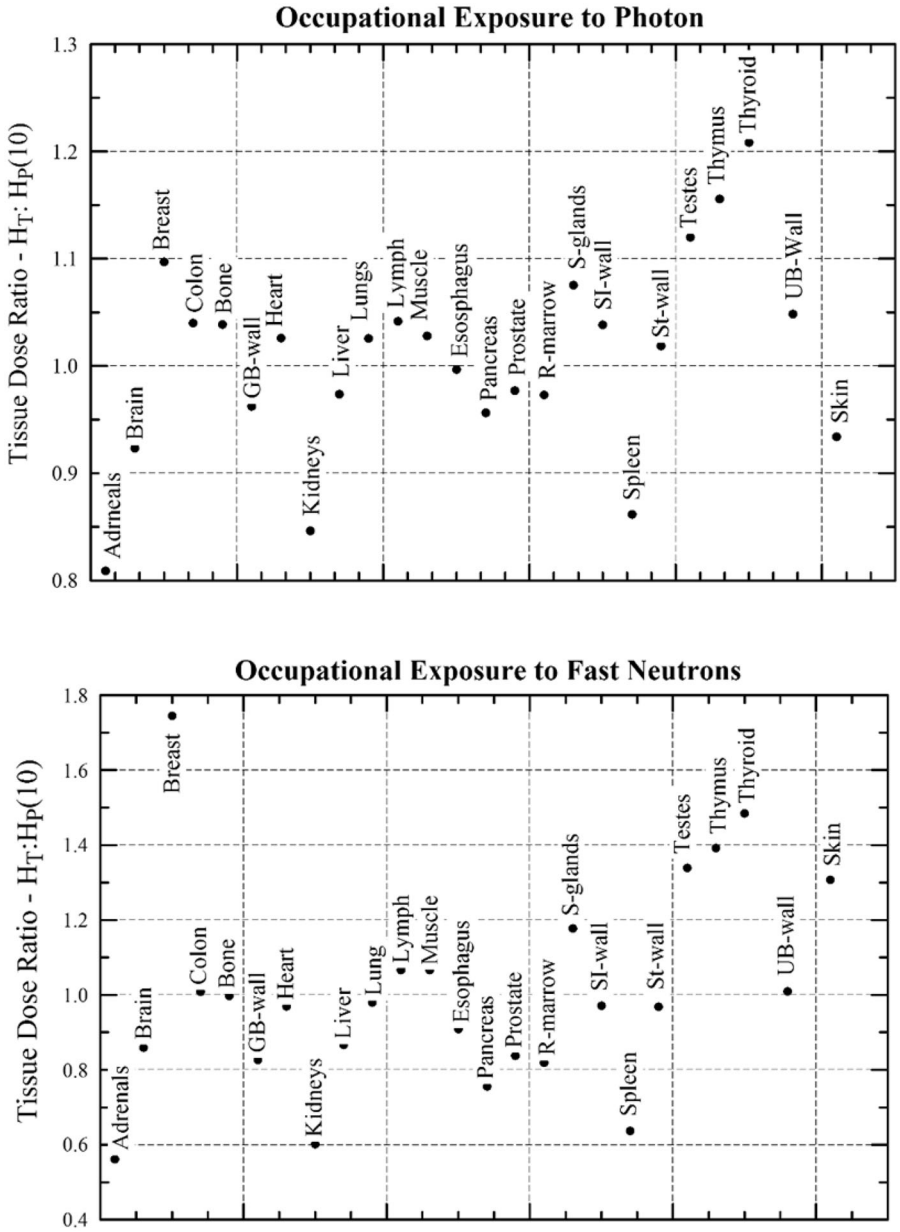

Figure 2. Ratio of photon tissue dose (top panel) to personnel equivalent dose and ratio of fast neutron tissue dose (bottom panel) to personnel equivalent dose for 25 tissues.

average lifetime tritium absorbed dose less than 3 mGy. The analyses assume a Dose Weighting Factor (DWF) of 1 for tritium, although higher values up to 3 are plausible (Cox et al. 2008; National Council on Radiation Protection and Measurements 2018c). Again, the tritium contribution to organ doses is so low that the DWF assumptions have a negligible effect. For example, the mean total dose to RBM for Pu (DWF = 1) and tritium (DWF = 1) is 12.4 mGy, and for a DWF of 2 for tritium, the mean dose to RBM increases only to 12.56 mGy while the maximum of 835 mGy remains the same.

Radiation dose reconstruction for internally deposited Pu

Many radionuclides were handled at LANL since the start of operations in 1943, but mostly in small quantities. By far the greatest potential for elevated doses from internal emitters arose from work with ^{238}Pu and ^{239}Pu, which were handled in relatively large quantities. Numerous short-term intakes of ^{239}Pu occurred over the years, particularly during early work involving reduction of Pu to metallic form and development of technology for use of Pu in a nuclear bomb. Later peacetime programs including the development of ^{238}Pu heat sources resulted in elevated intakes of ^{238}Pu. Since 1943, 6499 LANL workers were monitored for ^{239}Pu or ^{238}Pu and 5142 (79.1%) had positive bioassays. The number of Pu bioassay records available for evaluation was 158,222, that is, 24.3 records per worker on average. To reduce the number of time-consuming case-by-case dose reconstructions for relatively noninformative low intakes of plutonium, screening criteria were developed. Effective doses were available and 10 mSv was taken as the minimum criterion for conducting comprehensive individual dose

reconstructions for the ^{238}Pu and ^{239}Pu intakes. There were 457 workers who met this screening level, and organ doses for 25 tissues were estimated for each calendar year after intake through the year 2017. The highest doses would be expected for those organs known to concentrate Pu after intake, that is, the lung, liver, bone and thoracic lymph nodes (Kathren and Tolmachev 2019).

Because of the possibility that low-dose radiation might be associated with increased risk of heart disease, estimates of dose to the heart from internal radiation were made and combined with the dose from external radiation and tritium as done in previous studies of MPS workers at the Mound and Mallinckrodt facilities (Boice et al. 2014; Golden et al. 2019). In the systemic model for plutonium, the heart is treated as a mass fraction of Other soft tissue, which is all soft tissue except the liver and kidneys. The activity in Other soft tissue is assumed to be uniformly distributed. The dose to the heart from ^{238}Pu or ^{239}Pu will be almost entirely self-dose from alpha particles contained in heart tissue plus alphas emitted from blood passing through the heart. There is a very small contribution to heart dose from other types of radiations emitted in the heart and surrounding tissues (crossfire dose). The heart dose from these non-alpha emissions represents only about 0.15% of the heart dose from alphas.

MPS dose reconstructions for monitoring Pu intake at LANL were based primarily on measurements of urinary Pu, the key component of a bioassay program instituted in 1944 for monitoring ^{239}Pu exposure and expanded in the late 1960s to monitor ^{238}Pu exposure. Details of the program are provided in publications by Campbell et al. (1972), Hempelmann et al. (1973), Lawrence (1978), Miller et al. (2008), and Efurd et al. (2008). The early measurement techniques involved sizable errors related to extremely high background counts and widely varying measurements over relatively short time periods for individual Pu workers. Continual improvements in urinary Pu measurements were made over time, and reasonably reliable techniques with relatively small errors appear to have been developed by 1957.

The bioassay data for Pu were supplemented with post-mortem measurements of ^{239}Pu in tissues of 28 LANL workers and ^{238}Pu measurements in tissues of 22 of these 28 workers (see for example McInroy et al. 1991; McInroy 1995). The autopsy data provided information on the relative contents of these Pu isotopes in different tissues including bone, liver, lungs, and tracheobronchial lymph nodes (TBLN). The relative content of Pu in lungs, TBLN, and bone plus liver is an indicator of the solubility of the inhaled material. The collective autopsy and bioassay data for these 28 workers provided checks on the reliability of the biokinetic model for systemic Pu used in the dose reconstructions for ^{238}Pu and ^{239}Pu (Leggett et al. 2005, 2018; International Commission on Radiological Protection 2019).

Additional information was provided by a LANL database of incidents involving potential intake of ^{238}Pu or ^{239}Pu. For each incident, the database records the date, worker identifier number, and abbreviations representing the nature of the exposure or reason for suspecting an intake. This database was used to assign exposure scenarios to observed increases over time in urinary Pu for the listed workers.

The biokinetic models used to interpret bioassay data for Pu generally were taken from Publication 141 of the International Commission on Radiation Protection ICRP), 'Occupational Intakes of Radionuclides: Part 4' (International Commission on Radiological Protection 2019). The respiratory model employed is an update of the ICRP's Human Respiratory Tract Model (HRTM) (International Commission on Radiological Protection 2015). ICRP Publication 141 (International Commission on Radiological Protection 2019) provides several sets of respiratory parameter values describing different absorption types for Pu, that is, different patterns over time of dissolution of the inhaled material in the respiratory tract and subsequent absorption of Pu to blood. For inhalation of ^{239}Pu or ^{238}Pu as Pu dioxide, the respiratory parameter values depict slower lung clearance of ^{239}Pu than ^{238}Pu based on results of animal studies and follow-up measurements on accidentally exposed workers. The faster lung clearance of ^{238}Pu is thought to be due to its relatively high specific activity, which results in gradual radiolytic fragmentation of ^{238}Pu particles and a subsequently increased rate of dissolution of the Pu-bearing material deposited in the lungs

The following Pu absorption types defined in ICRP Publication 141 (International Commission on Radiological Protection 2019) were applied in ^{239}Pu dose reconstructions for LANL workers: generic absorption types F, M, and S (applicable to both ^{238}Pu and ^{239}Pu) representing fast, moderate, and slow dissolution and absorption from the respiratory tract to blood; an absorption type-specific to Pu nitrate (also applicable to both ^{238}Pu and ^{239}Pu); and an absorption type-specific to $^{239}PuO_2$. The following Pu absorption types were applied in ^{238}Pu dose reconstructions for LANL workers: generic absorption types F, M, and S; an absorption type-specific to ceramic $^{238}PuO_2$ (used in the production of ^{238}Pu heat sources); an absorption type-specific to non-ceramic $^{238}PuO_2$ (representing all forms of $^{238}PuO_2$ other than ceramic $^{238}PuO_2$); and two variations of the ICRP's respiratory parameter values for ceramic $^{238}PuO_2$ depicting shorter peak urinary ^{238}Pu times (about 550 and 1100 days) than predicted by the parameter values for ceramic $^{238}PuO_2$ given in Publication 141 (about 1500 days). The indicated variations of the ICRP's model for ceramic $^{238}PuO_2$ allowed improved model fits urinary ^{238}Pu data for many LANL workers whose ^{238}Pu excretion patterns were qualitatively similar to that indicated by the ICRP's model for ceramic $^{238}PuO_2$ but showed earlier peaks than predicted by the ICRP's parameter values.

Incident or autopsy data were not available for the preponderance of LANL Pu workers with positive ^{238}Pu or ^{239}Pu bioassay. In the absence of such data, assignments of intake times and absorption types were based as feasible on comparisons of worker-specific patterns of time-dependent urinary Pu with patterns predicted by ICRP models for different forms of Pu. Differences in model-predicted patterns of 24-h or cumulative urinary ^{238}Pu or ^{239}Pu are illustrated

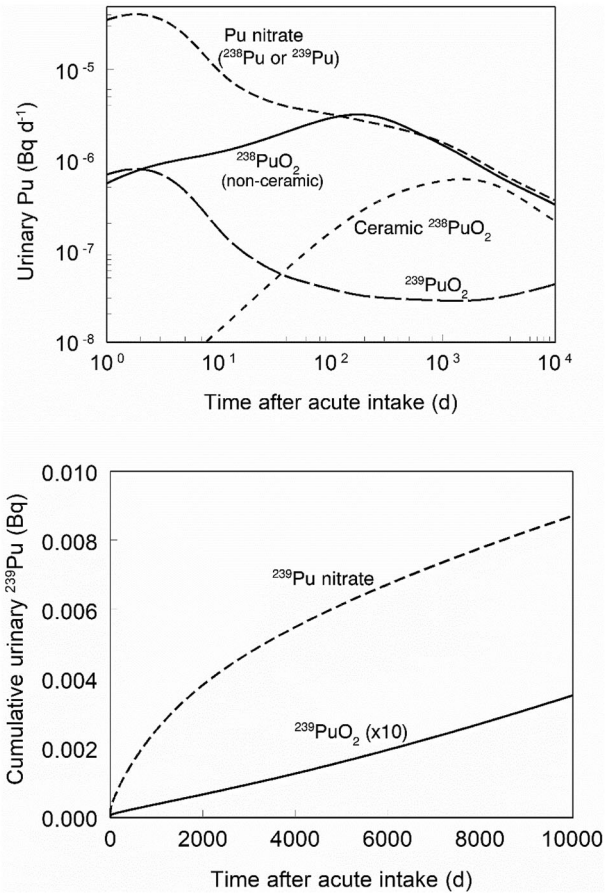

Figure 3. Illustrations of different patterns of daily and cumulative urinary Pu activity predicted for different absorption types considered in dose reconstructions for LANL workers. An intake of 1 Bq ^{238}Pu or ^{239}Pu of particle size 5 µm AMAD is assumed. In the lower panel, the cumulative activity curve for inhaled $^{239}PuO_2$ is raised 10-fold for ease of viewing.

in the upper panel of Figure 3 for selected forms of Pu. An intake of 1 Bq ^{238}Pu or ^{239}Pu of particle size 5 µm AMAD (Activity Median Aerodynamic Diameter) is assumed: 50% of the activity in the aerosol is associated with particles of aerodynamic diameter greater than the AMAD. For example, the predicted time post intake at which the peak urinary excretion rate occurs is a few days for $^{239}PuO_2$, ^{239}Pu nitrate, or ^{238}Pu nitrate; a few months for non-ceramic $^{238}PuO_2$; and a few years for ceramic $^{238}PuO_2$ (as depicted by the ICRP's model for ceramic $^{238}PuO_2$).

An indication of the solubility of the inhaled material often can be gained from inspection of the cumulative excretion curve inferred from the collective 24-h urinary Pu data. This is indicated in the lower panel of Figure 3 by model-predicted cumulative urinary ^{239}Pu curves for inhalation of the moderately soluble form ^{239}Pu nitrate and the relatively insoluble form $^{239}PuO_2$. In general, the curve for cumulative urinary ^{239}Pu for inhalation of a relatively soluble or moderately soluble form of ^{239}Pu will be concave downward, while the cumulative excretion curve for a relatively insoluble form will be a nearly straight line or may even be slightly concave upward.

Uncertainties in dose estimates for internally deposited Pu may be divided into the following categories:

Measurement of urinary Pu

Measurement errors for urinary Pu appear to have represented an important source of error in reconstructed doses for ^{239}Pu intake in the first year or two of operations, a smaller but still important source of error from the mid-1940s to 1957, and a generally less important source of error after the introduction of a relatively sensitive measurement technique in 1957.

Mode of Pu intake

The mode of intake of Pu by an individual worker was based on LANL's database of incidents when the worker and mode of intake were listed in the database and the listed date of exposure was consistent with increases in the worker's urinary Pu. In most cases of elevated urinary Pu, however, the time of increase in urinary Pu could not be matched to records in the incident database and intake via inhalation was assumed. This assumption could have resulted in order-of-magnitude overestimates of lung dose in many cases in which the preponderance of intake was via wounds. Estimated doses to tissues outside the respiratory and alimentary tract were only moderately sensitive to erroneous assignment of the mode of intake. This is because the latter tissue doses were back-calculated from the time course of urinary excretion of Pu, which largely reflects the time-dependent systemic behavior of Pu regardless of the pathway of entry of Pu into the systemic circulation.

Assignment of an absorption-type to inhaled Pu

Assignment of an absorption-type often was straightforward for ^{238}Pu because the urinary ^{238}Pu patterns frequently resembled the characteristic excretion curves for inhalation of either ceramic or non-ceramic $^{238}PuO_2$. For many workers with positive ^{239}Pu bioassay data and a smaller subset of workers with positive ^{238}Pu data, the data could be produced about equally well with different plausible exposure scenarios, that is, different combinations of intake time(s), intake mode(s), and/or respiratory absorption-type(s). In such cases, the exposure was assumed to be via inhalation, and absorption types representing intermediate residence times in the lungs were selected in an effort to avoid large overestimates or underestimates of lung dose. It is expected that the errors in lung dose estimates usually were less than a factor of three for inhaled ^{239}Pu and a factor of two for inhaled ^{238}Pu except in cases where Pu inhalation was erroneously assigned as the mode of intake.

Biokinetic model for systemic Pu

Autopsy data together with bioassay data for 28 workers allowed checks on the reliability of the biokinetic model for systemic Pu used in the dose reconstructions for ^{238}Pu and ^{239}Pu (Leggett et al. 2005; International Commission on Radiological Protection 2019). Model predictions based on urinary Pu measurements were found to be reasonably consistent with the postmortem systemic burdens, with the rate of urinary excretion of systemic Pu, and with observed

mean or median ratios of bone Pu to liver Pu, although the relative Pu contents of liver and skeleton varied from worker to worker. Acute intake of Pu was assumed in all cases. Chronic exposure to Pu is an unlikely scenario for LANL and most other sites. The times of acute exposure were based on time-dependent urinary Pu patterns. These findings suggested that the systemic model for Pu typically was not a major source of error in dose estimates from internally deposited Pu but could represent a substantial (greater than a factor of 2) error in estimated doses to the liver, bone surface, or bone marrow for some individuals.

Career doses

In addition to the dosimetry records available for workers at LANL 'on site', dosimetry records documenting radiation exposure received before or after working at LANL were sought from eight additional sources: DOE Radiation Exposure Monitoring System (REMS) (Department of Energy 2018); other historic DOE radiation exposure data not included in DOE REMS; the Nuclear Regulatory Commission Radiation Exposure Information and Reporting System (REIRS) (Hagemeyer et al. 2018; Nuclear Regulatory Commission 2019); the US Navy Dosimetry System (Naval Dosimetry Center 2019) and US Army and US Air Force dosimetry files (Department of Army 2012); the DOD Nuclear Test Personnel Review program for military veterans who participated in the U.S. atmospheric nuclear tests from 1944 to 1962 (Till et al. 2014); and Landauer, Inc. dosimetry records (National Council on Radiation Protection and Measurements 2018b; Yoder et al. 2020). All nonoverlapping doses from each source were added together for each calendar year to obtain the total external dose received by each worker, following the procedures outlined in Boice, Leggett, et al. (2006) and Ellis, Boice, et al. (2018) which also describe how the calendar year organ-specific organ doses following intakes of radionuclides are incorporated into the individual dosimetry files.

Statistical analysis

Standardized Mortality Ratio (SMR) analyses were conducted by comparing the observed number of deaths with those expected based on mortality rates in the comparable general population of the United States. Observed numbers of deaths from cancers and other diseases were counted by age, sex, and calendar year for LANL workers overall and for subgroups defined by employer, education, year of birth, age, calendar year, ethnicity (e.g. Hispanic), type of radiation monitoring, and years of follow up. Expected values were based on general population rates for white males and females. Technically, Hispanic is an ethnicity and not a race. Hispanic ethnicity, when known, is often classified as white with white general population rates used for comparison. The SMR analyses were based on the underlying cause of death. The follow-up time for each worker began 30 days after the date of first employment at LANL, and ended at his or her date of death, or the date when the worker reached age 95, or the date lost to follow-up, or 31 December 2017, whichever came first. Statistical variability was evaluated by the 95% exact Poisson confidence interval (CI) of the SMR assuming that the observed number of deaths followed a Poisson distribution. Comparisons and ratios of SMR values were conducted following the methods of Breslow and colleagues (Breslow et al. 1983).

Internal, or within-cohort, analyses were conducted using Cox proportional hazards models which were developed to compute risks across categories of estimated radiation dose to specific organ/tissues (Cox 1972). Such internal analyses are conducted to account for the 'healthy worker effect' often seen in occupational studies (Monson 1986). All Cox modeling was conducted using SAS/STAT software (SAS/STAT software, Version 9.4 of the SAS System for Windows, SAS Institute Inc., Cary, NC, USA). Excess Relative Risks (ERR) at 100 mGy were estimated using the Peanuts program in Epicure (Preston et al. 2015). To increase statistical power for infrequent causes of death such as leukemia, the cause-specific internal analyses include both the underlying and contributing causes of death obtained from the National Death Index and available death certificates. Year of birth (4 categories), sex and education (5 categories) were included in all models. Extensive and detailed interview studies of early LANL workers had found that educational status was directly and strongly correlated with cigarette smoking (Mahoney and Wilkinson 1987; Wilkinson et al. 1987). Education for all workers was then used as a measure of socioeconomic status (SES) for all workers to account for smoking and other lifestyle factors (Cohen et al. 2018).

For the internal cohort analyses, radiation dose was treated as a categorical measure, with categories defined based on the distribution of dose for each organ/tissue of interest. The dose category was then treated as a time-dependent measure, allowing workers to be assigned to increasingly higher dose categories over time as their individual radiation doses accrued. Doses accrued over time include both external doses and internal doses from the decay of radionuclides that had been retained in the body after inhalation or ingestion. Age was used as the underlying timescale for the hazard function. To allow for a possible latent period between radiation exposure and any effect consequent to it, doses were lagged, that is, excluded if they occurred during some assumed interval prior to the event of interest. A 10-year lag was applied for solid cancers and other chronic conditions and a 2-year lag for leukemia, myelodysplastic syndrome (MDS) and bone cancer. Sensitivity analyses were conducted assuming a 5-year lag for selected cancers. Parameter estimates and standard errors for the dose categories in the Cox time-dependent regression models were used to obtain hazard ratios (HR) and 95% confidence intervals (CI) for death due to the cause under investigation compared with those in the referent group taken as the workers with low cumulative radiation dose (<5 mGy). Trend tests treated the radiation dose as a single continuous measure, and two-sided p-values are presented.

HRs at 100 mGy were computed for selected causes of death (Golden et al. 2018).

In the primary analysis for lung, liver and bone cancers, non-Hodgkin lymphoma (NHL) and liver cirrhosis, a dose weighting factor (DWF) of 20 was applied to alpha-particle absorbed doses from intakes of plutonium-239 and plutonium-238, that is, the biological effectiveness of the absorbed dose from Pu intakes was assumed to be 20 times that of the absorbed dose alone. The unit weighted-dose, for example, weighted-mGy, is used for such analyses. Additional analyses were performed assuming dose weighting factors of 1 or 10 as possible indicators of biological effectiveness for these alpha-particle absorbed doses. In the absence of a complete understanding of the biological effectiveness of alpha particles to cause-specific outcomes, the use of various DWFs provide a range of possibilities and boundary conditions. Other than for the lung, liver, thoracic lymph nodes (NHL) and bone, a DWF of 1 was used for other organs since Pu concentration was negligible, for example, the mean dose to the esophagus changed from 12.8 mGy (DWF = 1) to 12.9 weighted-mGy (DWF = 20).

Results

Descriptive characteristics of workers at LANL are shown in Table 1: 76.6% were employed only by LANL, 16.1% only by ZIA, and 7.3% by both sometime during their career. Overall, 75.2% were male, 80.7% white and 12.8% Hispanic. Fewer than a quarter of the workers had a high school education or less, and 38.1% had a college degree or higher. Approximately one-quarter of the study population was born before 1920. Workers were first hired in the 1940s, 1950s, 1960s and 1970–1984 for 31.8%, 23.5%, 19.7%, and 25.0% of the cohort, respectively. At the end of vital status tracing, 40% of the workers were alive, 59.9% had died, and only 32 (0.1%) were lost to follow-up (Figure 1). The cause of death was obtained for all but 1.2% of those who died. The mean duration of follow-up was 44.9 years.

Overall, 66.8% of workers at LANL were monitored for any type of radiation, 64.5% for external radiation, 43.6% for neutrons, 7.8% for tritium, 14.5% for ^{238}Pu and 24.7% for ^{239}Pu. (Table 2). There were 6499 workers who were monitored for either ^{238}Pu or ^{239}Pu of whom 1357 (21%) did not have a positive assay. For the 5142 workers with a positive assay, approximately 8.3% had an effective dose >10 mSv which triggered individual case-by-case dose reconstructions for 25 organs or tissues. For the remainder, 88% had effective doses <1 mSv; 1.7% between 1–5 mSv; and 2% between 5–10 mSv. Effective dose is a radiation protection unit and is not appropriate for epidemiologic analyses (Cox and Kellerer 2003). A crude characterization of the low organ doses received by workers not meeting the 10 mSv screening level, however, can be made by assuming various absorption types for the plutonium intakes contributing to the effective dose calculations, for example, 50% nitrate and 50% oxide. If done, crude characterizations of organ doses for lung, endosteal bone surface, and liver might be of the order of 3–4 times the effective dose and substantially less for other organs.

Table 2. Radiation monitoring history by source of exposure for the 26,328 LANL workers first employed 1943–1980 and followed through 2017.

Radiation monitoring	*n*	%
Any radiation monitoring (any type)		
Yes	17,588	66.8
None	8,740	33.2
Any external		
Yes	16,965	64.4
LANL only	10,792	41.0
LANL + Other facilities	5,288	20.1
Other facilities only	885	3.4
None	9,363	35.6
Any neutrons		
Yes	12,192	46.3
None	14,136	53.7
Any tritium		
Yes	2,075	7.9
None	24,253	82.1
Any ^{238}Pu		
Not monitored	22,514	85.5
Monitored, no positive assay	624	2.4
Monitored, positive Assay, <10 mSv[a]	2,965	2.4
Monitored, positive Assay, >10 mSv	225	0.8
Any ^{239}Pu		
Not Monitored	19,829	75.3
Monitored, no positive assay	1,301	4.9
Monitored, positive Assay, <10 mSv[a]	4,767	18.1
Monitored, positive Assay, >10 mSv	431	1.6
Any ^{238}Pu or ^{239}Pu		
Not monitored for either ^{238}Pu or ^{239}Pu	19,829	75.3
Monitored, no positive assay for either ^{238}Pu or ^{239}Pu	1,357	5.2
Monitored, positive Assay, <10 mSv[a] for ^{238}Pu and ^{239}Pu	4,685	17.8
Monitored, positive Assay, >10 mSv for either ^{238}Pu or ^{239}Pu	457	1.7

[a]10 mSv effective dose was taken as the minimum criterion for conducting comprehensive individual dose reconstructions for Pu intakes.

There were 6173 (23.4%) workers who were monitored for radiation other than at LANL (mean dose, 4.2 mGy, median dose 0.1 mGy, max dose 506 mGy), including 55 who were at the TRINITY detonation test and 335 who participated at other atmospheric nuclear weapons testing. Additional dosimetry information was obtained for 301 workers who served In the U.S. Navy, 138 in the U.S. Air Force and 19 in the U.S. Army. There were 554 who worked at a nuclear power plant, and 4500 who received doses at DOE facilities other than LANL: notably the Nevada National Security Site (~30%), Hanford (21%), Rocky Flats (7%), and Lawrence Livermore National Lab (6%). For the 8740 workers not monitored for radiation at LANL, 11 (0.1%) were monitored elsewhere (mean dose, 0.16 mGy, median 0.1, max dose 0.6 mGy). The nonmonitored LANL workers were more likely to be female, employed prior to 1960 and less educated than the monitored workers.

Table 3 provides summary statistics for 15 tissue-specific radiation absorbed doses (mGy) among LANL workers monitored for radiation. The organ-specific doses combine doses from photons, neutrons, tritium, ^{238}Pu and ^{239}Pu. Three different Dose Weighting Factors (DWF) were applied to the ^{238}Pu and ^{239}Pu alpha particle doses (1, 5, 10, and 20), and a DWF of 1 was applied to tritium doses. The weighting factors used for neutron doses were 2.5 (thermal) and 16 for nonthermal neutrons. Similar to the convention

Table 3. Tissue-specific radiation absorbed dose (weighted-mGy)[a], combining external and internal sources, for three Dose Weighting Factors (DWF) for Pu among the 17,053[b] LANL workers monitored for radiation.

Tissue	DWF	Mean	Median	Std.	Max.
Lung	1	13.9	0.90	48.7	1,248
	10	20.9	0.90	134.9	8,620
	20	28.6	0.90	251.6	16,811
Bone	1	13.8	0.89	47.4	924
	10	19.7	0.90	112.1	3,881
	20	26.4	0.90	204.6	7,701
Liver	1	13.5	0.87	46.8	864
	10	20.9	0.87	134.8	4,731
	20	29.2	0.87	253.9	9,413
Colon	1	13.6	0.87	47.3	906
	10	13.6	0.90	47.4	908
	20	13.7	0.91	47.5	909
Prostate	1	12.5	0.80	43.1	844
	10	12.6	0.85	43.2	846
	20	12.6	0.85	43.4	849
Esophagus	1	12.8	0.83	44.2	858
	10	12.8	0.86	44.3	860
	20	12.9	0.87	44.4	862
Brain	1	11.6	0.76	39.4	760
	10	11.7	0.79	39.5	762
	20	11.7	0.79	39.6	764
Stomach	1	13.3	0.86	46.5	893
	10	13.4	0.88	46.6	895
	20	13.4	0.90	46.7	897
Pancreas	1	12.1	0.80	41.7	815
	10	12.2	0.82	41.8	815
	20	12.2	0.83	41.9	815
Bladder	1	13.7	0.89	47.9	907
	10	13.8	0.91	48.0	909
	20	13.8	0.93	48.1	911
Kidneys	1	10.8	0.72	36.8	772
	10	11.0	0.76	37.1	772
	20	11.1	0.76	37.6	772
Breast	1	15.1	0.95	53.4	1,140
	10	15.1	0.99	53.5	1,140
	20	15.2	0.99	53.7	1,140
Heart	1	13.4	0.87	46.6	893
	10	13.4	0.90	46.7	895
	20	13.5	0.90	46.8	897
Red bone marrow	1	12.4	0.84	42.4	835
	5	12.7	0.85	43.3	845
Thoracic lymph nodes	1	36.5	0.89	419	25,600
	20	479.9	0.90	8,256	503,015

[a]Cumulative organ doses include doses from photons, neutrons, tritium, ^{238}Pu and ^{239}Pu. The weighting factors used for neutron doses were 2.5 (thermal), 16 (fast) and 16 (fission). Three different Dose Weighting Factors (DWF) were applied to the ^{238}Pu and ^{239}Pu doses (1, 10, and 20). A DWF of 1 was assumed for tritium doses.

[b]17,053 is the number of workers with dose information and differs from the 17,588 workers in Table 2 who were monitored for radiation. 535 workers were excluded who were only monitored for Pu and whose intake levels were very low and below the 10 mSv effective dose threshold for organ dose estimation.

used in the Life Span Study (LSS) of Japanese atomic bomb survivors, we refer to the neutron-weighted absorbed doses as weighted absorbed doses in Gy.

The mean and median doses were similar for most organs for DWFs of 1. For the lung (DWF of 1), the mean organ dose was 13.9 mGy and the range was broad and up to 1.25 Gy. For a DWF of 20, the mean lung dose was 28.6 weighted-mGy with a maximum of 16.8 weighted-Gy. The organs with a meaningful uptake of plutonium showed a doubling of the mean dose when a weighting factor of 20 is applied, specifically, the lung, bone (skeleton), liver and thoracic lymph nodes. The mean dose to the heart using a DWF of 1 was 13.4 mGy and the maximum was 893 mGy. For the heart and other organs/tissues with minimal uptake of plutonium isotopes, the mean and maximum doses were similar regardless of the DWF. DWFs of 1 and 5 are presented for red bone marrow since there does not appear to be much of increased biological effectiveness associated with alpha particle dose to the red bone marrow in causing leukemia in humans (Boice 1993; U.S. Environmental Protection Agency 1999; Daniels et al. 2006).

Table 4 shows the relative contribution of each radiation source to each mean tissue-specific dose among the 17,053 LANL workers monitored for radiation. External photons contribute about 84% of the dose for those organs that do not concentrate plutonium. But this percentage drops to below 50% for the organs that concentrate plutonium, that is, the lung, bone, liver and thoracic lymph nodes, and the predominant source comes from plutonium depositions.

Table 5 shows the SMRs for over 40 causes of death among the 26,328 LANL workers by sex. There were 1,181,472 person-years of follow-up, and the SMR for all causes of death was 0.76 (95%CI 0.75, 0.78). There were 839 deaths from lung cancer (SMR 0.54, 95%CI 0.51, 0.58). The SMRs for lung cancer did not differed by whether the workers were monitored for plutonium (SMR 0.55, 95%CI 0.51, 0.59; $n = 612$) or not (SMR 0.53, 95%CI 0.46, 0.60; $n = 227$). The SMR for leukemia other than CLL was 0.98 (95%CI 0.82, 1.16; $n = 136$). Most causes of death were significantly below or close to expectation, for example, the liver (SMR 0.82; $n = 110$), kidney (SMR 0.51; $n = 62$) and NHL (SMR 0.85; $n = 162$). The SMRs for liver cancer differed by whether the workers were monitored for plutonium (SMR 0.78, 95%CI 0.61, 0.98; $n = 76$) or not (SMR 0.94, 95%CI 0.65, 1.32; $n = 34$), but the difference was not statistically significant. Ischemic heart disease (IHD) also occurred below population expectation (SMR 0.60; $n = 3043$) as did cerebrovascular disease (CeVD) (SMR 0.72; $n = 871$). Cancer of the bone occurred close to expectation (12 deaths observed compared with 10.8 expected) as did liver cirrhosis (SMR 1.02; $n = 319$). However, the SMRs for bone cancer differed by whether the workers were monitored for plutonium (SMR 2.44, 95%CI 0.98,5.03; $n = 7$) or not (SMR 0.63, 95%CI 0.20, 1.48; $n = 5$), and the ratio (3.86) was statistically significant (95%CI 1.22, 12.2). Cancers of the pleura and mesothelioma were not in excess (SMR 0.94; $n = 20$). Causes of death that occurred significantly above expectation were suicides (SMR 1.16; $n = 309$), notably among women, and berylliosis (SMR 23.0; $n = 4$), notably among men. Deaths due to dementia, Alzheimer's, Parkinson's, and other motor neuron disease were not increased (SMR 0.96, $n = 973$), nor were deaths due to mental and behavioral disorders (SMR 0.99; $n = 520$).

SMR analyses were computed by subgroups that included sex, race/ethnicity, education, employer (LANL, Zia) and others (data not shown). The all-cause SMR of death for women was significantly low (SMR 0.85, 95%CI 0.82, 0.88; $n = 3545$) as it was for men (SMR 0.74, 95%CI 0.73, 0.76; $n = 12,231$). There were no significantly high SMRs among women except for all external causes of death (SMR 1.17, 95%CI 1.00,1.35; $n = 175$) which was attributed to a significantly high risk of suicide (SMR 1.92; $n = 49$). For men,

Table 4. The relative contribution of radiation source to each mean tissue-specific dose (weighted-mGy)[a] among the 17,053 LANL workers monitored for radiation.

Tissue	Mean dose[a]	Percentage of photons (%)	Percentage of neutrons (%)	Percentage of tritium (%)	Percentage of plutonium (%)
Lung	28.6	81.8	14.1	1.3	2.8
Bone	26.4	82.1	13.9	1.3	2.8
Liver	29.2	81.6	14.2	1.3	2.9
Colon	13.7	82.8	15.0	1.3	0.9
Prostate	12.6	83.3	14.4	1.4	0.9
Esophagus	12.9	83.2	14.4	1.4	0.9
Brain	11.7	84.0	13.6	1.4	1.0
Stomach	13.4	82.8	15.0	1.3	0.9
Pancreas	12.2	83.7	14.1	1.4	0.9
Bladder	13.8	82.7	15.1	1.3	0.9
Kidneys	11.1	83.8	13.5	1.4	1.2
Breast	15.2	81.6	16.2	1.3	0.9
Heart	13.5	82.8	14.9	1.3	0.9
Red bone marrow	12.4	83.7	14.1	1.4	0.8
Thoracic lymph nodes	36.5	81.9	14.2	1.3	2.6

[a]Cumulative organ doses include the doses from photons, neutrons, tritium, ^{238}Pu and ^{239}Pu. The weighting factors used for neutron doses were 2.5 (thermal), 16 (fast) and 16 (fission). A Dose Weighting Factor of 20 was applied to the ^{238}Pu and ^{239}Pu doses in this table for all tissues except red bone marrow and thoracic lymph nodes which had a Dose Weighting Factor of 1 applied. A Dose Weighting Factor of 1 was used for tritium doses in this table.

only death due to berylliosis was significantly high (SMR 26.1, 95%CI 7.08, 66.8; $n = 4$). Among the Hispanic population, both sexes combined, the all-cause of death SMR also was significantly low (SMR 0.83, 95%CI 0.79, 0.86; $n = 1917$). However, there were a number of causes of death that were significantly high among the Hispanic population, that is, cancers of the stomach (SMR 2.40; $n = 39$) and liver (SMR 1.59; $n = 23$), mental and behavioral disorders (SMR 1.52; $n = 67$), cirrhosis of the liver (SMR 2.24; $n = 82$), non-malignant kidney disease (SMR 1.68; $n = 49$), diabetes (SMR 1.44; $n = 71$) and accidents (SMR 1.73; $n = 157$).

Significantly high SMRs among whites were seen only for berylliosis (SMR 20.0; $n = 3$) and suicides (SMR 1.22; $n = 284$). The SMRs for lung cancer by educational status were highest for workers with a high school education (0.80; $n = 101$) or less (0.76; $n = 179$) and the lowest SMR were for those holding a college (0.44; $n = 164$) or graduate (0.22; $n = 68$) degree (data not shown). Both LANL (SMR 0.74; $n = 11{,}322$) and ZIA (SMR 0.90; $n = 4454$) workers had significantly low all-cause-of-death SMRs. Significantly high SMRs among LANL workers were seen for berylliosis (SMR 24.5; $n = 3$) and suicide (SMR 1.19; $n = 240$). Among Zia employees, significantly high SMRs were seen for mental and behavioral disorders (SMR 1.47; $n = 147$), cirrhosis of the liver (SMR 1.73; $n = 132$) and accidents (SMR 1.45; $n = 264$). Somewhat higher SMRs were observed for workers hired 1942–1949 where 3 of the 4 deaths due to berylliosis occurred.

Table 6 shows the hazard ratios (HR) and excess relative risks (ERRs) for lung cancer for DWF of 1, 10, and 20. There were 839 deaths due to lung cancer. The dose distribution was broad and up to 1.25 Gy for a DWF of 1 for plutonium intakes, and for a DWF of 20 it was up to 16.8 weighted-Gy. The ERR at 100 weighted-mGy was 0.01 (95%CI −0.02, 0.03), and there was no evidence for a dose-response (Figure 4). There was no statistically significant differences in lung cancer radiation risk estimates between men and women related in large part to the smaller number of women, their overall lower dose to lung, and the absence of any suggestion of a radiation association overall or for either sex. Assuming radiation weighting factors of 10 and 20 did not change the pattern of risk by dose or the risk coefficients.

Table 7 presents the HRs and ERRs for selected causes of death. A DWF of 20 was applied for those tissues that concentrate plutonium, that is, lung, liver, bone and thoracic lymph nodes (for NHL). A DWF of 1 was applied and presented for those tissues with minimal plutonium deposition since there were no meaningful variations in the patterns of risk for higher DWFs. The only significant dose-response was seen for esophageal cancer with the ERR at 100 mGy of 0.29 (95%CI 0.02, 0.55; $n = 106$). For sites with increased internal exposures to plutonium such as the liver and thoracic lymph nodes, there was no evidence for an association with radiation dose. The ERRs at 100 weighted-mGy were −0.01 (95%CI −0.14, 0.12; $n = 110$), −0.74 (95%CI −1.52, 0.03; $n = 319$), and −0.01 (95%CI −0.04, 0.02; $n = 162$) for liver cancer, liver cirrhosis and NHL, respectively. Neither was there a significant association seen for leukemia other than chronic lymphocytic leukemia (non-CLL) [ERR per 100 mGy −0.43 (95%CI −1.11, 0.24); $n = 160$)] nor for the combination of non-CLL leukemia and myelodysplastic syndrome (MDS) [(-0.35 (95%CI −0.92, 0.22)]. Cancers of the colorectum, stomach and bladder were not significantly increased. Multiple myeloma also failed to show a statistically meaningful radiation association. CLL was not increasing with the ERR per 100 mGy of 0.04 (95%CI −0.59, 0.66; $n = 58$). Other sites not convincingly or consistently linked to ionizing radiation also showed little evidence of a dose-response such as cancers of the prostate, brain (for adults) and pancreas, or ischemic heart disease. For ischemic heart disease, the ERR per 100 mGy was −0.06 (95%CI −0.16, 0.04; $n = 3043$) (Figure 5). For cerebrovascular disease (CeVD) the ERR per 100 mGy was −0.11 (95%CI −0.35, 0.12; $n = 871$). For prostate cancer, the ERR per 100 mGy was −0.01 (95%CI −0.24, 0.23; $n = 383$), and for brain cancer, it was 0.20 (95%CI −0.27, 0.67; $n = 94$). There was no evidence for a dose-response for the combined causes of

Table 5. Standardized Mortality Ratios (SMR) for 26,328 workers at LANL first employed 1943–1980 and followed through 2017 by sex.

	Males		Females		Total		
Persons-at-risk	19,808		6,520		26,328		
Person-years	867,912		313,561		1,181,472		
Cause of death (ICD9)[a]	Obs	SMR	Obs	SMR	Obs	SMR	95%CI
All causes of death (001–999)	12,231	0.74*	3,545	0.85*	15,776	0.76*	0.75–0.78
All malignant neoplasms (140–208)	2,886	0.72*	881	0.87*	3,767	0.75*	0.73–0.77
Buccal cavity & pharynx (140–149)	45	0.55*	9	0.80	54	0.58*	0.44–0.76
Esophagus (150)	95	0.81*	11	1.08	106	0.83	0.68–1.01
Stomach (151)	113	1.01	14	0.75	127	0.98	0.81–1.16
Colon (153)	228	0.70*	67	0.74*	295	0.71*	0.63–0.79
Rectum (154)	55	0.81	11	0.75	66	0.80	0.62–1.02
Biliary passages & liver (155,156)	87	0.79*	23	0.98	110	0.82*	0.68–0.99
Pancreas (157)	204	0.96	46	0.80	250	0.92	0.81–1.05
Pleura & peritoneum (158.8, 158.9, 163) and mesothelioma (ICD10 C45)[b]	17	0.88	3	1.63	20	0.94	0.57–1.45
Larynx (161)	23	0.53*	0	0.00	23	0.50*	0.31–0.74
Bronchus, trachea, & lung (162)	653	0.50*	186	0.78*	839	0.54*	0.51–0.58
Bone (170)	11	1.25	1	0.51	12	1.11	0.58–1.95
Connective & other soft tissue (171)	23	1.09	8	1.36	31	1.15	0.78–1.64
Female breast (174)			192	1.11	192	1.11	0.96–1.27
Male breast (175)	3	0.59			3	0.59	0.12–1.173
All uterine (Females only) (179–182)			34	0.74	34	0.74	0.51–1.03
Cervix Uteri (180)			10	0.52*	10	0.52*	0.25–0.96
Ovary and other female genital organs (183–184)			66	1.00	66	1.00	0.77–1.27
Prostate (185)	383	0.96			383	0.96	0.87–1.06
Testes & other male genital organs (186, 187)	11	1.12			11	1.12	0.56–2.00
Kidney (189.0–189.2)	49	0.48*	13	0.74	62	0.51*	0.39–0.66
Bladder & other urinary (188, 189.3–189.9)	93	0.67*	10	0.65	103	0.67*	0.55–0.81
Melanoma of skin (172)	70	1.03	15	1.29	85	1.07	0.86–1.32
Other malignant neoplasm of skin (173)	21	0.82	4	1.32	25	0.87	0.56–1.28
Eye (190)	3	1.33	0	0.00	3	1.06	0.21–3.10
Brain & central nervous system (191–192)	71	0.74*	23	0.98	94	0.79*	0.64–0.97
Thyroid & other endocrine glands (193–194)	10	0.86	1	0.24	11	0.69	0.35–1.24
All lymphatic, hematopoietic tissue (200–208)	376	0.92	77	0.80	453	0.90*	0.82–0.98
Non-Hodgkin lymphoma (200, 202)	126	0.83*	36	0.92	162	0.85*	0.72–0.99
Hodgkin lymphoma (201)	19	1.08	2	0.55	21	0.99	0.61–1.51
Leukemia (202.4, 204–208)	154	1.01	26	0.79	180	0.97	0.83–1.12
Chronic lymphocytic leukemia (CLL) (202.4, 204.1, 204.9)	34	0.89	9	1.29	43	0.95	0.69–1.28
Leukemia other than CLL	119	1.05	17	0.66	136	0.98	0.82–1.16
Acute lymphocytic leukemia (204.0)	8	1.41	0	0.00	8	1.13	0.49–2.23
Acute myeloid leukemia (205.0, 205.3, 206.0, 207.0, 207.2)	66	1.16	9	0.71	75	1.07	0.85–1.35
Chronic myeloid leukemia (205.1, 206.1)	16	1.23	3	1.02	19	1.19	0.71–1.85
Multiple myeloma (203)	68	0.96	11	0.62	79	0.89	0.71–1.11
Smoking related cancers (140–150, 157, 161–162, 188–189)	1,163	0.58*	275	0.78*	1,438	0.61*	0.58–0.64
Non-smoking related cancers	1,723	0.86*	606	0.91*	2,329	0.87*	0.84–0.91
Polycythemia Vera (238.4)	2	0.67	0	0.00	2	0.53	0.06–1.92
Myelodysplastic syndrome (238.7)	21	0.73	4	0.65	25	0.71	0.46–1.05
Diabetes (250)	263	0.72*	67	0.62*	330	0.70*	0.62–0.78
Mental and behavioral disorders (290–319)	361	1.04	159	0.90	520	0.99	0.75–0.78
Parkinson's disease (332)	156	1.12	37	1.38	193	1.16	1.00–1.34
Dementia and Alzheimer's disease(290.0–290.4, 331.0)	462	0.93	273	0.89	735	0.92*	0.85–0.98
Dementia, Alzheimer's, Parkinson's disease & other motor neuron (290.0–290.4; 331.0; 332; 335.2)	654	0.97	319	0.93	973	0.96	0.90–1.02
Diseases of the Nervous System (320–389)	580	0.95	235	1.02	815	0.97	0.90–1.03
All Heart Disease (390–398, 404, 410–429)	3,544	0.63*	822	0.69*	4,366	0.64*	0.62–0.66
Ischemic heart disease (410–414)	2,517	0.59*	526	0.68*	3,043	0.60*	0.58–0.63
Cerebrovascular disease (430–438)	625	0.70*	246	0.80*	871	0.72*	0.68–0.77
Nonmalignant respiratory disease (460–519)	1,209	0.77*	382	0.94	1,591	0.80*	0.76–0.84
Bronchitis, emphysema, asthma (490–493)	458	0.73*	170	0.95	628	0.78*	0.72–0.84
Berylliosis (503)	4	26.04*	0	0	4	23.04*	6.20–59.0
Cirrhosis of liver (571)	267	1.00	52	1.14	319	1.02	0.91–1.14
Nephritis & nephrosis (580–589)	164	0.73*	31	0.50*	195	0.68*	0.59–0.78
AIDS (042–044)	11	0.34*	0	0	11	0.32*	0.16–0.58
All external causes of death (800–999)	973	1.00	175	1.17*	1,148	1.02	0.96–1.08
Accidents (850–949)	647	1.00	117	1.05	764	1.00	0.93–1.08
Suicides (950–959)	260	1.08	49	1.92*	309	1.16*	1.03–1.30

[a]ICD denotes International Classification of Disease. ICD Revision 9 codes are shown; [b]mesothelioma did not have an explicit code in ICD9 but did in ICD10 as denoted.

*Indicates SMR is significantly different from 1.0; $p < 0.05$.

Table 6. Internal cohort dose-response analyses for lung cancer over categories of lung-specific radiation doses among 26,328 workers at LANL first employed 1943-1980 and followed through 2017 by sex and for different Dose Weighting Factors (DWF)

	DWF = 1 for Pu				DWF = 10 for Pu				DWF = 20 for Pu			
Dose (mGy)[a]	Number of Workers	Number of cases	HR	95% CI	Number of Workers	Number of cases	HR	95% CI	Number of Workers	Number of cases	HR	95% CI
Lung Cancer												
<5	21,728	694	1.0	REF	21,705	694	1.0	REF	21,704	694	1.0	REF
5 – <50	3,539	112	0.89	0.73; 1.10	3,403	104	0.87	0.70; 1.08	3,369	104	0.88	0.71; 1.09
50 - <100	503	14	0.77	0.45; 1.30	506	13	0.72	0.41; 1.24	473	12	0.71	0.40; 1.26
≥100	558	19	1.01	0.64; 1.59	714	28	1.08	0.74; 1.58	782	29	1.02	0.70; 1.49
P for trend		839		*0.87 (+)*		839		*0.65 (-)*		839		*0.64 (-)*
HR (95% CI) at 100 mGy			1.01	0.88; 1.19			1.01	0.96; 1.07			1.01	0.98; 1.04
ERR (95% CI) at 100 mGy			0.01	−0.15; 0.17			0.01	−0.04; 0.06			0.01	−0.02; 0.03

	MALES: DWF = 20 for Pu				FEMALES: DWF = 20 for Pu			
Dose (mGy)[a]	Number of Male Workers	Number of cases	HR	95% CI	Number of Female Workers	Number of cases	HR	95% CI
Lung Cancer								
<5	15,425	515	1.0	REF	6,279	179	1.0	REF
5 – <50	3,212	97	0.86	0.69; 1.07	157	7	*Categorical model doesn't converge*[b]	
50 - <100	445	12	0.75	0.43; 1.34	28	0		
≥100	722	29	1.11	0.51; 1.07	60	0		
P for trend		653		*0.52 (+)*		186		
P for heterogeneity for sex[b]								
HR (95% CI) at 100 mGy			1.01	0.98; 1.03				
ERR (95% CI) at 100 mGy			0.01	−0.02; 0.03				

Note: Models include radiation doses lagged by 10 years. Doses were analyzed as a time-dependent measure. Outcomes include deaths from underlying causes of death. All models adjusted for sex, education (5 categories, as in Table 1) and year of birth (4 categories, as in Table 1). P-value for test for linear trend in the relative risk (i.e., hazard ratio) computed for continuous lung dose. P-values are two-sided. REF denotes the referent category. HR denotes Hazards Ratio; CI denotes Confidence Interval; ERR denotes Excess Relative Risk.

[a]Cumulative weighted absorbed doses to the lung (weighted-mGy) include the contributions of photons, neutrons, tritium, ^{238}Pu and ^{239}Pu. The DWFs used for neutron doses are 2.5 (thermal), 16 (fast) and 16 (fission). Three different Dose Weighting Factors (DWF) are applied to the ^{238}Pu and ^{239}Pu doses (1, 10, and 20). A DWF of 1 was assumed for tritium doses.

[b]Small numbers of cases among females in the upper dose categories created an unstable model. A crude contrast of females with > 5 weighted-mGy to those with < 5 weighted-mGy yields a Risk Ratio of 1.00 (95% CI 0.47, 2.13). A similar crude contrast for males yields a Risk Ratio of 0.95 (95% CI 0.78, 1.14) (Rothman and Boice 1979). These estimates are consistent (p for heterogeneity = 0.88), but the number of female cases with high lung doses is small.

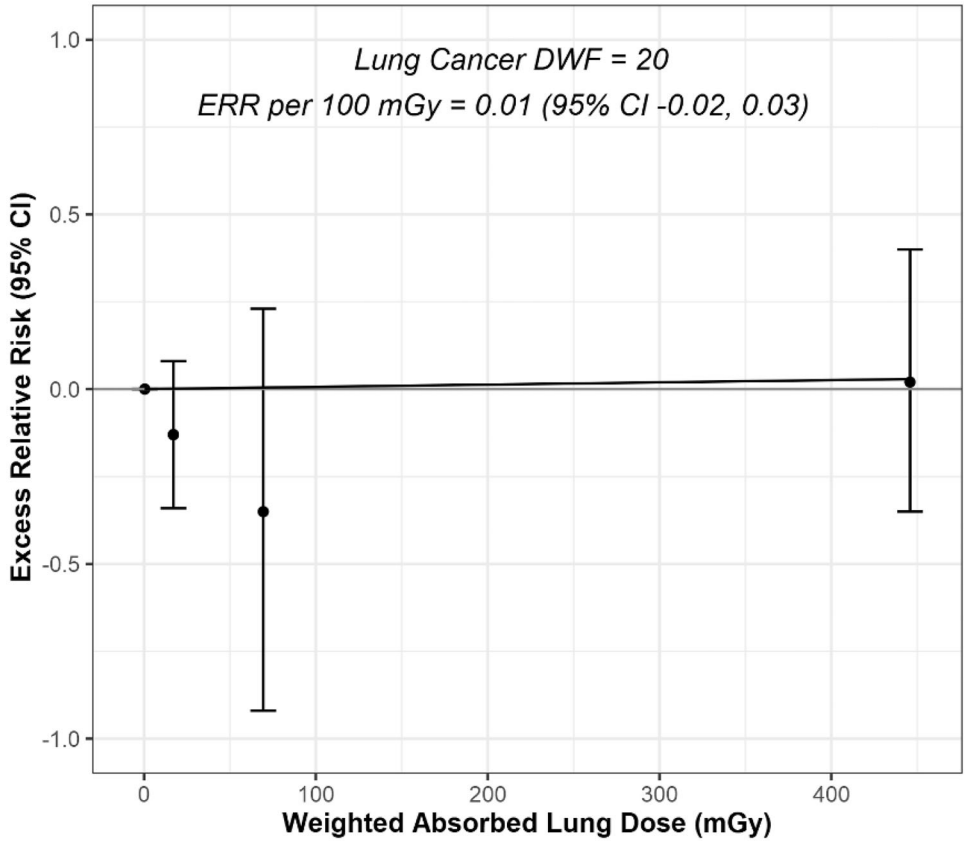

Figure 4. Excess Relative Risk (ERR) of lung cancer by weighted absorbed dose to lung among 26,328 workers at the Los Alamos National Laboratory (LANL) first employed 1943–1980 and followed through 2017. Cox proportional hazards models include radiation dose lagged by 10 years, adjusting for sex, education and year of birth. Dose was analyzed in a time-dependent manner. The ERR and 95% confidence intervals within selected dose categories are plotted at the mean dose within the category (Table 6). The linear trend line for a continuous measure of radiation dose to the lung is presented.

death from dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease with the ERR per 100 mGy of 0.01 (95%CI −0.19, 0.16; $n = 973$). There was a suggested dose-response for Parkinson's disease, although not at the level of statistical significance: ERR per 100 mGy of 0.16 (95%CI −0.07, 0.40; $n = 273$). There was no evidence for a dose-response for deaths from suicide.

Table 8 shows the relative risk (hazards ratio) for lung cancer over categories of external dose and internal plutonium dose for 26,324 workers first employed at LANL between 1943–1980 and followed through 2017. External dose to the lung was taken as the contributions of dose from photons, neutrons, and tritium. The referent group was taken as the 21,745 workers with cumulative lung doses <5 mGy for both external lung dose and internal plutonium alpha-particle lung dose. Modeling the joint effects of external and internal exposures is imprecise since only 19 lung cancers occurred among the 447 workers with >5 weighted-mGy lung doses from plutonium intakes. Nonetheless, adjusting for sex, education, year of birth, and external dose to the lung, the HR at 100 weighted-mGy plutonium dose were 1.15 (95%CI 0.66,1.99; $n = 839$). The trend was not statistically significant ($p = .62$).

Linkage with the U.S. Renal Data System (USRDS) identified 334 former LANL workers with end-stage renal disease (ESRD). The earliest diagnosis was in 1975 and the last in 2018. Overall, 123 of the incident cases were attributable to diabetes, 83 to hypertension, 48 to glomerulonephritis, 8 to cystic kidney disease, 15 to other urologic disorders, and 57 to other or unknown conditions. Among the 6459 workers who were monitored for plutonium, there were 92 incident cases of ESRD (1.4%) of which 17 (18.5%) were attributed to glomerulonephritis. Among the larger number of 19,829 workers not monitored for plutonium, there were 242 incident cases of ESRD (1.3%) of which 31 (12.8%) were attributed to glomerulonephritis. Of the 334 workers who developed ESRD, 285 died by end of follow-up, including 2 from kidney cancer, 45 from nonmalignant kidney disease (nephritis or nephrosis) and 44 from diabetes. Both kidney cancers and 18 of the 45 deaths from nephritis or nephrosis were among the workers monitored for Pu.

Discussion

The study of 26,328 workers at the Los Alamos National Laboratory first employed between 1943 and 1980 is notable because of its size; comprehensive approach for individual dose reconstruction that incorporates doses from photons, neutrons, tritium and plutonium; inclusion of over 6000 female workers; complete and long-term follow-up of up to 75 years; and the inclusion of a Hispanic population of over 3000 workers. There were no statistically significant associations between radiation and lung cancer, liver cancer, NHL, leukemia other than CLL, or ischemic heart disease. The

Table 7. Internal cohort dose-response analyses for selected causes of death by organ-specific dose among 26,328 workers at LANL first employed 1943–1980 and followed through 2017[a,b].

Dose (weighted-mGy)	Workers	Cases	HR	95%CI
Esophageal cancer (ICD9 150)				
<5	21,901	80	1.0	REF
5 to <50	3,433	20	1.22	0.74; 2.01
≥50	994	6	1.24	0.54; 2.88
P for trend		106		0.03 (+)
HR (95%CI) at 100 mGy			1.33	1.02; 1.73
ERR (95%CI) at 100 mGy			0.29	0.02; 0.55
Stomach cancer (ICD9 (151)				
<5	21,832	105	1.0	REF
5 to <50	3,474	16	0.90	0.52; 1.54
50 to <100	484	4	1.60	0.58; 4.39
≥100	538	2	0.76	0.19; 3.10
P for trend		127		0.76 (−)
HR (95%CI) at 100 mGy			0.92	0.55; 1.56
ERR (95%CI) at 100 mGy			−0.08	−0.61; 0.45
Colorectal cancer (ICD9 153, 154)				
<5	21,789	303	1.0	REF
5 to <50	3,503	54	0.97	0.72; 1.31
50 to <100	488	7	0.86	0.41; 1.83
≥100	548	7	0.82	0.39; 1.75
P for trend		371		0.81 (−)
HR (95%CI) at 100 mGy			0.97	0.74; 1.27
ERR (95%CI) at 100 mGy			−0.03	−0.31; 0.24
Liver cancer (ICD9 155, 156)				
<5	21,797	91	1.0	REF
5 to <50	3,313	15	0.96	0.55; 1.69
≥50	1,218	2	0.69	0.25; 1.87
P for trend		110		0.88 (−)
HR (95%CI) at 100 mGy			0.99	0.87; 1.13
ERR (95%CI) at 100 mGy			−0.01	−0.14; 0.12
Pancreas cancer (ICD9 157)				
<5	22,000	207	1.0	REF
5 to <50	3,375	36	0.98	0.68; 1.40
≥50	953	7	0.69	0.32; 1.47
P for trend		250		0.54 (−)
HR (95%CI) at 100 mGy			0.87	0.57; 1.35
ERR (95%CI) at 100 mGy			−0.13	−0.57; 0.30
Female breast (ICD9 174)				
<5	6,285	183	1.0	REF
≥50	239	8	1.31	0.64; 2.68
P for trend		191		0.58 (+)
HR (95%CI) at 100 mGy			1.22	0.61; 2.42
ERR (95%CI) at 100 mGy			0.20	−0.49; 0.88
Prostate Cancer (ICD9 185)				
<5	15,647	294	1.0	REF
5 to <50	3,238	72	0.93	0.71; 1.20
≥50	923	17	0.71	0.43; 1.15
P for trend		383		0.95 (−)
HR (95%CI) at 100 mGy			0.99	0.79; 1.25
ERR (95%CI) at 100 mGy			−0.01	−0.24; 0.23
Bladder & other urinary (ICD9 188, 189.3–189.9)				
<5	21,769	73	1.0	REF
5 to <50	3,518	23	1.40	0.86; 2.26
50 to <100	487	4	1.60	0.58; 4.42
≥100	554	3	1.11	0.35; 3.56
P for trend		103		0.40 (+)
HR (95%CI) at 100 mGy			1.15	0.83; 1.58
ERR (95%CI) at 100 mGy			0.14	−0.18; 0.46
Brain cancer (ICD9 191–192)[c]				
<5	22,071	77	1.0	REF
5 to <50	3,330	11	0.86	0.45; 1.65
≥50	927	6	1.67	0.71; 3.89
P for trend		94		0.37 (+)
HR (95%CI) at 100 mGy			1.24	0.78; 1.98
ERR (95%CI) at 100 mGy			0.20	−0.27; 0.67
Non-Hodgkin lymphoma (ICD9 200, 202.0–202.1, 202.8–202.9)				
<5	21,709	130	1.0	REF
5 to <50	3,360	23	0.93	0.59; 1.49
50 to <100	443	3	0.88	0.28; 2.78
≥100	816	6	0.95	0.4; 2.18
P for trend		162		0.47 (−)
HR (95%CI) at 100 mGy			0.99	0.96; 1.02
ERR (95%CI) at 100 mGy			−0.01	−0.04; 0.02
Multiple myeloma (ICD9 203)				
<5	21,931	61	1.0	REF
≥5	4,397	18	1.08	0.63; 1.85
P for trend		79		0.19 (−)
HR (95%CI) at 100 mGy			0.36	0.08; 1.64
ERR (95%CI) at 100 mGy			−1.02	−2.54; 0.50
Non-CLL leukemia (ICD9 204.0, 204.2, 204.3–204.9, 205–208)				
<5	21,820	122	1.0	REF
5+	4,508	37	1.09	0.75; 1.59
P for trend		160		0.21 (−)
HR (95%CI) at 100 mGy			0.65	0.33; 1.28
ERR (95%CI) at 100 mGy			−0.43	−1.11; 0.24
CLL (ICD9 204.1, 202.4)				
<5	21,931	41	1.0	REF
5 to <50	3,425	12	1.32	0.68; 2.58
50 to <100	476	2	1.43	0.34; 5.99
≥100	496	3	2.01	0.61; 6.63
P for trend		58		0.91 (+)
HR (95%CI) at 100 mGy			1.04	0.56; 1.93
ERR (95%CI) at 100 mGy			0.04	−0.59; 0.66
Non-CLL leukemia + MDS (ICD9 204.0, 204.2, 204.3–204.9, 205–208, 238.7)				
<5	21,820	139	1.0	REF
≥5	4,508	46	1.13	0.80; 1.60
P for trend	185		0.23 (−)	
HR (95%CI) at 100 mGy		0.71	0.40; 1.25	
ERR (95%CI) at 100 mGy		−0.35	−0.92; 0.22	
Dementia, Alzheimer's disease, Parkinson's disease, motor neuron disease (ICD9 290.0–290.4, 331.0, 332, 335.2)				
<5	22,071	786	1.0	REF
5 to <50	3,330	136	0.89	0.74; 1.08
50 to <100	458	25	1.07	0.72; 1.60
≥100	469	26	0.97	0.65; 1.44
P for trend		973		0.90 (−)
HR (95%CI) at 100 mGy			0.99	0.83; 1.18
ERR (95%CI) at 100 mGy			−0.01	−0.19; 0.16
Parkinson's Disease (ICD9 332)				
<5	22,071	213	1.0	REF
5 to <50	3,330	37	0.74	0.51; 1.05
50 to <100	458	14	1.83	1.06; 3.17
≥100	469	9	1.05	0.53; 2.06
P for trend		273		0.18 (+)
HR (95%CI) at 100 mGy			1.18	0.93; 1.49
ERR (95%CI) at 100 mGy			0.16	−0.07; 0.40
Ischemic heart disease (ICD9 410–414)				
<5	21,816	2,484	1.0	REF
5 to <50	3,489	429	0.96	0.87; 1.07
50 to <100	484	70	1.11	0.87; 1.41
≥100	539	60	0.91	0.70; 1.17
P for trend		3,043		0.23 (−)
HR (95%CI) at 100 mGy			0.94	0.85; 1.04
ERR (95%CI) at 100 mGy			−0.06	−0.16; 0.04
Cerebrovascular disease (ICD9 430–438)				
<5	22,071	742	1.0	REF
5 to <50	3,330	102	0.87	0.69; 1.06
50 to <100	458	15	0.90	0.54; 1.50
≥100	469	12	0.68	0.38; 1.21
P for trend		871		0.35 (−)
HR (95%CI) at 100 mGy			0.89	0.71; 1.13
ERR (95%CI) at 100 mGy			−0.11	−0.35; 0.12
Cirrhosis of liver (571)				
<5	21,821	279	1.0	REF
5 to <50	3,470	35	0.85	0.59; 1.22
50 to <100	498	4	0.72	0.27; 1.95
≥100	539	1	0.18	0.026; 1.31
P for trend		319		0.06 (−)
HR (95%CI) at 100 mGy			0.48	0.22; 1.03
ERR (95%CI) at 100 mGy			−0.74	−1.52; 0.03
Suicides (ICD9 950–959)				
<5	22,071	262	1.0	REF
5 to <50	3,330	40	1.15	0.82; 1.62
50 to <100	458	2	0.43	0.11; 1.72
≥100	469	5	1.15	0.47; 2.81
P for trend		309		0.79 (+)

(*continued*)

Table 7. Continued.

Dose (weighted-mGy)	Workers	Cases	HR	95%CI
HR (95%CI) at 100 mGy			1.05	0.72; 1.53
ERR (95%CI) at 100 mGy			0.05	−0.32; 0.43

MDS denotes Myelodysplastic Syndrome; CLL denotes Chronic lymphocytic leukemia; HR denotes Hazards Ratio; CI denotes Confidence Interval; REF denotes the referent category.

[a]Models are for radiation doses lagged by 10 years for all outcomes except Non-CLL and Non-CLL + MDS which uses radiation doses lagged by 2 years. Doses were analyzed as a time-dependent measure. Outcomes include deaths from underlying causes of death only, except for Non-CLL, CLL, and Parkinson's disease. Models adjusted for sex, education (5 categories, as in Table 1) and year of birth (4 categories, as in Table 1). *p*-Value for test for linear trend in the relative risk (i.e. hazard ratio) computed for continuous organ dose. *p*-Values are two-sided.

[b]Cumulative organ doses include dose contributions from photons, neutrons, tritium, ^{238}Pu and ^{239}Pu. The weighting factors used for neutron doses are 2.5 (thermal), 16 (fast) and 16 (fission). A DWF of 1 was assumed for tritium doses. For most organs with small plutonium depositions, a DWF =1 was used since analyses with DWFs of 10 and 20 for Pu were essentially the same. For organs that concentrate plutonium after intake, a DWF of 20 for plutonium was used, that is, a DWF of 20 was assumed for cancers of the lung, liver and bone, for liver cirrhosis and for the thoracic lymph nodes. The cumulative organ doses are weighted absorbed doses.

[c]First two categories of Year of birth collapsed for model convergence

only significant radiation dose-response was for cancer of the esophagus. Measurable intakes of plutonium likely contributed to a small but significant excess of bone cancer. Plutonium may have contributed to a small but nonsignificant increase in lung cancer, but results were inconclusive. Workers in the 1940s showed a significant excess of deaths due to berylliosis related to beryllium exposure, based on 4 overall deaths. A dose-response of borderline significance was seen for Parkinson's disease which is consistent with a recent report among Mayak workers in Russia (Azizova et al. 2020). There were no meaningful differences between radiation risk for females compared with male workers, most notably for lung cancer, but the doses for women were low. The Hispanic population did not reveal any radiation dose-response relationships. Consistent with studies emerging from the Million Person Study, there was little evidence that radiation exposures received gradually over time significantly increased the risk of cancers and ischemic heart disease; however, the narrow dose ranges and associated sampling variability is such that radiation risks consistent with current understanding cannot be ruled out (Hauptmann et al. 2020).

Plutonium worker studies

Studies of plutonium workers in Russia have reported increased cancers of the lung, liver and bone for relatively high levels of plutonium intakes, (Koshurnikova et al. 2000; Gilbert et al. 2000, 2013; United Nations Scientific Committee on the Effects of Atomic Radiation 2008; ATSDR 2010; International Agency for Research on Cancer 2012; Sokolnikov et al 2008, 2015; Gillies, Kuznetsova, et al. 2017; Grellier et al. 2017). In some instances, intakes of plutonium were sufficiently large as to cause pulmonary sclerosis of the lung, a deterministic effect (Claycamp et al. 2000). There was little statistical evidence for radiation risks for other organs with lower levels of plutonium deposition (Shilnikova et al. 2003; Hunter et al. 2013; Sokolnikov et al. 2015; Kuznetsova et al. 2016). Studies of plutonium workers in the US and the UK involved much lower levels of plutonium, and radiation-related increases in cancer are not consistent (Wilkinson et al. 1987; Gilbert, Cragle, et al. 1993; Gilbert, Omohundro, et al. 1993; Wiggs et al. 1994; Voelz et al 1997; Omar et al. 1999; Brown et al. 2004; Wing et al. 2004; Wing and Richardson 2005; Agency for Toxic Substances and Disease Registry 2010; Boice et al. 2014).

Lung cancer

The mean cumulative lung dose for the 17,053 workers monitored for radiation was 13.9 mGy (maximum 1.2 Gy), with 1061 workers receiving >50 mGy. Applying a DWF of 20 for plutonium dose, the mean cumulative lung dose was 28.6 weighted-mGy (maximum 16.8 Gy). There were 836 deaths due to lung cancer, and no evidence for increasing risk with increasing radiation dose, regardless of applying radiation weighting factors for plutonium of 1, 10 or 20. ERRs per 100 weighted-mGy higher than 0.03 could be excluded with 95% confidence. There was no difference in the radiation-related lung cancer risks between men (19,808) and women (6520), but women had low radiation doses and number of cases were small. These findings for lung cancer and radiation are generally consistent with seven other cohort studies within the Million Person Study consisting of 385,778 workers (Boice et al. 2011, 2014; Boice, Ellis, et al. 2019; Golden et al. 2019; Boice et al. 2020; Boice, Cohen, Mumma, Hagemeyer, et al. 2021). A recently completed study of over 100,000 male and female medical radiation workers within the MPS found a statistically significant increase in lung cancer (Yoder et al. 2018, 2020; Boice, Cohen, et al. 2019; Boice, Cohen, Mumma, Yoder, et al. 2021), whereas a study of over 13,000 female workers at the Tennessee Eastman Corporation site did not find lung cancer to be associated with radiation lung doses from uranium dust inhalation (Boice, Cohen, Mumma, Golden, et al. 2021). Studies of Hanford workers reported a decrease in lung cancer risk with increasing radiation lung doses, though not statistically significant (Peterson et al. 1990). Studies of tuberculosis patients who received multiple chest fluoroscopies during the monitoring of lung collapse therapy found no evidence for radiation-related lung cancer risk, and there was no evidence that women had a higher risk than men (Boice, Ellis, et al. 2019). A recent study of medical radiological technicians also found little evidence for increasing risk of lung cancer with estimates of radiation dose (Velazquez-Kronen et al. 2020).

In contrast to the studies above, studies of the Japanese atomic bomb survivors exposed acutely to radiation in 1945 indicate a significant association between lung cancer and radiation dose and that women were at 2–3 times the excess relative risk as men (Cahoon et al. 2017). Studies of 22,374 Mayak workers also reported a significant difference between the female and male radiation risks for lung cancer, with females being 2–4 times higher than males based on

incidence or mortality (Gillies, Kuznetsova, et al. 2017). The mean cumulative lung dose was 455 mGy (maximum 7.6 Gy) from gamma radiation and approximately 129–176 mGy (maximum 17–20 Gy) from ^{239}Pu. The ERR per Gy for lung cancer mortality for external lung dose was estimated to be about 0.38–0.40 (95%CI 0.22, 0.61) based on 158 lung cancer deaths. Similar to studies of Japanese atomic bomb survivors, smoking rates were very different in males (74%) and females (4%) for those with known smoking histories. When the analysis was restricted to workers who received less than about 200 mGy plutonium dose, there apparently was no difference in the male and female estimates of radiation risk for lung cancer. The overall lost-to-follow-up rate was relatively high at 22% (Preston et al. 2017). The estimates of plutonium dose were somewhat uncertain because few workers had urine bioassays during the time of exposure, and the average number of bioassays was less than 2 (Khokhryakov et al. 2013). Radiation estimates were based on incomplete coverage of only 42% of the workers employed at the plutonium facilities (Gillies, Kuznetsova, et al. 2017). A recent comprehensive dose uncertainty analysis found that accounting for uncertainty had a minor effect on the external gamma-ray dose-response, whereas it strikingly increased the width of the confidence intervals for the plutonium dose-response (Stram et al. 2021). Another large study involved the U.K. Sellafield workers which included 23,443 workers (Gillies, Kuznetsova, et al. 2017). The mean dose to the lung from external exposure was 73 mGy (maximum 1.8 Gy), and the dose from intakes of plutonium was of the order of 1.9–5.5 mGy (maximum 0.5–0.7 Gy) depending upon assumptions regarding solubility. These low doses were such that statistically significant associations between lung dose and lung cancer were not observed; however, pooled analyses with the higher-dose Mayak workers were informative, with the pooled ERR point estimates for lung cancer in relationship to plutonium lung dose within the range of 50–80 per 100 mGy. The risk coefficients for lung cancer for external exposure for LANL and Mayak workers are not statistically compatible, whereas they are compatible for plutonium dose although the LANL estimate is not statistically significant.

Whether there is a statistically meaningful difference in lung cancer risk between men and women is of importance to NASA (National Council on Radiation Protection and Measurements 2021). NASA bases its radiation protection standard for deep space exploration on individual lifetime cancer mortality predictions (National Aeronautics and Space Administration 2015, 2021). The lifetime cancer mortality models currently used are based on the atomic bomb survivor data, which limits the amount of time female astronauts can spend in space (National Academies/National Research Council 2012). This is because Japanese women exposed acutely to ionizing radiation were at a 2–3 times higher excess relative risk of lung cancer than men (National Council on Radiation Protection and Measurements 2016; Boice, Ellis, et al. 2019). The studies of plutonium workers exposed to mixed radiation fields (external low-LET photons and internal high-LET alpha particles) are one of the few terrestrial analogs capable of providing estimates of risks directly relevant for space radiation which consists of both low-LET radiation and high-LET high-energy heavy particle radiation (galactic cosmic rays (GCR)) (National Council on Radiation Protection and Measurements 2019; Boice, Ellis, et al. 2019; Boice 2019; Boice, Cohen, Mumma, Hagemeyer, et al. 2021). It might be noted that the exposures inside a space vehicle differ from those outside because of the interactions with shielding. Low energy alpha particles are a significant portion of the GCR exposure experienced inside a space vehicle, and much of the high-LET portion of radiation space exposure is actually from low energy alpha particles and protons (National Council on Radiation Protection and Measurements 2014; Slaba et al. 2016; Boice, Quinn et al. 2021).

Liver

The liver is similar to the lung, bone, and thoracic lymph nodes in being a primary site where plutonium would concentrate and be retained for extended periods (Voelz 1991; Agency for Toxic Substances and Disease Registry 2010; Kathren and Tolmachev 2019). Liver cancer has been found to be significantly increased among Japanese atomic bomb survivors for both males and females (Ozasa et al. 2012), whereas a negative dose-response was reported among INWORKS occupationally-exposed workers (Richardson et al. 2018). The radiation estimates among Japanese survivors are based on combined doses from external gamma and neutron radiation, whereas the INWORKS considered only external gamma radiation and excluded any concurrent worker doses from intakes of radionuclides or from external neutrons (National Council on Radiation Protection and Measurements 2018a). Significant excesses of liver cancer have been reported among the Mayak workers and appeared concentrated among workers with estimated plutonium absorbed doses >1 Gy (Gilbert et al. 2000; Sokolnikov et al. 2008). Among workers in the other MPS cohorts, no radiation-related increases of liver cancer were found among workers at the Rocketdyne (Boice, Cohen et al. 2006; Boice et al. 2011), Mound (Boice et al. 2014), or Mallinckrodt (Golden et al. 2019) facilities, nor among atomic veterans (Boice et al. 2020). Among LANL workers there was no evidence for an increased risk of liver cancer related to external or internal plutonium doses. The overall dose-response was negative, but only relatively high ERRs per 100 mGy >0.46 could be excluded with 95% confidence.

Bone

High bone doses from alpha-particle emitting radionuclides have been found to cause bone cancer, for example, among radium dial painters (Rowland et al. 1983; United Nations Scientific Committee on the Effects of Atomic Radiation 2008) and among Mayak plutonium workers (Koshurnikova et al. 2000, Sokolnikov et al. 2008). There is limited evidence that low-LET radiation causes bone cancer at relatively low doses below several Gy (United Nations Scientific

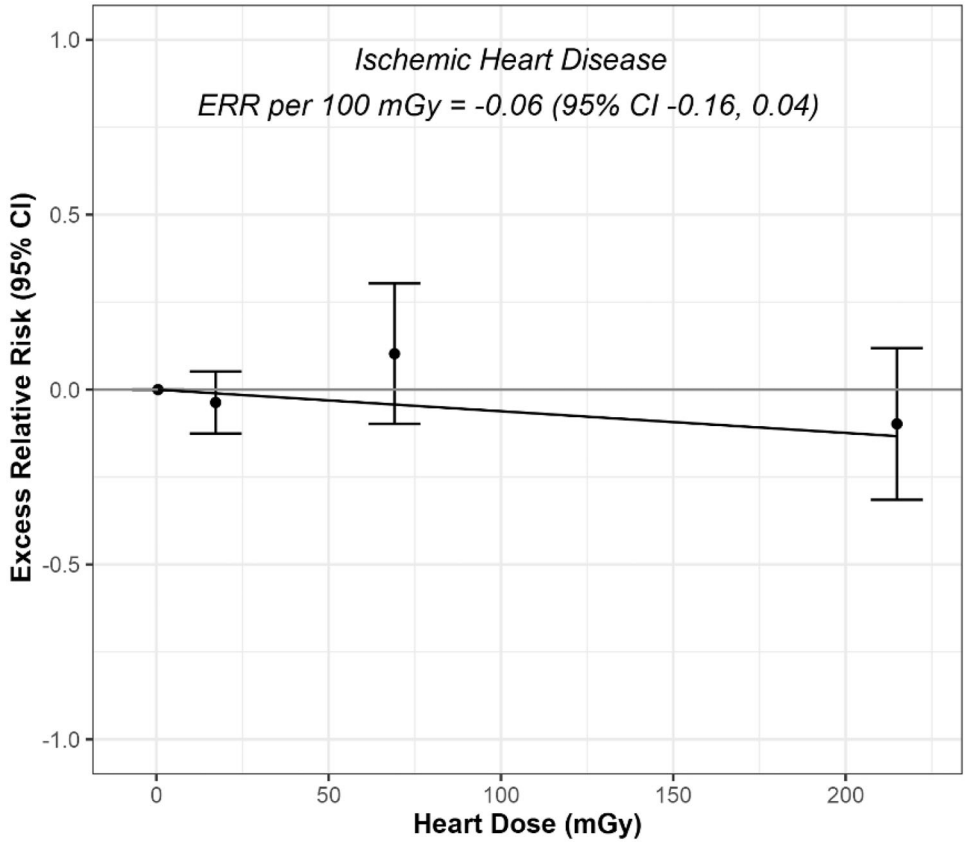

Figure 5. Excess Relative Risk (ERR) of ischemic heart disease by radiation dose among 26,328 workers at the Los Alamos National Laboratory (LANL) first employed 1943–1980 and followed through 2017. Cox proportional hazards models include radiation dose lagged by 10 years, adjusting for sex, education and year of birth. Dose was analyzed in a time-dependent manner. The ERR and 95% confidence intervals within selected dose categories are plotted at the mean dose within the category (Table 7). The linear trend line for a continuous measure of radiation dose to the heart is presented.

Table 8. Relative risks for lung cancer over categories of external[a] lung dose by internal plutonium lung dose among 26,328 workers at LANL first employed 1943–1980 and followed through 2017.

	External lung dose (mGy)[a]		
Internal plutonium lung dose (weighted-mGy)	<5	5–49	50+
<5			
No. of Workers	21,708	3337	836
No. of lung cancers	694	103	23
RR (95%CI)	1.0 (REF)	0.88 (0.71, 1.09)	0.83 (0.55, 1.26)
5–49			
No. of Workers	19	23	20
No. of lung cancers	0	2	1
RR (95%CI)	0.00 (0.00, 6.30)	1.86 (0.46, 7.46)	0.93 (0.13, 6.62)
50+			
No. of Workers	114	114	157
No. of lung cancers	3	6	7
RR (95%CI)	0.62 (0.20, 1.92)	1.26 (0.56, 2.82)	1.11 (0.53, 2.34)

[a]Absorbed doses to the lung are lagged 10 years. External dose to the lung is taken as the sum of photons, neutrons and tritium doses. The weighting factors used for neutron doses are 2.5 (thermal), 16 (fast) and 16 (fission). Internal dose to lung includes any intakes of ^{238}Pu or ^{239}Pu. Dose weighting factor (DWF) of 20 was applied to the ^{238}Pu and ^{239}Pu doses. RR denotes Relative Risk; CI denotes Confidence Interval; REF denotes Referent group

Committee on the Effects of Atomic Radiation 2008). The number of bone cancers occurring among the LANL workers was low and only 12 in total. There was a small but statistically significant increase in bone cancer among the workers monitored for plutonium, possibly attributable to prior plutonium intakes. It had been previously reported that one of the 26 earliest plutonium workers at LANL who were intensely studied clinically for over 50 years, had died of bone cancer (Hempelmann et al. 1973; Voelz 1991; Voelz and Lawrence 1991; Voelz et al. 1997). For this individual, our estimate of dose to the bone surface of about 55 mGy is 8 times lower than previous estimates of 440 mGy (Voelz 1991; Voelz and Lawrence 1991). This difference is related to differences in the ICRP biokinetic models used. In earlier models, the endosteum was assumed to be a 10-μm-thick layer that covered the surfaces of the bone, whereas new

models assume the thickness to be 50-μm. The models predict the same activity in bone but the increase in mass results in a much lower dose. Assuming a DWF of 20, the dose to the bone for this worker is 1.10 weighted-Gy.

NHL

Because plutonium radionuclides inhaled in relatively soluble form tend to migrate to the thoracic lymph nodes, lymphoma is a plausible adverse health outcome (Kathren and Tolmachev 2019). Nearly 7000 LANL workers had positive assays reflecting intakes of ^{238}Pu and/or ^{239}Pu. This resulted in a contribution of dose to the thoracic lymph nodes that, on average, was about 3 times higher than the contribution from external sources of exposure. There was no evidence for a radiation-related excess of NHL among the LANL employees. The upper 95%CI about the ERR per 100 mGy of approximately 0.17 indicates that mortality risks higher than this level can be excluded with 95% confidence. A positive, but not significant, dose-response for NHL was reported among Mallinckrodt uranium processing workers for whom dose to the thoracic lymph nodes from intakes of uranium and radium also was evaluated (Golden et al. 2018). Studies of uranium processors (Silver et al. 2013; Zablotska et al. 2013) and uranium millers (Boice et al. 2008) do not find significant associations between radiation and NHL (United Nations Scientific Committee on the Effects of Atomic Radiation 2017). A relationship between radiation with either external gamma or internal plutonium for NHL was not seen among Mayak workers (Kuznetsova et al. 2016). External radiation has not generally been considered a cause of NHL (United Nations Scientific Committee on the Effects of Atomic Radiation 2008), although an excess was reported among male but not female atomic bomb survivors (Hsu et al. 2013). NHL was not associated with radiation in recent studies of nuclear weapons test participants (Boice et al. 2020) or US radiological technologists (Linet et al. 2020).

Leukemia, CLL, and MDS

Leukemia other than CLL is frequently found to be in excess among populations exposed to ionizing radiation. Excesses have been reported after 2 years from initial exposure, and the radiation risk coefficient is several times higher than observed for solid cancers. The mean dose to red bone marrow for LANL workers was 12.4 mGy and the maximum was 835 mGy. Leukemia other than CLL was not significantly elevated: ERR per 100 mGy −0.43 (95%CI −1.11, 0.24); $n = 130$. The upper 95%CI about the ERR per 100 mGy of 0.24 indicates that the data are consistent in a statistical sense with radiation risk estimates up to this level with 95% confidence; that is, the data are not inconsistent with those reported in studies of male atomic bomb survivors (Hsu et al. 2013) and in large occupational studies (Leuraud et al. 2015; National Council on Radiation Protection and Measurements 2018a; Gillies et al. 2019). Significant associations between non-CLL leukemia and radiation also have been seen in larger MPS populations of nuclear power plant workers and industrial radiographers (National Council on Radiation Protection and Measurements 2018a; Boice, Cohen, Mumma, Hagemeyer, et al. 2021). For Mayak workers, there was a significant risk of leukemia other than CLL associated with relatively high levels of gamma-ray exposures where nearly 20% of the exposed population receive greater than 3 Gy cumulative dose: ERR per Gy = 0.99 (90%CI 0.45; 2.12), n = 77, but there was no association with plutonium exposures (Shilnikova et al. 2003; Kuznetsova et al. 2016). Radiation associations among LANL workers were not found for CLL, consistent with studies of Mayak workers (Kuznetsova et al. 2016), and recent studies of nuclear weapons test participants (Boice et al. 2020) and US radiological technologists (Linet et al. 2020). MDS and MDS combined with AML also were not found to be associated with radiation, consistent with recent studies of nuclear weapons test participants (Boice et al. 2020) and US radiological technologists (Linet et al. 2020).

It is worth mentioning that MDS represents a grouping of heterogeneous diseases, and its association with radiation exposure is very uncertain (United Nations Scientific Committee on the Effects of Atomic Radiation 2020). The classification of MDS has evolved over the years, and in the past MDS cases were often misdiagnosed as AML. The United Nations Scientific Committee on the Effects of Atomic Radiation (2020) recently questioned whether MDS should be included in the assessment of leukemia risk. Among Japanese atomic bomb survivors included in the Life Span Study (LSS), MDS has been discussed but not included in the analyses of leukemia or lymphoma (Hsu et al. 2013). Radiation has been associated with MDS among long-term atomic bomb survivors at Nagasaki, a study which included survivors who were not in the LSS (Iwanaga et al. 2011). The results are difficult to interpret because of the extremely long latency following childhood exposures, up to 50 years which is inconsistent with the much shorter latencies seen for AML where a wave-like pattern of risk overtime is seen with peak excesses occurring 10 to 15 years after exposure and then risk diminishes over time.

Esophageal cancer

A significant association was seen between estimated dose to the esophagus and radiation among the LANL workers. The mean dose to esophagus was 12.8 mGy and the maximum was 858 mGy. Esophageal cancer also was significantly associated with radiation among Mayak workers (ERR per 100 mGy 0.13; 95%CI 0.04, 0.33) (Sokolnikov et al. 2015) and comparable to our ERR per 100 mGy of 0.29 (95%CI 0.02,0.55). Among workers at the Mound facility in Ohio, a significant positive dose-response trend for esophageal cancer was reported where the estimated excess relative risk at 100 mSv was 0.54 (05% CI 015–1.07) (Boice et al. 2014). A non-significant increase in esophageal cancer among nuclear weapons test participants was seen (ERR per 100 mGy 0.19; 95%CI −0.23, 0.60), although smoking habits among enlisted personnel may have been a contributing factor

(Boice et al. 2020). A significant excess risk of esophageal cancer related to radiation was seen in Japanese atomic bomb survivors for both cancer incidence (Preston et al. 2007) and mortality (Ozasa et al. 2012), although significance was apparent only among the female survivors. Increased ERRs per Gy were seen for esophageal cancer among the INWORKS consortium, but not at the level of statistical significance (Richardson et al. 2018).

Nephrotoxicity

Plutonium is an actinide heavy metal that has the potential to damage the kidneys (New Brunswick Laboratory 2015). There is little evidence, however, from human occupational studies or canine experimental studies for associations between plutonium intakes and malignant or nonmalignant kidney disorders (Agency for Toxic Substances and Disease Registry 2010). Similarly, there was no increase in nonmalignant kidney disease among all LANL workers, nor among the 6459 workers monitored for plutonium (SMR 0.86; 95%CI 0.67, 1.09). The ESRD registry has revealed increases in renal toxicity, especially glomerulonephritis in studies of workers exposed to silica dust and other non-radioactive materials (Steenland 2005). Linkage with the USRDS registry did not reveal increased numbers of glomerulonephritis cases among workers monitored for plutonium compared with those not monitored for plutonium. Additional evidence is thus provided that plutonium is an unlikely cause of serious kidney failure leading to either death or dialysis.

Ischemic heart disease

There was no evidence for a radiation-related association for ischemic heart disease based on 3043 confirmed deaths. The ERR per 100 mGy was −0.06 (95%CI 0.16, 0.04) indicating that risks higher than an ERR per 100 mGy of 0.04 could be rejected with 95% confidence. The absence of an association with ischemic heart disease is consistent with other MPS cohort studies that do not find increases in IHD over categories of radiation dose to the heart: Mallinckrodt (Golden et al. 2018), Rocketdyne (Boice, Cohen, et al. 2006), nuclear power plant workers and industrial radiographers (National Council on Radiation Protection and Measurements 2018a; Boice, Cohen, Mumma, Hagemeyer, et al. 2021), and atomic veterans (Boice et al. 2020). IHD was raised but not significantly so in a pooled analysis of Mayak and Sellafield nuclear workers: ERR per Sv of 0.22 (95%CI −0.06, 0.57) (Azizova, Batistatou, et al. 2018). A significant radiation risk for IHD was reported in the INWORKS study: ERR per 100 mSv = 0.017 (95%CI 0.0002, 0.036; $n = 17{,}279$). The INWORKS results need to be interpreted with caution, however, because of significant heterogeneity in the estimates of radiation risk, that is, significant radiation associations were seen for white-collar workers and not blue-collar workers and for female workers and not male workers (Gillies, Richardson, et al. 2017). The absence of information on internal radiation exposures and on potential confounders associated with lifestyle factors was also noted.

A recent report among the Japanese atomic bomb survivors found no association between radiation and IHD (Takahashi et al. 2017). Inconsistencies among studies may be related to the inability to control for potential confounding factors such as cigarette smoking and other lifestyle behaviors; medical conditions, such as diabetes and blood pressure; misclassification of death certificate causes of death; or whole-body radiation effects on renal function (Ozasa et al. 2017; de Vocht et al. 2020). Whether radiation doses to the heart <0.5 Gy can result in increased deaths due to IHD is an area of intense interest and study (Tran et al. 2017; National Council on Radiation Protection and Measurements 2018a; Wakeford 2019; Boice, Held, et al. 2019; EPRI 2020; Richardson et al. 2020; Tapio et al. 2021).

Cerebrovascular disease

There was no evidence for a radiation association for cerebrovascular (CeVD) disease based on 871 confirmed deaths among LANL workers. The ERR per 100 mGy was −0.11 (95%CI −0.35, 0.12), indicating that ERR per 100 mGy greater than 0.12 could be excluded with 95% confidence. Cerebrovascular disease was significantly raised among Mayak nuclear workers but only for incidence and not mortality (Azizova et al. 2011). The authors commented that differences in radiation risk between cerebrovascular disease incidence and mortality could not be ruled out, and discussed the possibility of surveillance bias which they concluded was unlikely. The total cumulative absorbed doses among Mayak were exceptionally large and reached up to 9 Gy. In a more recent mortality study that also included the Sellafield worker cohort, there were no radiation associations for CeVD (Azizova, Batistatou, et al. 2018). The dose-response was in relation to personal dose equivalent (Hp(10)). For Mayak, the ERR per 100 mSv for CeVD mortality was 0.00 (95%CI −0.006, 0.008) and for Sellafield it was 0.005 (95%CI −0.046, 0.079). The absence of a radiation association for CeVD mortality in both the Mayak and Sellafield workers is consistent with the LANL findings, although the statistical uncertainties are large.

Comparisons with the study of the Japanese atomic bomb survivors are not straightforward based on the published data because CeVD is not separated out from circulatory disease (Ozasa et al. 2012). However, Gillies, Richardson, et al. (2017, Table 7) obtained the LSS data on adult survivors and, using colon dose in the dose response, reported the CeVD mortality risk to be: ERR per 100 mSv = 0.008 (90% CI −0.0003, 0.018; $n = 7708$). Significant radiation associations for CeVD mortality were reported in the INWORKS study: ERR per 100 mSv = 0.049 (90% CI 0.011, 0.092; $n = 4399$) (Gillies, Richardson, et al. 2017). The authors raised caution in interpreting these findings because of the heterogeneity in the estimated radiation risks and the absence of information on internal radiation exposures as well as potential confounders associated with lifestyle factors. It was noted that a radiation risk was apparent only among blue-collar workers and not among white-collar workers. For the 15-Country Study using colon dose, the ERR per

100 mSv was 0.088 (95%CI −0.067, 0.316; $n = 1224$) (Gillies, Richardson, et al. 2017).

Berylliosis

Beryllium was used at LANL in the 1940s to develop and build implosion-assembly devices and more recently for operations related to nuclear reactors and weapons production, machining, fabrication, and testing of components (Stefaniak et al. 2003). At sufficiently high cumulative levels of intake, beryllium can cause chronic beryllium disease, lung cancer, and other adverse health effects (International Agency for Research on Cancer 2018). Excessive exposure to beryllium at LANL is evident by the significant increase in berylliosis, a disease that is caused only by beryllium exposure, although based on only 4 deaths. The risk of berylliosis and beryllium-associated diseases has not been comprehensively evaluated at the level of mortality within DOE facilities and future studies within the MPS will consider a broader evaluation by pooling results from other weapons facilities, including Mound, Rocky Flats, Fernald, Savannah River, Oak Ridge (K-25, Y-12, ORNL) and Hanford where beryllium exposure has occurred (Kreiss et al. 1993; Stange et al. 1996; Viet et al. 2000; Welch et al. 2013; Department of Energy 2019; Tolmachev et al. 2019; Boice, Quinn, et al. 2021).

Parkinson's disease

Parkinson's disease and other neurological conditions are generally not considered outcomes associated with ionizing radiation (Yamada et al. 2009; Pasqual et al. 2021). A recent study of Mayak workers, however, reported a significant correlation between low-LET external radiation and Parkinson's disease (Azizova et al. 2020). LANL workers also showed a significant increase in Parkinson's disease in comparison with the general population, SMR 1.16 (95%CI 1.00, 1.34), $n = 193$. A positive association with radiation was seen, ERR per 100 mGy of 0.16 (95%CI −0.07, 0.40), consistent with that among Mayak workers ERR per 100 mGy of 0.10 (95%CI 0.06, 0.17). There was no radiation-related increase seen for other neurological disorders including dementia, Alzheimer's disease, and motor neuron disease: ERR per 100 mGy of −0.01 (95%CI 0.19, 0.16; $n = 973$) for the combined neurological causes of death. Possible associations between neurological disorders and high-LET radiation as experienced in lengthy exposures during space exploration are of importance to NASA since animal experiments simulating galactic cosmic ray exposures find elevations in Alzheimer's disease as well as diminution of cognitive function (Cherry et al. 2012; National Council on Radiation Protection and Measurements 2016; Boice 2017, 2019; Simonsen et al. 2020; National Aeronautics and Space Administration 2021). There is also an interest in persistent depression-like behavior, including anxiety disorders, seen in animal experiments following exposures to analogs of spaceflight radiation (Clément et al. 2020).

Other sites

There was no evidence for significant radiation association for colorectal cancer (ERR per 100 mGy of −0.03, $n = 371$); brain cancer (0.20, $n = 94$); pancreatic cancer (−0.13, $n = 250$); prostate cancer (-0.01, $n = 383$); stomach cancer (−0.08, $n = 127$); bladder cancer (0.14, $n = 103$); liver cirrhosis (−0.74, $n = 319$) or suicide (0.05, $n = 309$). Similarly, there was no evidence for a radiation association for multiple myeloma, consistent with studies of Mayak workers (Kuznetsova et al. 2016) and recent studies of nuclear weapons test participants (Boice et al. 2020) and US radiological technologists (Linet et al. 2020). Japanese atomic bomb survivors (Hsu et al. 2013) and large occupational studies (Leuraud et al. 2015) provide little evidence for radiation associations with multiple myeloma. Melanoma among LANL workers was not associated with radiation consistent with previous LANL studies (Acquavella et al. 1983) and with Mayak studies (Azizova, Bannikova, et al. 2018). Brain cancer was not significantly associated with radiation consistent with recent studies of Mayak workers (Hunter et al. 2013; Sokolnikov et al. 2015), radiological technologists (Kitahara et al. 2017), INWORKS participants (Richardson et al. 2018), and atomic veterans (Boice et al. 2020). A recent study of CNS tumors in the Japanese LSS reported a significant radiation association for gliomas based on 67 incident cases: ERR per 100 mGy = 0.17 (95%CI 0.012, 0.53) (Brenner et al. 2020). The association was apparent only among males as females showed a negative dose response, though not statistically significant. Most of the survivors who developed glioma were under age 20 at exposure.

Plutonium dosimetry

There have been other approaches to plutonium dosimetry for LANL workers (Poudel et al. 2018) as well as for plutonium workers at other sites in the US, UK, and Russia (Leggett et al. 2005, 2018; Daniels et al. 2006; Birchall et al. 2010; Puncher and Riddell 2016; Bingham et al. 2017; Gregoratto and Bailey 2018). Differences in dose estimates based on the different approaches arise mainly from the application of different biokinetic models, assumptions concerning the form(s) of inhaled Pu, and data fitting methods. Other large uncertainties, known and unknown, might arise from missing or absent monitoring, different levels of detectability and contaminated urine samples. Reuse and contamination of glass collection bottles, for example, have been reported in the early operational years at a UK plutonium facility (Riddell et al. 2000).

As part of a case-control study of the association between external radiation exposures and leukemia mortality in workers from five US facilities including 4 DOE nuclear installations, Daniels et al. (2006) assessed the intake of Pu as a potential confounder. Of the 1269 workers studied in the five cohorts, 173 had worked at LANL, and 62 of the 173 had been monitored for Pu intake. The equivalent dose to active bone marrow was used as the exposure variable. Estimated equivalent doses to active marrow were based on the latest ICRP models at the time (since updated by the

ICRP), including the original Human Respiratory Tract Model of ICRP Publication 66 (International Commission on Radiological Protection 1994a), the gastrointestinal tract model of ICRP Publication 30 (International Commission on Radiological Protection 1979), and the systemic model for Pu applied in ICRP Publication 68 (International Commission on Radiological Protection 1994b). The intake of Pu was assumed to be via inhalation. For each monitored worker with positive urinary Pu measurements, a single inhalation intake was assumed to have occurred three days prior to the first positive measurement. The solubility of the inhaled material was characterized as 50% Type M (moderately soluble) and 50% Type S (relatively insoluble). The cumulative active marrow doses for the monitored LANL workers averaged about 15 mSv with a DWF of 20 applied for alpha particle dose. Daniels et al. (2006) addressed only a tiny portion of all LANL workers, old models were used and the only dose to active bone marrow was calculated.

Sensitivity analyses

An overview of the approach to sensitivity analyses and uncertainty propagation techniques is found in Ellis, Girardi, et al. (2018) for handling external and internal exposures at the Mallinckrodt Chemical Works that processed uranium and then in the comprehensive NCRP publications (Bouville et al. 2015; Dauer et al. 2018; National Council on Radiation Protection and Measurements 2018b) that were specific for the MPS cohorts. These publications provided a standard approach for developing organ doses useful in epidemiologic studies that incorporate the application of dose calculation methods in a wide range of investigations and exposures. They build upon other NCRP publications related to various aspects of uncertainty (National Council on Radiation Protection and Measurements 2009). Uncertainties surrounding the estimation of plutonium dose to tissue in LANL workers are described in the dosimetry section above and in papers by Leggett (2003) and Leggett et al. (2005, 2018).

Uncertainty analysis for external doses followed the approach outlined by Gilbert (1998), Gilbert and Fix (1996) and Gilbert et al. (1996) for evaluating errors in estimated external radiation doses for Hanford workers. There was a particular concern for the estimates of exposure for the earlier workers with the highest exposures and for which a greater uncertainty is possible (Wakeford 2018). Bias factors for recorded external photon doses as estimates of lung dose were assumed to be similar for LANL workers as for Hanford workers (see Table 1 in Gilbert 1998). Our analyses are generally consistent with the Hanford analyses, that is, even if very conservative assumptions about the magnitude of errors were made, they did not seriously distort the dose-response analyses. As discussed by Gilbert and Fix (1996) 'The reason for the lack of distortion appears to be that larger doses, which are the most influential in dose-response analyses, are the sum of independent measurements from many dosimeters; thus, the relative error in such doses is small'. The Hanford analyses were not able to account for doses from internally-deposited radionuclides, which we were able to do. A remaining uncertainty, however, is the possible underestimation of neutron doses in the early years. Nonetheless, the extensive industrial hygiene procedures in place for the Manhattan Project workers help minimize uncertainties, that is, the careful monitoring of external exposures, the extensive bioassay programs, the air sampling measurements, comprehensive job histories, and available medical monitoring data.

As discussed in the Lung Cancer section, Stram et al. (2021) recently conducted an innovative uncertainty analysis of plutonium and external gamma radiation doses to lung among Mayak workers in Russia. While Mayak workers received doses to the lung that were substantially greater than those received by Los Alamos workers, the Mayak findings are informative. Accounting for uncertainty in the gamma-ray doses had a minor effect on the dose-response, whereas it markedly increased the width of the confidence intervals for the plutonium dose-response. This is consistent with our uncertainty evaluation of external gamma-ray doses not affecting the dose-response. While the importance of the uncertainty in plutonium doses is noted and is an area of active examination, the mean cumulative contribution of total plutonium dose to LANL workers was only 2.8% (Table 4) so that any uncertainty likely would have minimal effect on the overall dose-response. It is also recognized that the relatively low plutonium doses and size of the Pu-exposed worker population limit the statistical ability to quantify any plutonium effect, which must await the future pooling of similar MPS cohort studies.

A number of analyses were conducted to evaluate the effects of using different model paraments, different DWFs and different approaches to the outcome selections. A 5-year lag instead of a 10-year lag was used for lung cancer without any change in the estimate of ERR per 100 mGy. DWFs of 1, 10 and 20 for plutonium organ doses were used for lung, liver, NHL (thoracic lymph nodes) and bone analyses with no change in the dose-response estimates or confidence limits. For the relatively infrequent outcomes, such as leukemia other than CLL, analyses based only on the underlying cause of death did not deviate from the finding based on combining the underlying and contributing causes of death, except that the confidence intervals were a bit wider. Assuming a DWF of 2 or 3 for tritium made no difference in the dose-response analyses since tritium was such a small contributor to the overall organ dose. For the 2085 workers with positive tritium readings, their mean absorbed dose was 1.46 mGy (max 157 mGy) for a DWF of 1, which increased to 4.39 mGy (max 473 mGy) for a DWF of 3.

Strengths and limitations

The strengths of the study of LANL workers include the cohort design, the long and complete follow-up of up to 75 years, and the relatively large number of workers eligible for the study, over 26,000 individuals, and the inclusion of women. Further, the comprehensive dose reconstruction included specific organ dose determinations from external

photons and neutrons, and internal intakes of tritium and two plutonium radionuclides. Occupational doses received both before and after employment at LANL were obtained. The available 158,222 urine bioassay samples (24.3 samples per worker monitored) provided unusually detailed and high-quality information for dose reconstruction for plutonium intakes. Another strength is the estimation of radiation dose to thoracic lymph nodes for NHL dose-response analyses, removing reliance on red bone marrow dose as a surrogate for dose to the lymphatic system. Linkage to identify serious renal disease within the USRDS, while qualitative, added additional understanding to the mortality findings which failed to reveal an increase in malignant or nonmalignant kidney disease. Other methodological strengths include the low percentage of workers who were lost-to-follow-up (0.1%) and the low percentage of deaths for which a specific cause was not available (1.4%). Another strength was the ability to cost-effectively build upon and enhance three previous epidemiologic investigations of this workforce (Wiggs 1987; Galke et al. 1992; Wiggs et al. 1994; DOE 2021), while providing special attention to a small group of 26 early plutonium workers who have been clinically followed for over 50 years (Hempelmann et al. 1973; Voelz et al. 1997; Inkret and Miller 1995). The dose reconstruction incorporated autopsy data for 28 LANL workers who had donated their bodies for scientific research (McInroy 1995; McInroy et al. 1991); this provided valuable checks on the solubility of the inhaled material and the reliability of the biokinetic models applied in the dose reconstruction.

Another strength was that cigarette use and smoking patterns were directly assessed and correlated in an interview study of 5507 early LANL employees (Voelz and Hempelmann 1975; Mahoney and Wilkinson 1987; Wilkinson et al. 1987).

The importance of adjusting for SES as a surrogate for tobacco use and other lifestyle factors was evident in that the SMRs for IHD for workers who had a high school education or less was 0.71, whereas workers with a college or graduate degree had SMRs for IHD that were significantly lower, 0.52 and 0.30, respectively. Comparable findings were seen for lung cancer where the SMRs were about 0.80 for those with a high school education or less, whereas those with a college or graduate degree had significantly lower SMRs, 0.44 and 0.22, respectively. Education was known for practically all employees, and adjustment for education had been found to be a robust way to control indirectly smoking and other lifestyle behaviors (Cohen et al. 2018).

The ability to identify over 3000 workers who were Hispanic provided an opportunity to evaluate cancer on noncancer mortality for a population with different baseline rates of disease. There was no evidence for radiation associations, although the number of causes of death was significantly increased in comparison with the general White population, that is, cancers of the stomach and liver, cirrhosis of the liver, nonmalignant kidney disease, and diabetes. Such elevations are consistent with the role that lifestyle, genetics and infections play in disease occurrence among the Hispanic population (Dominguez et al. 2015; Miller et al. 2018).

Limitations of the study include the incomplete knowledge of concomitant exposures to toxic occupational hazards such as asbestos or beryllium. The absence of an increase in cancers of the pleura, mesothelioma and asbestosis, however, indicates a limited exposure to asbestos. The excess of berylliosis indicates a meaningful exposure to beryllium but the small number of deaths, only four, suggests that any associations with other causes of death are likely to be minimal. Nonetheless, our inability to control solvents and other laboratory chemical exposures in the workplace remains a limitation. Despite the comprehensive estimation of radiation dose and the completeness of the vital status follow-up, the statistical precision of risk estimates was limited. The 95% confidence limits were often consistent with both an absence of a radiation effect and an effect even 2 times higher than those reported in other investigations. Similarly, despite LANL workers experiencing some of the highest intakes of plutonium in the US, they were much lower than those experienced by Mayak workers in Russian, and not sufficient to convincingly discern radiation effects directly from plutonium dose to specific organs. The increase of bone and possibly lung cancer among plutonium workers at LANL indicates that combining similar MPS cohort studies, such as Rocky Flats and Hanford workers, should be informative and directly address these limitations of small numbers. Another limitation is the difficulty in assigning meaningful, defensible, quantitative uncertainties in dose estimates. While the approaches taken for external radiation (Gilbert et al. 1996) and for internal radiation (related to the systemic model used for Pu) did not suggest major sources of error in dose estimates, nonetheless, additional work is needed and planned (National Council on Radiation Protection and Measurements 2018b; Stram et al. 2021).

Conclusions

An extended mortality follow-up of over 26,000 workers at the Los Alamos National Laboratory failed to reveal significant associations between radiation dose and cancers of the lung, liver and NHL, sites that would have received the highest doses from intakes of plutonium, nor excesses due to leukemia or ischemic heart disease. A plutonium-related excess of bone cancer was plausible among workers with the highest intakes, but the numbers were small. An association between esophageal cancer and radiation is noted, and the association with Parkinson's disease is provocative given a recent investigation of workers at the Mayak facility in Russia. Beryllium exposure among early workers in the 1940s could be tied to a small number of deaths from berylliosis. The population of Hispanic workers could be evaluated separately but numbers were too small to evaluate any unique patterns of death following radiation exposure. Analyses focusing on plutonium dose were generally inconclusive, although the association with bone cancer was plausible. The LANL cohort study is notable in having nearly complete follow-up for up to 75 years, comprehensive

external and internal organ dose determination, the inclusion of women, and relatively large numbers.

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References

Acquavella JF, Wilkinson GS, Tietjen GL, Key CR, Stebbings JH, Voelz GL. 1983. A melanoma case-control study at the Los Alamos National Laboratory. Health Phys. 45(3):587–592.

Agency for Toxic Substances and Disease Registry (ATSDR). 2010. Toxicological profile for plutonium. Atlanta (GA): ATSDR, Public Health Service, US Department of Health and Human Services; [accessed 2020 December 5]. https://www.atsdr.cdc.gov/toxprofiles/tp143.pdf

Azizova TV, Muirhead CR, Moseeva MB, Grigoryeva ES, Sumina MV, O'Hagan J, Zhang W, Haylock RJ, Hunter N. 2011. Cerebrovascular diseases in nuclear workers first employed at the Mayak PA in 1948-1972. Radiat Environ Biophys. 50(4):539–552.

Azizova TV, Bannikova MV, Grigoryeva ES, Rybkina VL. 2018. Risk of malignant skin neoplasms in a cohort of workers occupationally exposed to ionizing radiation at low dose rates. PLoS One. 13(10): e0205060.

Azizova TV, Batistatou E, Grigorieva ES, McNamee R, Wakeford R, Liu H, de Vocht F, Agius RM. 2018. An assessment of radiation-associated risks of mortality from circulatory disease in the cohorts of Mayak and Sellafield nuclear workers. Radiat Res. 189(4): 371–388.

Azizova TV, Bannikova MV, Grigoryeva ES, Rybkina VL, Hamada N. 2020. Occupational exposure to chronic ionizing radiation increases risk of Parkinson's disease incidence in Russian Mayak workers. Int J Epidemiol. 49(2):435–447.

Bingham D, Bérard P, Birchall A, Bull R, Cardis E, Challeton-de Vathaire C, Grellier J, Hurtgen C, Puncher M, Riddell A, et al. 2017. Reconstruction of internal doses for the alpha-risk case-control study of lung cancer and leukaemia among European nuclear workers. Radiat Prot Dosimetry. 174(4):485–494.

Birchall A, Puncher M, Harrison J, Riddell A, Bailey MR, Khokryakov V, Romanov S. 2010. Plutonium worker dosimetry. Radiat Environ Biophys. 49(2):203–212.

Boice JD. Jr. 1993. Leukemia risk in thorotrast patients. Radiat Res. 36(2):301–302.

Boice JD. 2017. Space: the final frontier-research relevant to mars. Health Phys. 112(4):392–397.

Boice JD. Jr. 2019. Relevance of the million person study to research needs for NASA and space exploration. Int J Radiat Biol. 1–9.

Boice JD, Cohen SS, Mumma MT, Dupree-Ellis E, Eckerman KF, Leggett RW, Boecker B, Brill A, Henderson B. 2006. Mortality among radiation workers at Rocketdyne (Atomics International), 1948-1999. Radiat Res. 166(1):98–115.

Boice JD, Leggett RW, Ellis ED, Wallace PW, Mumma MT, Cohen SS, Brill AB, Bandana C, Boecker BB, Yoder RC. 2006. A comprehensive dose reconstruction methodology for former Rocketdyne/Atomics International radiation workers. Health Phys. 90(5): 409–430.

Boice JD, Cohen SS, Mumma MT, Chadda B, Blot WJ. 2008. A cohort study of uranium millers and miners of Grants, New Mexico, 1979-2005. J Radiol Prot. 28(3):303–325.

Boice JD, Cohen SS, Mumma MT, Ellis ED, Eckerman KF, Leggett RW, Boecker BB, Brill AB, Henderson BE. 2011. Updated mortality analysis of radiation workers at Rocketdyne (Atomics International), 1948-2008. Radiat Res. 176(2):244–258.

Boice JD, Cohen SS, Mumma MT, Ellis ED, Cragle DL, Eckerman KF, Wallace PW, Chadda B, Sonderman JS, Wiggs LD, et al. 2014. Mortality among mound workers exposed to polonium-210 and other sources of radiation, 1944-1979. Radiat Res. 181(2):208–228.

Boice JD, Jr, Cohen SS, Mumma MT, Ellis ED. 2019. The Million Person Study, whence it came and why. Int J Radiat Biol. 1–14. DOI: 10.1080/09553002.2019.1589015

Boice JD, Jr, Ellis ED, Golden AP, Zablotska LB, Mumma MT, Cohen SS. 2019. Sex-specific lung cancer risk among radiation workers in the Million Person Study and among TB-fluoroscopy patients. Int J Radiat Biol. 1–12. DOI:10.1080/09553002.2018.1547441

Boice JD, Held KD, Shore RE. 2019. Radiation epidemiology and health effects following low-level radiation exposure. J Radiol Prot. 39(4): S14–S27.

Boice JD, Jr, Cohen SS, Mumma MT, Chen H, Golden AP, Beck HL, Till JE. 2020. Mortality among US military participants at eight aboveground nuclear weapons test series. Int J Radiat Biol. 1–22. DOI:10.1080/09553002.2020.1787543

Boice JD, Jr, Cohen SS, Mumma MT, Hagemeyer DA, Chen H, Golden AP, Yoder RC, Dauer LT. 2021. Mortality from leukemia, lung cancer and heart disease among U.S. nuclear power plant workers. Int J Radiat Biol.

Boice JD, Jr, Cohen SS, Mumma MT, Yoder RC, Dauer LT. 2021. Mortality among medical radiation workers in the United States, 1965–2016. Int J Radiat Biol.

Boice JD, Jr, Cohen SS, Mumma MT, Golden AP, Howard S, Girardi DJ, Dupree Ellis ED, Bellamy M, Dauer LT, Samuels C, et al. 2021. Mortality study of women and men working at a uranium processing facility during World War II., 1943–1947. The Tennessee Eastman Corporation (Y-12) Worker Study. Int J Radiat Biol.

Boice JD, Jr, Quinn B, Ansari A, Blake PK, Blattnig SR, Caffrey EA, Cohen SS, Golden AP, Held KD, Jokisch DW, et al. 2021. A million persons, a million dreams: A vision for a National Center of Radiation Epidemiology and Biology. Int J Radiat Biol.

Bouville A, Toohey RE, Boice JD, Beck HL, Dauer LT, Eckerman KF, Hagemeyer D, Leggett RW, Mumma MT, Napier B, et al. 2015. Dose reconstruction for the Million Worker Study: status and guidelines. Health Phys. 108(2):206–220.

Brenner AV, Sugiyama H, Preston DL, Sakata R, French B, Sadakane A, Cahoon EK, Utada M, Mabuchi K, Ozasa K. 2020. Radiation risk of central nervous system tumors in the Life Span Study of atomic bomb survivors, 1958-2009. Eur J Epidemiol. 35(6):591–600.

Breslow NE, Lubin JH, Marek P, Langholz D. 1983. Multiplicative models and cohort analysis. J Am Stat Assoc. 78(381):1–12.

Brown SC, Schonbeck MF, McClure D, Barón AE, Navidi WC, Byers T, Ruttenber AJ. 2004. Lung cancer and internal lung doses among plutonium workers at the rocky flats plant: a case-control study. Am J Epidemiol. 160(2):163–172.

Cahoon EK, Preston DL, Pierce DA, Grant E, Brenner AV, Mabuchi K, Utada M, Ozasa K. 2017. Lung, laryngeal and other respiratory cancer incidence among Japanese atomic bomb survivors: an updated analysis from 1958 through 2009. Radiat Res. 187(5):538–548.

Campbell EE, Milligan MF, Moss WD, Schulte HF. 1972. History of the plutonium bioassay program at the Los Alamos Scientific Laboratory, 1944-1972. LA-5008, UC-41. October 1972. Los Alamos (NM): Los Alamos Scientific Laboratory; [accessed 2018 September 20]. https://www.osti.gov/servlets/purl/4587709

Campbell KM, Deck D, Krupski A. 2008. Record linkage software in the public domain: a comparison of Link Plus, The Link King, and a 'basic' deterministic algorithm. Health Informatics J. 14(1):5–15.

Cherry JD, Liu B, Frost JL, Lemere CA, Williams JP, Olschowka JA, O'Banion MK. 2012. Galactic cosmic radiation leads to cognitive impairment and increased a beta plaque accumulation in a mouse model of Alzheimer's disease. PLoS One. 7(12):1e53275.

Claycamp HG, Okladnikova ND, Azizova TV, Belyaeva ZD, Boecker BB, Pesternikova VS, Scott BR, Shekhter-Levin S, Sumina MV, Sussman NB, et al. 2000. Deterministic effects from occupational radiation exposures in a cohort of Mayak PA workers: data base description. Health Phys. 79(1):48–54.

Clément GR, Boyle RD, George KA, Nelson GA, Reschke MF, Williams TJ, Paloski WH. 2020. Challenges to the central nervous system during human spaceflight missions to Mars. J Neurophysiol. 123(5):2037–2063.

Cohen SS, Mumma MT, Ellis ED, Boice JD. Jr. 2018. Validating the use of census data on education as a measure of socioeconomic status in an occupational cohort. Int J Rad Biol. 1–6. DOI:10.1080/09553002.2018.1549758

Cox D. 1972. Regression models and life-tables. J R Stat Soc Ser B. 34(2):187–220.

Cox R, Kellerer AM. 2003. A current view in radiation weighting factors and effective dose. ICRP Publication 92. Ann ICRP. 33:1–4.

Cox R, Menzel HG, Preston J. 2008. Internal dosimetry and tritium–the ICRP position. J Radiol Prot. 28(2):131–135.

Daniels RD, Lodwick CJ, Schubauer-Berigan MK, Spitz HB. 2006. Assessment of plutonium exposures for an epidemiological study of US nuclear workers. Radiat Prot Dosimetry. 118(1):43–55.

Dauer LT, Bouville A, Toohey RE, Boice JD, Jr, Beck HL, Eckerman KF, Hagemeyer D, Leggett RW, Mumma MT, Napier B, et al. 2018. Dosimetry and uncertainty approaches for the million-worker study of radiation workers and veterans: overview of the recommendations in NCRP Report No. 178. A review. Int J Rad Biol. 1–10. DOI:10.1080/09553002.2018.1536299

Department of Army. 2012. Occupational dosimetry and dose recording for exposure to ionizing radiation. Pamphlet 385-25. Washington (DC): Department of Army; [Accessed 2021 June 4]. https://armypubs.army.mil/epubs/DR_pubs/DR_a/pdf/web/p385_25.pdf.

Department of Energy. 2018. DOE 2017 Occupational radiation exposure. Washington (DC): US Department of Energy, Office of Environment, Health, Safety and Security, The Radiation Exposure Monitoring System (REMS).

Department of Energy. 2019. Former worker medical screening program report. 2019 Annual Report. Washington (DC): Office of Environment, Health, Safety and Security; [accessed 2020 December 7]. https://www.energy.gov/sites/prod/files/2020/06/f75/2019-FW-Medical-Screening-Program-Annual-Report.pdf

Department of Energy. 2021. Comprehensive epidemiological data resource (CEDR). Washington (DC): Office of Environment, Health, Safety and Security; [accessed 2021 March 3]. https://oriseapps.orau.gov/cedr/default.aspx

de Vocht F, Hidajat M, Martin RM, Agius R, Wakeford R. 2020. Ischemic heart disease mortality and occupational radiation exposure in a nested matched case-control study of British nuclear fuel cycle workers: investigation of confounding by lifestyle, physiological traits and occupational exposures. Radiat Res. 194(4):431–444.

Dominguez K, Penman-Aguilar A, Chang MH, Moonesinghe R, Castellanos T, Rodriguez-Lainz A, Schieber R. 2015. Vital signs: leading causes of death, prevalence of diseases and risk factors, and use of health services among Hispanics in the United States - 2009-2013. MMWR Morb Mortal Wkly Rep. 64(17):469–478.

Efurd DW, Steiner RE, Lamont SP, Lewis D. 2008. History of the plutonium bioassay program at the Los Alamos National Laboratory, 1944-2006. J Radioanal Nucl Chem. 276(2):499–504.

Ellis ED, Boice JD, Golden AP, Girardi DJ, Cohen SS, Mumma MT, Shore RE, Leggett RW, Kerr GD. 2018. Dosimetry is key to good epidemiology: workers at Mallinckrodt Chemical Works had seven different source exposures. Health Phys. 114(4):386–397.

Ellis ED, Girardi D, Golden AP, Wallace PW, Phillips J, Cragle DL. 2018. Historical perspective on the Department of Energy mortality studies: focus on the collection and storage of individual worker data. Int J Radiat Biol. 1–8. DOI:10.1080/09553002.2018.1547851

EPRI. 2020. Cardiovascular risks from low dose radiation exposure: review and scientific appraisal of the literature. Palo Alto (CA): EPRI. [accessed 2020 December 19]. https://www.epri.com/research/products/000000003002018408

Galke WA, Johnson ER, Tietjen GL. 1992. Mortality in an ethnically diverse radiation exposed occupational cohort. Los Alamos (NM): Los Alamos National Laboratory. Occupational Medicine Group (HS-2).

Gilbert ES. 1998. Accounting for errors in dose estimates used in studies of workers exposed to external radiation. Health Phys. 74(1):22–29.

Gilbert ES, Fix JJ. 1996. Laboratory measurement error in external dose estimates and its effects on dose-response analyses of Hanford worker mortality data. PNL-11289. Richland (WA): Pacific Northwest Laboratory. [accessed 2020 December 10]. https://www.osti.gov/servlets/purl/379945

Gilbert ES, Cragle DL, Wiggs LD. 1993. Updated analyses of combined mortality data for workers at the Hanford site, Oak Ridge National Laboratory, and Rocky Flats Weapons Plant. Radiat Res. 136(3):408–421.

Gilbert ES, Omohundro E, Buchanan JA, Holter NA. 1993. Mortality of workers at the Hanford site: 1945-1986. Health Phys. 64(6):577–590.

Gilbert ES, Fix JJ, Baumgartner WV. 1996. An approach to evaluating bias and uncertainty in estimates of external dose obtained from personal dosimeters. Health Phys. 70(3):336–345.

Gilbert ES, Koshurnikova NA, Sokolnikov M, Khokhryakov VF, Miller S, Preston DL, Romanov SA, Shilnikova NS, Suslova KG, Vostrotin VV. 2000. Liver cancers in Mayak workers. Radiat Res. 154(3):246–252.

Gilbert ES, Sokolnikov ME, Preston DL, Schonfeld SJ, Schadilov AE, Vasilenko EK, Koshurnikova NA. 2013. Lung cancer risks from

plutonium: an updated analysis of data from the Mayak worker cohort. Radiat Res. 179(3):332–342.
Gillies M, Kuznetsova I, Sokolnikov M, Haylock R, O'Hagan J, Tsareva Y, Labutina E. 2017. Lung cancer risk from plutonium: a pooled analysis of the Mayak and Sellafield worker cohorts. Radiat Res. 188(6):645–660.
Gillies M, Richardson DB, Cardis E, Daniels RD, O'Hagan JA, Haylock R, Laurier D, Leuraud K, Moissonnier M, Schubauer-Berigan MK, et al. 2017. Mortality from circulatory diseases and other non-cancer outcomes among nuclear workers in France, the United Kingdom and the United States (INWORKS). Radiat Res. 188(3):276–290.
Gillies M, Haylock R, Hunter N, Zhang W. 2019. Risk of leukemia associated with protracted low-dose radiation exposure: updated results from the National Registry for Radiation Workers Study. Radiat Res. 192(5):527–537.
Golden AP, Cohen SS, Chen H, Ellis ED, Boice JD. Jr. 2018. Evaluation of statistical modeling approaches for epidemiologic studies of low-dose radiation health effects. Int J Radiat Biol. 1–8. DOI:10.1080/09553002.2018.1554924
Golden AP, Ellis ED, Cohen SS, Mumma MT, Leggett RW, Wallace PW, Girardi DJ, Watkins JP, Shore RE, Boice JD. Jr. 2019. Updated mortality analysis of the Mallinckrodt uranium processing workers. Int J Radiat Biol. 1–17. DOI:10.1080/09553002.2019.1569773
Gregoratto D, Bailey MR. 2018. Estimation of lung absorption parameters for oxides of ^{238}Pu. J Radiol Prot. 38(2):831–853.
Grellier J, Atkinson W, Bérard P, Bingham D, Birchall A, Blanchardon E, Bull R, Guseva Canu I, Challeton-de Vathaire C, Cockerill R, et al. 2017. Risk of lung cancer mortality in nuclear workers from internal exposure to alpha particle-emitting radionuclides. Epidemiology. 28(5):675–684.
Hagemeyer D, Nichols G, Mumma MT, Boice JD, Jr, Brock TA. 2018. 50 years of the radiation exposure information and reporting system and importance to the Million Person Study. Int J Radiat Biol. 1–4. DOI:10.1080/09553002.2018.1540896
Hauptmann M, Daniels RD, Cardis E, Cullings HM, Kendall G, Laurier D, Linet MS, Little MP, Lubin JH, Preston DL, et al. 2020. Epidemiological studies of low-dose ionizing radiation and cancer: summary bias assessment and meta-analysis. J Natl Cancer Inst Monogr. 2020(56):188–200.
Hempelmann LH, Langham WH, Richmond CR, Voelz GL. 1973. Manhattan Project plutonium workers: a twenty-seven year follow-up study of selected cases. Health Phys. 25(5):461–479.
History Associates Incorporated. 1997. Los Alamos National Laboratory: a guide to records series supporting epidemiologic studies conducted for the Department of Energy. U.S. Department of Energy, Office of Epidemiology and Health Surveillance, prepared under Contract No. DE-AC01-93EH89246. Rockville (MD): HAI; [accessed 2020 December 4]. https://www.osti.gov/servlets/purl/477726
Hunter N, Kuznetsova IS, Labutina EV, Harrison JD. 2013. Solid cancer incidence other than lung, liver and bone in Mayak workers: 1948-2004. Br J Cancer. 109(7):1989–1996.
Hsu WL, Preston DL, Soda M, Sugiyama H, Funamoto S, Kodama K, Kimura A, Kamada N, Dohy H, Tomonaga M, et al. 2013. The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. Radiat Res. 179(3):361–382.
Inkret WC, Miller G. 1995. On the front lines: plutonium workers past and present share their experiences. Los Alamos Science. 23: 125–173.
International Agency for Research on Cancer. 2012. A review of human carcinogens. Part D: radiation. Vol 100D. Lyon (France): IARC Press.
International Agency for Research on Cancer. 2018. Beryllium and beryllium compounds. IARC Monogr Eval Carcinog Risks Hum. 100C:1–477.
International Commission on Radiological Protection. 1979. ICRP Publication 30, Part 1. Limits on intakes of radionuclides for workers. Ann ICRP. 2(3–4):1–116.
International Commission on Radiological Protection. 1994a. ICRP Publication 66. Human respiratory tract model for radiological protection. Ann ICRP. 24(1–3):1–482.
International Commission on Radiological Protection. 1994b. ICRP Publication 68. Dose coefficients for intake of radionuclides by workers. Ann ICRP. 24(4):1–83.
International Commission on Radiological Protection. 2007. ICRP publication 103. The 2007 recommendations of the international commission on radiological protection. Ann ICRP. 37(2–4):1–332.
International Commission on Radiological Protection. 2010. ICRP Publication 116. Conversion coefficients for radiological protection quantities for external radiation exposures. Ann ICRP. 40(2–5): 1–257.
International Commission on Radiological Protection. 2015. ICRP Publication 130. Occupational intake of radionuclides, Part 1. Ann ICRP. 44 (2):1–188.
International Commission on Radiological Protection. 2019. Occupational intakes of radionuclides: part 4. ICRP Publication 141. Ann ICRP. 48(1):1–514.
Iwanaga M, Hsu WL, Soda M, Takasaki Y, Tawara M, Joh T, Amenomori T, Yamamura M, Yoshida Y, Koba T, et al. 2011. Risk of myelodysplastic syndromes in people exposed to ionizing radiation: a retrospective cohort study of Nagasaki atomic bomb survivors. JCO. 29(4):428–434.
Kathren RL, Tolmachev SY. 2019. The US Transuranium and Uranium Registries (USTUR): a five-decade follow-up of plutonium and uranium workers. Health Phys. 117(2):118–132.
Khokhryakov VV, Khokhryakov VF, Suslova KG, Vostrotin VV, Vvedensky VE, Sokolova AB, Krahenbuhl MP, Birchall A, Miller SC, Schadilov AE, et al. 2013. Mayak Worker Dosimetry System 2008 (MWDS-2008): assessment of internal dose from measurement results of plutonium activity in urine. Health Phys. 104(4):366–378.
Kitahara CM, Linet MS, Balter S, Miller DL, Rajaraman P, Cahoon EK, Velazquez-Kronen R, Simon SL, Little MP, Doody MM, et al. 2017. Occupational radiation exposure and deaths from malignant intracranial neoplasms of the brain and CNS in U.S. Radiologic Technologists, 1983-2012. AJR Am J Roentgenol. 208(6):1278–1284.
Koshurnikova NA, Gilbert ES, Sokolnikov M, Khokhryakov VF, Miller S, Preston DL, Romanov SA, Shilnikova NS, Suslova KG, Vostrotin VV. 2000. Bone cancers in Mayak workers. Radiat Res. 154(3): 237–245.
Kreiss K, Mroz MM, Zhen B, Martyny JW, Newman LS. 1993. Epidemiology of beryllium sensitization and disease in nuclear workers. Am Rev Respir Dis. 148(4):985–991.
Kuznetsova IS, Labutina EV, Hunter N. 2016. Radiation risks of leukemia, lymphoma and multiple myeloma incidence in the Mayak cohort: 1948-2004. PLoS One. 11(9):e0162710.
Lawrence JNP. 1978. A history of PUQFUA – plutonium body burden (Q) from urine assays. LA-7403-H, History, UC-41. Los Alamos, NM: Los Alamos Scientific Laboratory. DOI:10.2172/6538507
Leggett RW. 2003. Reliability of the ICRP's dose coefficients for members of the public. III. Plutonium as a case study of uncertainties in the systemic biokinetics of radionuclides. Radiat Prot Dosimetry. 106(2):103–120.
Leggett RW, Eckerman KF, Khokhryakov VF, Suslova KG, Krahenbuhl MP, Miller SC. 2005. Mayak worker study: an improved biokinetic model for reconstructing doses from internally deposited plutonium. Radiat Res. 164(2):111–122.
Leggett RW, Eckerman KF, Bellamy M. 2018. MPS dose reconstruction for internal emitters: some site-specific issues and approaches. Int J Radiat Biol. 1–13. DOI:10.1080/09553002.2018.1558302
Leuraud K, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, Hamra GB, Haylock R, Laurier D, Moissonnier M, et al. 2015. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. Lancet Haematol. 2(7):e276–e281.
Linet MS, Little MP, Kitahara CM, Cahoon EK, Doody MM, Simon SL, Alexander BH, Preston DL. 2020. Occupational radiation and haematopoietic malignancy mortality in the retrospective cohort

study of US radiologic technologists, 1983-2012. Occup Environ Med. 77(12):822–831.
Mahoney MC, Wilkinson GS. 1987. Smoking patterns among Los Alamos National Laboratory employees. Report LA-10650. Los Alamos (NM): Los Alamos National Laboratory; [accessed 2020 December 4]. https://www.osti.gov/biblio/6403953-smoking-patterns-among-los-alamos-national-laboratory-employees
McInroy JF. 1995. A true measure of exposure - the human tissue analysis program at Los Alamos. Los Alamos Sc. 23:235–249.
McInroy JF, Kathren RL, Voelz GL, Swint MJ. 1991. U.S. Transuranium Registry report on the ^{239}Pu distribution in a human body. Health Phys. 60(3):307–333.
Miller G, Bertelli L, Guilmette R, McNaughton MW, Eisele WF. 2008. A study of early Los Alamos internal exposures to plutonium. Radiat Prot Dosim. 130(4):503–509.
Miller KD, Goding Sauer A, Ortiz AP, Fedewa SA, Pinheiro PS, Tortolero-Luna G, Martinez-Tyson D, Jemal A, Siegel RL. 2018. Cancer statistics for Hispanics/Latinos, 2018. CA Cancer J Clin. 68(6):425–445.
Monson R. 1986. Observations on the healthy worker effect. J Occup Med. 28(6):425–433.
Mumma MT, Cohen SS, Sirko JL, Ellis ED, Boice JD. Jr. 2018. Obtaining vital status and cause of death on a million persons. Int J Radiat Biol. 1–7. DOI:10.1080/09553002.2018.1539884
Naval Dosimetry Center. 2019. [accessed 2020 May 13]. Naval Dosimetry Center. https://www.cnic.navy.mil/regions/ndw/installations/nsa_bethesda/about/tenant_orgs/ndc.html
National Academies/National Research Council. 2012. Technical evaluation of the NASA model for cancer risk to astronauts due to space radiation. Washington (DC): National Academies Press. [accessed 2021 March 3]. https://www.nap.edu/catalog/13343/technical-evaluation-of-the-nasa-model-for-cancer-risk-to-astronauts-due-to-space-radiation
National Aeronautics and Space Administration. 2015. NASA space flight human-system standard, volume 1, revision A: crew health. NASA STD-3001. Houston (TX): NASA Johnson Space Center [accessed 2021 April 10]. https://standards.nasa.gov/standard/nasa/nasa-std-3001-vol-1
National Aeronautics and Space Administration. 2021. NASA human research program roadmap. Washington (DC): NASA; [accessed April 10]. https://humanresearchroadmap.nasa.gov/
National Council on Radiation Protection and Measurements. 2009. Report No. 164 - uncertainties in internal radiation dose assessment. Bethesda (MD): NCRP.
National Council on Radiation Protection and Measurements. 2014. Commentary No. 23 - radiation protection for space activities: supplement to previous recommendations. Bethesda (MD): NCRP.
National Council on Radiation Protection and Measurements. 2016. Commentary No. 25 - potential for central nervous system effects from radiation exposure during space activities phase 1: overview. Bethesda (MD): NCRP.
National Council on Radiation Protection and Measurements. 2018a. Commentary No. 27 - implications of recent epidemiologic studies for the linear-nonthreshold model and radiation protection. Bethesda (MD): NCRP.
National Council on Radiation Protection and Measurements. 2018b. Report No. 178 - deriving organ doses and their uncertainty for epidemiologic studies (with a focus on the One Million U.S. Workers and Veterans Study of Low-Dose Radiation Health Effects). Bethesda (MD): NCRP.
National Council on Radiation Protection and Measurements. 2018c. Report No. 181 - evaluation of the relative effectiveness of low-energy photons and electrons in inducing cancer in humans. Bethesda (MD): NCRP.
National Council on Radiation Protection and Measurements. 2019. Report No. 183 - radiation exposures in space and the potential for central nervous system effects: phase II. Bethesda (MD): NCRP.
National Council on Radiation Protection and Measurements. 2021. Scientific Committee 1-27: evaluation of sex-specific differences in lung cancer radiation risks and recommendations for use in transfer and projection models. Bethesda (MD): NCRP; [accessed 2021 April 10]. https://ncrponline.org/program-areas/sc-1-27-evaluation-of-sex-specific-differences-in-lung-cancer-radiation-risks-and-recommendations-for-use-in-transfer-and-projection-models/
New Brunswick Laboratory. 2015. Safety data sheet plutonium metal. Argonne (IL): US Department of Energy; [accessed 2020 December 2]. https://science.osti.gov/-/media/nbl/pdf/price-lists/SDS/SDS-Plutonium_Metal.pdf
Nuclear Regulatory Commission. 2019. Radiation exposure information and reporting system (REIRS). Rockville (MD): US Nuclear Regulatory Commission; [accessed 2020 February 7]. https://www.reirs.com/
Omar RZ, Barber JA, Smith PG. 1999. Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. Br J Cancer. 79(7–8):1288–1301.
Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, Sakata R, Sugiyama H, Kodama K. 2012. Studies of the mortality of atomic bomb survivors, report 14, 1950–2003: an overview of cancer and noncancer diseases. Radiat Res. 177(3):229–243.
Ozasa K, Takahashi I, Grant EJ, Kodama K. 2017. Cardiovascular disease among atomic bomb survivors. Int J Radiat Biol. 93(10):1145–1150.
Pasqual E, Boussin F, Bazyka D, Nordenskjold A, Yamada M, Ozasa K, Pazzaglia S, Roy L, Thierry-Chef I, de Vathaire F, et al. 2021. Cognitive effects of low dose of ionizing radiation - Lessons learned and research gaps from epidemiological and biological studies. Environ Int. 147:106295.
Peterson GR, Gilbert ES, Buchanan JA, Stevens RG. 1990. A casecohort study of lung cancer, ionizing radiation, and tobacco smoking among males at the Hanford Site. Health Phys. 58(1):3–11.
Poudel D, Miller G, Klumpp JA, Bertelli L, Waters TL. 2018. Bayesian analysis of plutonium bioassay data at Los Alamos National Laboratory. Health Phys. 115(6):712–726. [accessed December 7. 2020]. https://www.epa.gov/sites/production/files/2015-05/documents/ornl-tm-2006-583.pdf.
Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. 2007. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res. 168(1):1–64.
Preston DL, Lubin J, Pierce D, McConney M, Shilnikova N. 2015. Epicure risk regression and person-year computation software: command summary and user guide. Ottawa (CA): Risk Sciences International.
Preston DL, Sokolnikov ME, Krestinina LY, Stram DO. 2017. Estimates of radiation effects on cancer risks in the Mayak worker, Techa River and atomic bomb survivor studies. Radiat Prot Dosimetry. 173(1–3):26–31.
Puncher M, Riddell AE. 2016. A Bayesian analysis of plutonium exposures in Sellafield workers. J Radiol Prot. 36(1):1–19.
Richardson DB, Cardis E, Daniels RD, Gillies M, Haylock R, Leuraud K, Laurier D, Moissonnier M, Schubauer-Berigan MK, Thierry-Chef I. 2018. Site-specific solid cancer mortality after exposure to ionizing radiation: a cohort study of workers (INWORKS). Epidemiology. 29(1):31–40.
Richardson DB, Abalo K, Bernier MO, Rage E, Leuraud K, Laurier D, Keil AP, Little MP. 2020. Meta-analysis of published excess relative risk estimates. Radiat Environ Biophys. 59(4):631–641.
Riddell AE, Battersby WP, Peace MS, Strong R. 2000. The assessment of organ doses from plutonium for an epidemiological study of the Sellafield workforce. J Radiol Prot. 20(3):275–286.
Rowland RE, Stehney AF, Lucas HF. 1983. Dose-response relationships for radium-induced bone sarcomas. Health Phys. 44(Suppl (1):15–31.
Shilnikova NS, Preston DL, Ron E, Gilbert ES, Vassilenko EK, Romanov SA, Kuznetsova IS, Sokolnikov ME, Okatenko PV, Kreslov VV, et al. 2003. Cancer mortality risk among workers at the Mayak nuclear complex. Radiat Res. 159(6):787–798.
Silver SR, Bertke SJ, Hein MJ, Daniels RD, Fleming DA, Anderson JL, Pinney SM, Hornung RW, Tseng CY. 2013. Mortality and ionising radiation exposures among workers employed at the Fernald Feed

Materials Production Center (1951-1985). Occup Environ Med. 70(7):453–463.
Simonsen LC, Slaba TC, Guida P, Rusek A. 2020. NASA's first ground-based galactic cosmic ray simulator: enabling a new era in space radiobiology research. PLoS Biol. 18(5):e3000669.
Slaba TC, Blattnig SR, Norbury JW, Rusek A, La Tessa C. 2016. Reference field specification and preliminary beam selection strategy for accelerator-based GCR simulation. Life Sci Space Res. 8:52–67.
Sokolnikov ME, Gilbert ES, Preston DL, Ron E, Shilnikova NS, Khokhryakov VV, Vasilenko EK, Koshurnikova NA. 2008. Lung, liver and bone cancer mortality in Mayak workers. Int J Cancer. 123(4):905–911.
Sokolnikov M, Preston D, Gilbert E, Schonfeld S, Koshurnikova N. 2015. Radiation effects on mortality from solid cancers other than lung, liver, and bone cancer in the Mayak worker cohort: 1948-2008. PLoS One. 10(2):e0117784.
Stange AW, Furman FJ, Hilmas DE. 1996. Rocky flats beryllium health surveillance. Environ Health Perspect. 104 Suppl 5(Suppl (5): 981–986.
Steenland K. 2005. One agent, many diseases: exposure response data and comparative risks of different outcomes following silica exposure. Am J Ind Med. 48(1):16–23.
Stefaniak AB, Weaver VM, Cadorette M, Puckett LG, Schwartz BS, Wiggs LD, Jankowski MD, Breysse PN. 2003. Summary of historical beryllium uses and airborne concentration levels at Los Alamos National Laboratory. Appl Occup Environ Hyg. 18(9):708–715.
Stram DO, Sokolnikov M, Napier BA, Vostrotin VV, Efimov A, Preston DL. 2021. Lung cancer in the Mayak workers cohort: risk estimation and uncertainty analysis. Radiat Res. 195(4):334–346.
Takahashi I, Shimizu Y, Grant EJ, Cologne J, Ozasa K, Kodama K. 2017. Heart disease mortality in the Life Span Study, 1950-2008. Radiat Res. 187(3):319–332.
Tapio S, Little MP, Kaiser JC, Impens N, Hamada N, Georgakilas AG, Simar D, Salomaa S. 2021. Ionizing radiation-induced circulatory and metabolic diseases. Environ Int. 146:106235.
Till JE, Beck HB, Aanenson JW, Grogan HA, Mohler HJ, Mohler SS, Voillequé PG. 2014. Military participants at the U.S. atmospheric nuclear weapons testing – methodology for estimating dose and uncertainty. Radiat Res. 181(5):471–484.
Tolmachev SY, Swint MJ, Bistline RW, McClellan RO, McInroy JF, Kathren RL, Filipy RE, Toohey RE. 2019. USTUR Special Session Roundtable-US Transuranium and Uranium Registries (USTUR): a five-decade follow-up of plutonium and uranium workers. Health Phys. 117(2):211–222.
Tran V, Zablotska LB, Brenner AV, Little MP. 2017. Radiation-associated circulatory disease mortality in a pooled analysis of 77,275 patients from the Massachusetts and Canadian tuberculosis fluoroscopy cohorts. Sci Rep. 7(1):1–10.
United Nations Scientific Committee on the Effects of Atomic Radiation. 2008. Effects of ionizing radiation. 2006 Report. Scientific Annex A: Epidemiological studies of radiation and cancer. New York (NY): UNSCEAR.
United Nations Scientific Committee on the Effects of Atomic Radiation. 2017. Sources, effects and risks of ionizing radiation. 2016 Report to the General Assembly. Volume 1. Scientific Annex D: Biological effects of selected internal emitters – uranium. New York (NY): UNSCEAR.
United Nations Scientific Committee on the Effects of Atomic Radiation. 2020. Sources, effects and risks of ionizing radiation. UNSCEAR 2019 Report to the General Assembly. Scientific Annex A: evaluation of selected health effects and inference of risk due to radiation exposure. New York (NY): UNSCEAR.
U.S. Environmental Protection Agency. 1999. Cancer risk coefficients for environmental exposure to radionuclides. Washington (DC): EPA. Federal Guidance Report No. 13, EPA-402-R99-001.
U.S. Renal Data System. 2020. USRDS 2019 annual data report: atlas of end-stage renal disease in the United States. Bethesda (MD): National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.
Velazquez-Kronen R, Gilbert ES, Linet MS, Moysich KB, Freudenheim JL, Wactawski-Wende J, Simon SL, Cahoon EK, Alexander BH, Doody MM, et al. 2020. Lung cancer mortality associated with protracted low-dose occupational radiation exposures and smoking behaviors in U.S. radiologic technologists, 1983-2012. Int J Cancer. 147(11):3130–3138.
Viet SM, Torma-Krajewski J, Rogers J. 2000. Chronic beryllium disease and beryllium sensitization at Rocky Flats: a case-control study. AIHAJ. 61(2):244–254.
Voelz GL. 1991. Health considerations for workers exposed to plutonium. Occup Med. 6(4):681–694.
Voelz GL, Hempelmann LH. 1975. Health study of plutonium workers - protocol for a morbidity and mortality study. Los Alamos (NM): Los Alamos Scientific Laboratory.
Voelz GL, Lawrence JN. 1991. A 42-y medical follow-up of Manhattan Project plutonium workers. Health Phys. 61(2):181–190.
Voelz GL, Lawrence JN, Johnson ER. 1997. Fifty years of plutonium exposure to the Manhattan Project plutonium workers: an update. Health Phys. 73(4):611–619.
Wakeford R. 2018. The growing importance of radiation worker studies. Br J Cancer. 119(5):527–529.
Wakeford R. 2019. Does low-level exposure to ionizing radiation increase the risk of cardiovascular disease? Hypertension. 73(6): 1170–1171.
Welch LS, Ringen K, Dement J, Bingham E, Quinn P, Shorter J, Fisher M. 2013. Beryllium disease among construction trade workers at Department of Energy nuclear sites. Am J Ind Med. 56(10): 1125–1136.
Wiggs LD. 1987. Mortality among females employed by the Los Alamos National Laboratory: an epidemiologic investigation [dissertation]. Norman (OK): University of Oklahoma.
Wiggs LD, Johnson ER, Cox-DeVore CA, Voelz GL. 1994. Mortality through 1990 among white male workers at the Los Alamos National Laboratory: considering exposures to plutonium and external ionizing radiation. Health Phys. 67(6):577–588.
Wilkinson GS, Tietjen GL, Wiggs LD, Galke WA, Acquavella JF, Reyes M, Voelz GL, Waxweiler RJ. 1987. Mortality among plutonium and other radiation workers at a plutonium weapons facility. Am J Epidemiol. 125(2):231–250.
Wing S, Richardson D, Wolf S, Mihlan G. 2004. Plutonium-related work and cause-specific mortality at the United States department of energy Hanford site. Am J Ind Med. 45(2):153–164.
Wing S, Richardson DB. 2005. Age at exposure to ionising radiation and cancer mortality among Hanford workers: follow up through 1994. Occup Environ Med. 62(7):465–472.
Yamada M, Kasagi F, Mimori Y, Miyachi T, Ohshita T, Sasaki H. 2009. Incidence of dementia among atomic bomb survivors - radiation effects research foundation adult health study. J Neurol Sci. 281(1–2):11–14.
Yoder RC, Dauer L, Balter S, Boice JD, Jr, Grogan H, Mumma M, Passmore CN, Rothenberg LN, Vetter RJ. 2018. Dosimetry for the study of medical radiation workers with a focus on the mean absorbed dose to the lung, brain and other organs. Int J Radiat Biol. 1–12. DOI:10.1080/09553002.2018.1549756
Yoder RC, Balter S, Boice JD, Jr, Grogan H, Mumma M, Rothenberg L, Passmore C, Vetter R, Dauer L. 2020. Using personal monitoring data to derive organ doses for medical radiation workers in the Million Person Study – considerations regarding NCRP Commentary No. 30. J Radiol Prot 1–15. DOI:10.1088/1361-6498/abcfcb.
Zablotska LB, Lane RS, Frost SE. 2013. Mortality (1950–1999) and cancer incidence (1969–1999) of workers in the Port Hope cohort study exposed to a unique combination of radium, uranium and c-ray doses. BMJ Open. 3(2):e002159.