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Mortality Among Mound Workers Exposed to Polonium-210 and Other Sources of Radiation, 1944–1979

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Polonium-210 is a naturally occurring radioactive element that decays by emitting an alpha particle. It is in the air we breathe and also a component of tobacco smoke. Polonium-210 is used as an anti-static device in printing presses and gained widespread notoriety in 2006 after the poisoning and subsequent death of a Russian citizen in London. More is known about the lethal effects of polonium-210 at high doses than about late effects from low doses. Cancer mortality was examined among 7,270 workers at the Mound nuclear facility near Dayton, OH where polonium-210 was used (1944–1972) in combination with beryllium as a source of neutrons for triggering nuclear weapons. Other exposures included external gamma radiation and to a lesser extent plutonium-238, tritium and neutrons. Vital status and cause of death was determined through 2009. Standardized mortality ratios (SMRs) were computed for comparisons with the general population. Lifetime occupational doses from all places of employment were sought and incorporated into the analysis. Over 200,000 urine samples were analyzed to estimate radiation doses to body organs from polonium and other internally deposited radionuclides. Cox proportional hazards models were used to evaluate dose-response relationships for specific organs and tissues. Vital status was determined for 98.7% of the workers of which 3,681 had died compared with 4,073.9 expected (SMR 0.90; 95% CI 0.88–0.93). The mean dose from external radiation was 26.1 mSv (maximum 939.1 mSv) and the mean lung dose from external and internal radiation combined was 100.1 mSv (maximum 17.5 Sv). Among the 4,977 radiation workers, all cancers taken together (SMR 0.86; 95% CI 0.79–0.93), lung cancer (SMR 0.85; 95% CI 0.74–0.98), and other types of cancer were not significantly elevated. Cox regression analysis revealed a significant positive dose-response trend for esophageal cancer [relative risk (RR) and 95% confidence interval at 100 mSv of 1.54 (1.15–2.07)] and a negative dose-response trend for liver cancer [RR (95% CI) at 100 mSv of 0.55 (0.23–1.32)]. For lung cancer the RR at 100 mSv was 1.00 (95% CI 0.97–1.04) and for all leukemias other than chronic lymphocytic leukemia (CLL) it was 1.04 (95% CI 0.63–1.71). There was no evidence that heart disease was associated with exposures [RR at 100 mSv of 1.06 (0.95–1.18)]. Assuming a relative biological effectiveness factor of either 10 or 20 for polonium and plutonium alpha particle emissions had little effect on the dose-response analyses. Polonium was the largest contributor to lung dose, and a relative risk of 1.04 for lung cancer at 100 mSv could be excluded with 95% confidence. A dose related increase in cancer of the esophagus was consistent with a radiation etiology but based on small numbers. A dose-related decrease in liver cancer suggests the presence of other modifying factors of risk and adds caution to interpretations. The absence of a detectable increase in total cancer deaths and lung cancer in particular associated with occupational exposures to polonium (mean lung dose 159.8 mSv), and to plutonium to a lesser extent (mean lung dose 13.7 mSv), is noteworthy but based on small numbers. Larger combined studies of U.S. workers are needed to clarify radiation risks following prolonged exposures and radionuclide intakes.

INTRODUCTION

Polonium-210 is a radioactive element that is widespread in the environment in small amounts (*1*). It is a decay product from airborne radon, a component of tobacco smoke, and is used as a static eliminator in the printing, photographic paper and textile industries. It was discovered in 1898 by Pierre and Marie Curie and named after Marie Curie's homeland, Poland. During World War II and for

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several decades after, polonium was used with beryllium as a neutron source to trigger nuclear weapons such as the first detonation at the Trinity site in 1945 and the Fat Man plutonium bomb that was detonated over Nagasaki. It is thought that polonium of about a microgram quantity, or the size of a grain of salt, was responsible for the 2006 poisoning that resulted in the death of a Russian citizen in London (*2*). More recently, the body of Yasser Arafat was exhumed to evaluate whether polonium-210 might have contributed to his death in 2004 (*3*). Human and animal data and models to estimate the alpha-radiation doses from polonium-210 to different organs and tissues have been evaluated (*4*).

Polonium-210 decays by emitting an alpha particle (two protons and two neutrons) and only a weak (low energy) gamma ray that is difficult to detect. It has an unusual property in that it ''creeps'' when exposed to the atmosphere and is difficult to contain (*1*). When ingested, polonium seeks out the soft tissues in the body and not the bone as is usually the case for alpha-particle-emitting radionuclides (*5*). Polonium intakes result in near whole-body exposure such that large doses can result in extensive cellular killing and acute radiation sickness (*4*). Polonium-210 may contribute to cigarette-induced lung cancer because of its deposition on tobacco leaves from atmospheric radon and, perhaps equally as importantly, its absorption through roots of tobacco plants grown in phosphate fertilizers rich in radium (*6, 7*). There is little known about the health effects after low-level exposure to polonium-210.

Previous studies of workers exposed to polonium-210 during 1944–1972 at the Mound, OH nuclear facility did not indicate significant increases in cancer deaths, but the follow-up was relatively short, and the dosimetry was based on early biokinetic models and did not account for intakes of plutonium or tritium (*8, 9*). A small but statistically significant risk of lung cancer was subsequently reported for white males employed 1943–1959, but was not related to duration of employment and exposure information was not evaluated (*10*).

A brief description of the Dayton and Miamisburg, OH facilities is found in the NIOSH dose reconstruction literature (http://www.cdc.gov/niosh/ocas/pdfs/tbd/mound1-r1.pdf): ''In 1943, the Manhattan Engineer District began the Dayton Project to investigate the chemistry and metallurgy of polonium. Between 1943 and 1948, this work was performed at locations around Dayton, all of which turned out to be too small for the job. As such, the Mound Plant was constructed in 1947 in Miamisburg, OH to replace these earlier laboratories. Mound was first occupied in May 1948 and became operational February 1949. The site's role grew to include nuclear weapons component development and production, and such secondary missions as radioactive waste management and recovery, the use of radioactive materials for non-weapons purposes, and the purification of nonradioactive isotopes for scientific and commercial research''.

Plutonium-238 was used at Mound to manufacture heat sources starting from 1959 through 1965 (*11*). Weapons-grade plutonium-239 was processed at Mound and also used in reactor fuel research. Studies of plutonium workers have not found consistent evidence of radiation risks except at rather high dose levels experienced by early weapons production workers in the former Soviet Union (*12–17*).

Tritium (hydrogen-3) was used extensively at Mound at the start of weapons component production in 1954 (*11*). To date there are no informative studies of workers exposed to tritium (*18*).

We extended and enhanced the original studies of Mound workers by adding 26 additional years of follow-up, reconstructing polonium doses using the latest biokinetic models, incorporating organ doses from plutonium and tritium into the analyses, and increasing the population size by 2,868 by including female and non-white workers. In addition to the historical importance of the Mound, OH nuclear facility, the study is by far the largest and only epidemiological study that can address directly the possible health effects from intakes of polonium experienced over 50 years ago.

METHODS

Human subjects research approval was received from the Oak Ridge Sitewide Institutional Review Board and the Vanderbilt University Institutional Review Boards.

COHORT DEFINITION

The previous study population was described by Wiggs *et al.* (*8*). In brief, 4,402 white males employed on or after January 1, 1944 were identified from the Mound nuclear weapons facility (1944–1972) located near Dayton, OH. The cohort was designed to evaluate polonium exposures and is the largest study to do so. We expanded the cohort to include 2,867 non-white and female workers who had not been previously studied, for a total of 7,269 employees first hired between 1944 and 1979. There were 4,977 workers who were monitored for radiation exposure and 2,292 workers who were not monitored.

VITAL STATUS AND OUTCOME DETERMINATION

Vital status as of December 31, 2009 for the Mound workers was determined from linkages of the study roster with the National Death Index (NDI); the California Death Statistical Master File and other state mortality files; the Social Security Administration (SSA) Death Master File; the SSA Epidemiological Vital Status Service (which confirmed alive status); Comserv, a computer services firm specializing in locating persons (www.comserv-inc.com); and LexisNexis, an online information service provider (www.lexisnexis.com). 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 to match the study roster against the SSA Death Master File and state mortality files using (*19*). SSA vital status files and other sources confirmed that 3,490 workers (48.1%) were alive in 2009 (Fig. 1). Cause of death was determined for all but

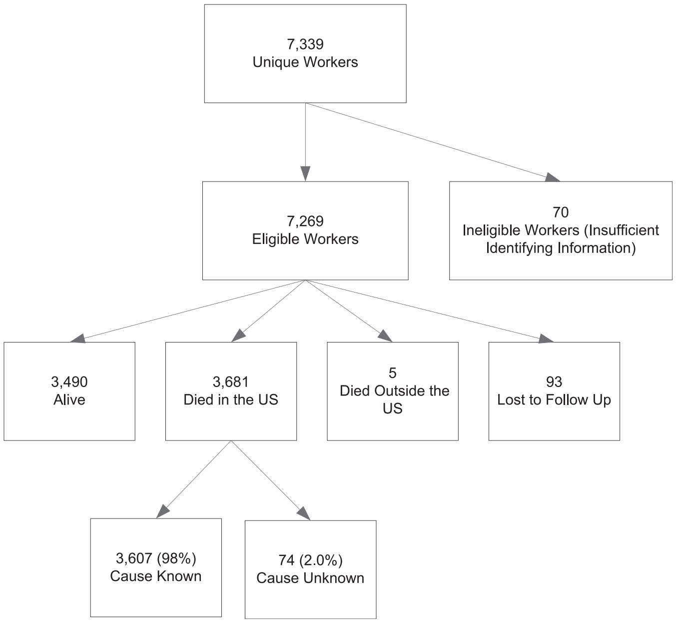

FIG. 1. Vital status of workers at the Mound nuclear facility near Dayton, OH, as of December 31, 2009.

74 (2.0%) of the 3,681 workers who had died. Workers without a SSA, state mortality file or NDI match ($n = 93$, 1.3%) were assumed alive until their date of last employment at Mound. In addition to mortality determinations, linkage with the Ohio Cancer Incidence Surveillance System (1996–2008) identified incident cases of cancer for the approximately 60% of the workforce who were living in Ohio in or after 1996 (http://www.odh.ohio.gov/odhprograms/dis/ociss/access1.aspx). Workers with serious renal disease were identified by linkage with the U.S. Renal Data System (1977–2008), which includes persons who received kidney dialysis or transplant (*20*).

DOSE RECONSTRUCTION

Urinary polonium bioassay data were available for study from 1944 to 1984. Although polonium work began at the Dayton laboratories in 1943, possible exposures to polonium in 1943 were assumed to be insignificant (*11*). From the beginning, all polonium workers were required to submit weekly spot urine samples, preferably at the beginning of the workweek. The polonium program was transferred to Mound in its entirety by 1949 and employees working in polonium operations continued to submit spot urine samples each workweek. The number of monitored workers increased from 1959 to 1963 and so did the number of urine samples per worker: two samples were usually collected on Monday and Wednesday or three samples were collected on Monday, Wednesday and Friday (*11*). Over 200,000 polonium urine samples were available for study, i.e., over 70 urine samples per polonium worker (https://www3.orau.gov/CEDR/). For convenience and consistency with the previous study (*8*), ''Mound facility'' is used in this paper to encompass all polonium processing facilities in Dayton and Miamisburg, OH, recognizing that the Mound facility did not become operational until 1949 and was located near Dayton.

The approach to estimating occupational doses received by Mound employees followed the procedures outlined by Boice *et al.* (*21, 22*). External dose estimates generally were based on personal film badge or thermoluminescent dosimeter monitoring of Mound workers. Estimated annual external radiation doses received before and after employment at Mound were obtained from the U.S. Department of Energy (*23*) REMS (Radiation Exposure Monitoring Systems) and other cohort worker databases, the U.S. Nuclear Regulatory Commission (*24*) REIRS (Radiation Exposure and Monitoring System) database and Landauer, Inc. and added to the external doses received at Mound. The importance of seeking career doses beyond those available at the Mound facility was apparent in that 1,814 unique matches (36.6% of the monitored workers) were found within these dosimetry databases. Radiation doses from intake of radionuclides generally were estimated for specific organs or tissues on the basis of bioassay data, primarily urinalyses. The bioassay data were interpreted using biokinetic models of the International Commission on Radiological Protection (ICRP) or updated versions of those models proposed for use in upcoming ICRP documents (*25–27*). In the absence of specific information on the mode of intake of a radionuclide, interpretation of bioassay data for a worker was based on the assumption that intake was by inhalation.

Polonium-210 was the radionuclide of greatest concern at Mound because of the number of exposed workers and the potential for high intakes. There was also a relatively high potential for intake of tritium (hydrogen-3) and various isotopes of plutonium, particularly plutonium-238 used in the production of heat sources. Over 2,800 workers had bioassays for polonium-210; about 1,500 workers had bioassays for plutonium; and over 4,100 workers had bioassays for tritium (Table 2). Not all bioassays resulted in measured radioactivity in the urine; thus the number of workers monitored compared with the number with estimated organ doses differs by over 25%. Several other radionuclides were handled to a limited extent in Mound experiments or operations, including radium-226, actinium-227, thorium-228, protactinium-231 and various uranium isotopes (*11*). Exposure data for these presumably minor contributors to doses to Mound workers were sparse. Internal deposition of radionuclides other than polonium-210, tritium, and plutonium isotopes is not addressed in this analysis.

With a few exceptions, the biokinetic models used to interpret bioassay data were taken from ICRP Publication 68 (*25*). One exception is the systemic model applied to polonium (*26*), which will replace the corresponding model of ICRP Publication 68 in upcoming ICRP documents. Also, the Human Respiratory Tract Model (HRTM) (*27*) as applied in ICRP Publication 68 was modified in two ways for application to polonium. First, Publication 68 recommends Type M (a set of default parameter values of the ICRP's HRTM representing inhaled material that is moderately soluble in the respiratory tract) as a default absorption type for inhaled polonium, but data for laboratory animals and accidentally exposed workers indicate that Type M parameter values substantially overestimate the retention time of polonium in the lungs. In the present analysis the long-term biological half-time of ~140 days for polonium in the deep lungs specified for Type M material was replaced with a half-time of 30 days. Second, a particle size of 1 μm activity median aerodynamic particle diameter (AMAD) is assumed for polonium rather than the default particle size of 5 μm AMAD recommended in ICRP Publication 68 (*25*) because airborne polonium likely existed as fine aerosols in view of the types of operations conducted at Mound. The aerosol size and the residence time of activity in the lungs are important sources of uncertainty in estimates of lung dose from airborne polonium. Also, the default assumption that urinary polonium arises only from inhaled polonium may result in sizable overestimates of lung dose for a portion of the Mound polonium workers, as the dominant intake may have been by puncture wound, absorption through intact skin or ingestion.

Another important uncertainty and potential source of bias in reconstruction of doses from intake of polonium-210 by Mound workers is the level of recovery of polonium from urine samples by the technique applied at Mound. That technique involved spontaneous deposition of polonium in urine onto a metal disc from which its decays were counted. The problem is that polonium excreted in urine may not be recovered to the same extent as tracer polonium added to urine (to determine the fraction recovered) unless there is wet ashing (acid digestion) of the urine prior to deposition on the disc, which was not the case with the Mound technique. Results of human and animal studies of the percentage of excreted polonium recovered from unashed urine are highly variable (*28–32*). The available data suggest that recovery of polonium from urine may vary with time after intake of polonium and with the animal species. In the present analysis it was assumed that recovery was 20%, which was selected as a central value based on reported data (*28–32*).

Dose estimates from intake of plutonium isotopes is an update of a previous dose reconstruction for Mound workers by MJW Corporation, Inc. (*33*). The MJW analysis involved development of detailed exposure scenarios consistent with the work history, incident reports and plutonium bioassay data for each worker. For example, an exposure scenario for a given plutonium worker might be divided into different chronic exposure periods with specified start and end dates and might also include acute intakes at specified dates. Each exposure scenario also specifies a likely or default solubility or mixture of solubility levels of inhaled activity for each chronic or acute exposure (e.g., 50% moderately soluble and 50% relatively insoluble material). The MJW estimates were based on a plutonium excretion model of Jones (*34*) [or in an apparently small number of cases an excretion model of Durbin (*35*)], together with the respiratory model and plutonium systemic model from ICRP Publication 30 (*36*) that were replaced in ICRP Publication 68 (*25*). Comparisons of MJW dose estimates for both hypothetical bioassay data and actual bioassay data from selected plutonium workers at Mound with estimates based on MJW's exposure scenarios for the same workers but using models of ICRP Publication 68 indicated that fixed adjustment factors could be used to modify MJW's dose estimates to reflect models of Publication 68 (*25*). The comparisons indicated that tissue dose estimates derived by this ''adjustment-factor'' approach typically were within 30% of estimates based on a direct dose reconstruction involving the updated models. This approach was applied to all identified plutonium exposures.

Dose estimates for tritium were based on the assumption that all measurements of tritium in urine reflect intake of tritiated water. The methods and results of a previous dose reconstruction for internally deposited tritium at Mound (*11*) were found to be reasonably consistent with estimates based on models of ICRP Publication 68 and were adopted for use in this study.

ANALYTIC METHODS

Standardized mortality ratio (SMR) analyses compared the numbers of deaths observed among Mound workers with the numbers expected based on general population rates in the U.S. for persons of the same age, race and gender over the same time periods using OCMAP software (*37*). The SMR analyses were based on the underlying cause of death. For workers with unknown race (13.4%), a weighted approximation based on the proportions of race for the 86.6% of workers with known race was used to compute expected numbers. For all workers, person-time began at the date of first hire at Mound and ended at the date of death, age 95, date lost to follow-up or December 31, 2009, or whichever came first. Because of incomplete information on dates of termination for many Mound employees, duration of employment could not be evaluated. For some analyses, observed and expected numbers of deaths were distributed over categories of external radiation dose, incorporating organ dose from radionuclides when possible, and trend analyses were conducted following the methods of Breslow and colleagues (*38*).

Within-cohort analyses (hereafter called internal analyses) were conducted using Cox proportional hazards models to compute risks among the 4,977 radiation workers (for whom 4,672 had complete data on covariates available) across categories of estimated radiation dose to specific organs (*39*). The non-monitored Mound workers were not included in the internal analyses because of substantial differences in overall and cause-specific mortality compared with the monitored workers, conceivably related to differences in lifestyle and socioeconomic factors. To increase statistical power, the cause-specific internal analyses included both the underlying and contributing causes of death obtained from the National Death Index and available death certificates. Year of birth, year of hire, gender and education were included in the models. Education was considered an indicator of socioeconomic status and as a possible surrogate for lifestyle factors such as tobacco use (*40*). Age was used as the timescale for the hazard function in the internal analyses. To allow for a possible latent period between radiation exposure and any effect consequent to it, doses were lagged, i.e., excluded if they occurred during some assumed interval prior to the event of interest. For the internal analyses, doses were lagged 10 years for solid cancers and 2 years for leukemia. All internal analyses were conducted with SAS/STAT software (SAS/STAT software, version 9.2 of the SAS System for Windows, SAS Institute Inc., Cary, NC).

For the internal cohort analyses, radiation workers entered the risk set at their first date of radiation monitoring at Mound. Radiation exposure category was treated as a time-dependent covariate, allowing workers to be assigned to increasingly higher dose categories over time as their individual radiation doses accrued. Parameter estimates and standard errors for the exposure categories in the Cox models were used to obtain hazard ratios and 95% confidence intervals for death due to the cause under investigation compared with those in the referent group taken as the workers with low radiation dose (<10 mSv for lung cancer analyses and <5 mSv for all others). Trend tests treated the radiation dose as a single continuous measure, and one-sided *P* values are presented. Relative risks at 100 mSv were computed for all leukemia excluding CLL, and for cancers of the lung and several other causes of death. In the baseline analysis, a relative biological effectiveness (RBE) of 1 was applied to alpha-particle doses from polonium or plutonium. Additional analyses were performed assuming an RBE of 10 or 20 for these alpha-particle doses. An RBE of 1 was assumed for tritium and of 10 for neutrons, consistent with the approach used in studies of Japanese atomic bomb survivors (*41*).

RESULTS

Most of the Mound workers were male (75.2%), white (80.3%), born before 1930 (56.0%), hired before 1960 (51.4%) and followed for more than 30 years (82.3%). Vital status was obtained for 98.7% of the population and 50.7% had died by 2009 (Table 1). The average follow-up was 40.4 years. Overall, 4,509 workers were monitored for external radiation (4,185 with a measurement >0), 2,816 for polonium (2,295 with dose >0), 1,501 for plutonium (837 with dose >0), 4,134 for tritium (1,125 with dose >0) and 2,292 were not monitored for radiation (Table 2). There were 1,814 (36.6%) workers monitored for radiation at other facilities either before or after employment at Mound (mean 2.5 mSv).

Table 2 presents descriptive statistics for radiation doses by specific type of exposure among Mound workers. The mean external dose for the 4,185 workers with measured external radiation dose was 26.1 mSv (maximum 939.1 mSv). Assuming an RBE of 1.0 for internal exposures, the mean lung dose was 100.1 mSv (max. 17.5 Sv) for the 4,977 workers with measured external and/or internal values. The mean liver dose from external and internal radiation was 34.6 mSv (maximum 2.3 Sv). The mean heart dose from external and internal radiation was 24.3 mSv

TABLE 1
Demographic and Occupational Characteristics of Workers at the Mound Nuclear Facility near Dayton, Ohio (1944–1979)

Radiation type: Number of workers:	Any external 4,185		Any internal 3,082		Any tritium 1,125	
Characteristic	*n*	%	*n*	%	*n*	%
Gender						
Male	3,422	81.8	2,647	85.9	1,045	92.9
Female	763	18.2	435	14.1	80	7.1
Race						
White	3,532	84.4	2,781	90.2	991	88.1
Non-white	277	6.6	154	5.0	71	6.3
Missing	376	9.0	147	4.8	63	5.6
Education						
Grade school	496	11.9	652	21.2	139	12.4
Some high school	2,125	50.8	1,518	49.3	656	58.3
High school graduate	880	21.0	561	18.2	196	17.4
Associate's degree	410	9.8	262	8.5	99	8.8
Unknown	42	1.0	47	1.5	8	0.7
Missing	232	5.5	42	1.4	27	2.4
Year of birth						
<1920	690	16.5	986	32.0	170	15.1
1920–1929	974	23.3	965	31.3	215	19.1
1930–1939	1,052	25.1	610	19.8	362	32.2
1940–1949	1,092	26.1	455	14.8	316	28.1
1950–1959	357	8.5	63	2.0	59	5.2
≥1960	20	0.5	3	0.1	3	0.3
Year of hire						
1944–1949	727	17.4	1,359	44.1	89	7.9
1950–1959	670	16.0	559	18.1	215	19.1
1960–1969	1,877	44.8	993	32.2	674	59.9
1970–1979	678	16.2	127	4.1	120	10.7
Missing[a]	233	5.6	44	1.4	27	2.4
Years of follow-up						
<1	1	0.0	3	0.1	0	0.0
1–4	21	0.5	25	0.8	3	0.3
5–9	33	0.8	44	1.4	6	0.5
10–19	178	4.3	194	6.3	49	4.4
20–29	305	7.3	303	9.8	90	8.0
30–39	1,185	28.3	554	18.0	263	23.4
40–49	1,784	42.6	1,094	35.5	573	50.9
≥50	678	16.2	865	28.1	141	12.5
Vital status as of 12/31/2009						
Alive[b]	2,510	60.0	1,309	42.7	701	62.3
Dead	1,669	39.9	1,753	56.7	424	37.7
Lost to follow-up	6	0.1	20	0.7	0	0.0
Total	4,185		3,082		1,125	

[a] Hire dates were imputed when missing.

[b] Five workers who died outside the U.S. were treated as alive up to the date last known alive in the U.S.

(maximum 941.2 mSv). Not all workers who were monitored with bioassays had positive measurements of radioactivity in their urine, and accordingly, their organ doses would be zero. Estimates of absorbed organ doses for external photon and radionuclide exposures are presented in units of mSv, whereas mGy technically might have been used. This was done to be consistent with previous studies and convention. When an RBE of 10 or 20 is assumed, this is noted and the unit mSv is also used, although ''weighted Gy'' might have been considered.

Table 3 presents the SMRs for 44 causes of death for the 4,977 workers monitored for radiation and the 2,292 workers not monitored for radiation. Overall, the number of observed deaths was below the expected: 3,681 deaths were observed and 4,073.9 were expected (SMR 0.90; 95% CI 0.88–0.93). There were 968 deaths from cancer compared with 1,082.8 expected (SMR 0.89; 95% CI 0.84–0.95). There were no appreciable differences in the SMRs between men and women with the all cause SMR and all cancer SMR being 0.91 and 0.89 for men and 0.89 and 0.93 for women, respectively (data not shown). The SMR for female breast cancer was 1.01 ($n = 42$). There was no statistically significant SMR elevation among the radiation workers. Mortality from lung cancer (SMR 0.85; $n = 204$)

TABLE 1
Extended.

Any polonium 2,295		Any plutonium 837		Any radiation 4,977		No radiation 2,292		Total population 7,269	
n	%	*n*	%	*n*	%	*n*	%	*n*	%
1,945	84.8	802	95.8	4,004	80.5	1,459	63.7	5,463	75.2
350	15.2	35	4.2	973	19.5	833	36.3	1,806	24.8
2,119	92.3	778	92.9	4,217	84.7	1,623	70.8	5,840	80.3
92	4.0	51	6.1	319	6.4	134	5.9	453	6.2
84	3.7	8	1.0	441	8.9	535	23.3	976	13.4
618	26.9	124	14.8	793	15.9	654	28.5	1,447	19.9
1,086	47.3	448	53.5	2,491	50.1	1,071	46.7	3,562	49.0
381	16.6	168	20.1	952	19.1	175	7.6	1,127	15.5
158	6.9	86	10.3	436	8.8	63	2.8	499	6.9
40	1.7	8	1.0	60	1.2	172	7.5	232	3.2
12	0.5	3	0.4	245	4.9	157	6.9	402	5.5
943	41.1	167	20.0	1,129	22.7	893	39.0	2,022	27.8
870	37.9	192	22.8	1,295	26.0	757	33.0	2,052	28.2
346	15.1	282	33.7	1,078	21.7	238	10.4	1,316	18.1
136	5.9	190	22.7	1,098	22.1	279	12.2	1,377	18.9
0	0.0	7	0.8	357	7.2	110	4.8	467	6.4
0	0.0	0	0.0	20	0.4	15	0.7	35	0.5
1,354	59.0	117	14.0	1,416	28.5	1,173	51.2	2,589	35.6
469	20.4	175	20.9	747	15.0	399	17.4	1,146	15.8
456	19.9	520	62.1	1,888	37.9	401	17.5	2,289	31.5
2	0.1	22	2.6	678	13.6	145	6.3	823	11.3
14	0.6	3	0.4	248	5.0	174	7.6	422	5.8
3	0.1	0	0.0	4	0.1	7	0.3	11	0.2
25	1.1	2	0.2	33	0.7	29	1.3	62	0.9
43	1.9	6	0.7	56	1.1	51	2.2	107	1.5
169	7.4	37	4.4	260	5.2	160	7.0	420	5.8
258	11.2	71	8.5	426	8.6	257	11.2	683	9.4
359	15.6	135	16.1	1,306	26.2	562	24.5	1,868	25.7
624	27.2	449	53.6	1,891	38.0	633	27.6	2,524	34.7
814	35.5	137	16.4	1,001	20.1	593	25.9	1,594	21.9
718	31.3	457	54.6	2,678	53.8	817	35.7	3,495	48.1
1,557	67.8	380	45.4	2,279	45.8	1,402	61.2	3,681	50.7
20	0.9	0	0.0	20	0.4	73	3.2	93	1.3
2,295		837		4,977		2,292		7,269	

and other smoking-related cancers (SMR 0.85; *n* = 303) were significantly low. In contrast, the workers not monitored for radiation had significantly increased risks for death due to nonmalignant respiratory disease (SMR 1.29; *n* = 104) and mental and behavioral disorders (SMR 1.63; *n* = 29). Heart disease was significantly below expectation among all workers (SMR 0.85; *n* = 1,189) and among radiation workers (SMR 0.81; *n* = 753).

Among radiation workers, no site of *a priori* interest was increased, i.e., cancers of the lung (SMR 0.85; *n* = 204), liver (SMR 0.82; *n* = 15), bone (SMR 0.0), kidney (SMR 1.08; *n* = 19) and leukemia other than CLL (SMR 0.88; 95% CI 0.53–1.38). Mortality from nonmalignant kidney disease, i.e., nephritis and nephrosis, also was not increased (SMR 0.77; *n* = 25). Significant deficits were seen for heart disease, cerebrovascular disease, cirrhosis of the liver, nonmalignant respiratory disease and all external causes of death. In contrast, workers not monitored for radiation had a slight but significant increased mortality for all causes of death (SMR 1.06) due to significant increases in mental disorders, nonmalignant respiratory disease and external causes. In contrast to the significant deficits seen for lung cancer among radiation workers, lung cancer was close to expectation among nonradiation workers (SMR 1.05; *n* = 106).

Table 4 presents SMRs for workers with positive bioassay data for polonium (*n* = 2,295), plutonium (*n* = 837), tritium (*n* = 1,125) and any radionuclide (*n* = 3,082). Not everyone

TABLE 2
Descriptive Statistics for Radiation Doses by Types of Radiation among Workers at the Mound Nuclear Facility near Dayton, OH

			Percentiles (mSv)				
Type of radiation	No. workers	Mean dose (mSv)	5th	25th	75th	95th	Maximum
External radiation							
Dose > 0	4,185	26.1	0.20	0.76	23.7	129.8	939.1
Dose = 0	324	-	-	-	-	-	-
Not monitored	2,760	-	-	-	-	-	-
Neutrons							
Dose > 0	320	5.14	0.01	0.08	1.04	8.86	341.4
Dose = 0	3,830	-	-	-	-	-	-
Not monitored	3,119	-	-	-	-	-	-
Tritium							
Dose > 0	1,125	7.96	0.03	0.19	6.19	42.5	195.5
Dose = 0	3,009	-	-	-	-	-	-
Not monitored	3,135	-	-	-	-	-	-
Polonium							
Dose to lung (RBE = 1)							
Dose > 0	2,295	159.8	0.35	3.09	106.3	784.5	17,477.5
Dose = 0	521	-	-	-	-	-	-
Not monitored	4,453	-	-	-	-	-	-
Dose to liver (RBE = 1)		10.6	0.02	0.18	6.32	46.3	2,280.4
Dose > 0	2,295						
Dose = 0	521	-	-	-	-	-	-
Not monitored	4,453	-	-	-	-	-	-
Dose to kidney (RBE = 1)		21.6	0.04	0.39	13.4	97.9	3,472.5
Dose > 0	2,295						
Dose = 0	521	-	-	-	-	-	-
Not monitored	4,453	-	-	-	-	-	-
Dose to heart (RBE = 1)							
Dose > 0	2,295	0.45	0.00	0.01	0.27	1.96	96.4
Dose = 0	521	-	-	-	-	-	-
Not monitored	4,453	-	-	-	-	-	-
Plutonium							
Dose to lung (RBE = 1)							
Dose > 0	837	13.7	2.05	4.51	12.1	41.4	496.4
Dose = 0	664	-	-	-	-	-	-
Not monitored	5,768	-	-	-	-	-	-
Dose to liver (RBE = 1)							
Dose > 0	837	33.5	4.1	10.0	29.7	109.9	1,439.6
Dose = 0	664	-	-	-	-	-	-
Not monitored	5,768	-	-	-	-	-	-
Dose to Kidney (RBE = 1)							
Dose > 0	837	0.69	0.09	0.21	0.61	2.27	29.8
Dose = 0	664	-	-	-	-	-	-
Not monitored	5,768	-	-	-	-	-	-
Dose to Heart (RBE = 1)							
Dose > 0	837	0.23	0.03	0.07	0.2	0.76	9.93
Dose = 0	664	-	-	-	-	-	-
Not monitored	5,768	-	-	-	-	-	-
Total organ dose[a]							
Lung dose (RBE = 1)	4,977	100.1	0.23	1.35	67.8	483.8	17,477.7
Lung dose (RBE = 10)	4,977	784.1	0.23	1.51	243.2	4,241.2	174,778.1
Lung dose (RBE = 20)	4,977	1,544.1	0.23	1.51	413.4	8,448.6	349,550.0
Liver dose (RBE = 1)	4,977	34.6	0.16	0.80	31.1	170.3	2,280.4
Liver dose (RBE = 10)	4,977	129.2	0.23	1.24	98.0	545.2	22,804.3
Liver dose (RBE = 20)	4,977	234.4	0.23	1.39	162.1	996.2	45,608.6
Kidney dose (RBE = 1)	4,977	34.2	0.20	0.89	31.9	162.1	3,472.5
Kidney dose (RBE = 10)	4,977	125.1	0.23	1.37	70.9	561.7	34,724.7
Kidney dose (RBE = 20)	4,977	226.0	0.23	1.47	98.2	1,062.6	69,449.4
Heart dose (RBE = 1)	4,977	24.3	0.02	0.42	17.9	128.5	941.2
Heart dose (RBE = 10)	4,977	26.5	0.10	0.69	22.0	133.8	964.0
Heart dose (RBE = 20)	4,977	29.0	0.18	0.79	25.7	139.6	1,928.0
Red marrow dose (RBE = 1)	4,977	26.4	0.09	0.60	20.5	137.7	943.6

[a] Includes external, neutron and tritium doses plus polonium and plutonium doses with indicated RBEs for polonium and plutonium applied.

monitored for radionuclide intakes tested positive, e.g., 18.7% of polonium workers and 44.2% of plutonium workers did not have positive bioassay measurements. Significant deficits for all cancers taken together were seen among workers with positive bioassays for polonium (SMR 0.89; $n = 388$), plutonium (SMR 0.78; $n = 105$), tritium (SMR 0.78; $n = 124$) and any internal emitter (SMR 0.88; $n = 459$). Tritium workers had a significantly low risk of lung cancer (SMR 0.71; $n = 39$), and plutonium workers had a significantly low risk of prostate cancer (SMR 0.36; $n = 4$). The cancers among polonium workers of *a priori* interest were close to expectation: lung (SMR 0.97; $n = 135$), kidney (SMR 1.00, $n = 10$), liver (SMR 0.79, $n = 8$) and leukemia other than CLL (SMR 0.96; $n = 12$).

Table 5 presents SMRs for workers monitored for radiation over categories of radiation absorbed dose from external exposures. The highest category of cumulative dose (>1,000 mSv) included 79 workers, and no cause of death was significantly elevated. Nearly 4.6% of the workers had cumulative doses over 500 mSv and 19% over 100 mSv. Trend analyses to indicate possible associations between radiation and mortality risk were conducted for a few categories recognizing that comparisons with the general population should be done with caution, that radionuclide contributions to organ dose were in large part not included in Table 5, and that the intra-cohort analyses in Tables 6 and 7 are the most appropriate. For all causes of death [$P(+) = 0.07$], all cancer deaths [$P(–) = 0.23$] and lung cancer [$P(–) = 0.34$] there were no significant trends over categories of increasing radiation absorbed dose. For cancers of *a priori* interest, i.e., cancers of the lung, liver and kidney and leukemia other than CLL, no increasing dose-response trends in the SMRs were observed. Positive dose-response trends were suggested for all heart disease ($P = 0.04$) and diseases of the nervous system ($P = 0.03$).

Table 6 shows internal cohort dose-response analyses for four cancers based on Cox proportional hazards models combining external radiation dose with organ-specific internal radiation dose and assuming RBEs of 1, 10 and 20. These cancers were selected because of *a priori* interest as radiosensitive sites, and likely polonium or plutonium concentrations, i.e., lung, kidney, liver and leukemia excluding CLL. These internal analyses are considered more valid than the SMR analyses because potential biases associated with general population comparisons are eliminated and internal radiation doses from intakes of radionuclides could be readily incorporated.

All doses are to specific organs or tissues and include external gamma ray, external neutron, polonium, plutonium and tritium contributions. Doses received before and after employment at Mound are included. Because of small numbers, high-dose categories had to be combined for model convergence for most sites. No analyses were conducted using effective dose, a unit used in radiation protection to monitor and control human exposure. The quantity effective dose is a risk-related (or risk-informed) dose quantity for the whole body. It is based on averaging age- and gender-related factors for a referent population and thus is not appropriate for retrospective epidemiologic evaluation of radiation risks to specific organs or tissue to individuals (*42*).

There were no significant dose-response trends seen for lung cancer, kidney cancer, liver cancer or leukemia other than CLL. The risk of leukemia (excluding CLL) tended to increase over categories increasing radiation dose to active bone marrow but the trend was not significant ($P = 0.33$). Liver cancer showed negative dose responses of borderline statistical significance for all assumptions concerning the RBE for alpha particles. The RR at 100 mSv was estimated as 1.00 (95% CI 0.97–1.04) for lung cancer, 0.82 (95% CI 0.32–2.09) for kidney cancer, 0.55 (95% CI 0.23–1.32) for liver cancer and 1.04 (95% CI 0.63–1.71) for leukemia (excluding CLL). There were no appreciable differences when RBEs of 10 or 20 were incorporated as weighting factors for polonium and plutonium.

Table 7 presents internal cohort dose-response analyses for deaths due to esophageal cancer, colon cancer, non-Hodgkin lymphoma, and heart disease. These causes of death were selected because of large numbers or because of suggested increases seen in the SMR analyses in Table 5. A statistically significant positive dose-response trend ($P = 0.002$) was seen for cancer of the esophagus whereas a negative trend ($P = 0.12$) was observed for cancer of the colon. A positive trend in non-Hodgkin lymphoma was suggested but was not close to significance ($P = 0.45$). In contrast to the positive dose-response trend seen for heart disease based on SMR population comparisons (Table 5), the intra-cohort dose response analyses for heart disease did not indicate a trend ($P = 0.14$). For esophageal cancer the RR at 100 mSv was estimated as 1.54 (95% CI 1.15–2.07).

To evaluate cancer incidence, linkage with the Ohio Incidence Surveillance System was conducted over the years 1996 through 2008. Sixty percent of the Mound workers known to be alive in 1996 were still living in Ohio based on Lexis Nexis residential history evaluations. This is consistent with the finding that 60% of all deceased workers had also died in Ohio. Linkage identified 493 incident cancers, including multiple primaries; whereas 554 would have been expected based on SEER cancer incidence rates (*43*) after reducing the expected value by 40% to account for non-Ohio residents [standardized incidence ratio (SIR) 0.89; 95% CI 0.81–0.97]. For radiation workers the overall observed number of incident cancers was 348 compared with 385 expected (SIR 0.90; 95% CI 0.81–1.00). For lung cancer, the observed number of incident cases was 54 compared with 59 expected (SIR 0.92; 95% CI 0.69–1.19).

Linkages with the U.S. Renal Data System identified 76 former Mound workers with serious renal disease, including the need for dialysis. There were no discernible patterns with dose: 56 were radiation workers, 30 had polonium exposures and 10 had plutonium exposures. One worker died of kidney cancer but had not been exposed to polonium

TABLE 3
Observed and Expected Numbers of Deaths and Standardized Mortality Ratios (SMRs) among Mound Workers, Followed 1944–2009, by Radiation Exposure Status

Cause of death (ICD9)	Radiation status											
	Any radiation Number of workers = 4,977 Person–years = 202,178				No radiation Number of workers = 2,292 Person–years = 91,284				Total population Number of workers = 7,269 Person–years = 293,462			
	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
All causes of death (001–999)	2,279	2,756.2	0.83*	0.79–0.86	1,402	1,319.0	1.06*	1.01–1.12	3,681	4,073.9	0.90*	0.88–0.93
All malignant neoplasms (140–208)	632	737.4	0.86*	0.79–0.93	336	345.7	0.97	0.87–1.08	968	1,082.8	0.89*	0.84–0.95
Buccal cavity and pharynx (140–149)	11	14.9	0.74	0.37–1.32	10	6.7	1.48	0.71–2.73	21	21.6	0.97	0.60–1.48
Esophagus (150)	19	19.8	0.96	0.58–1.50	11	7.6	1.45	0.72–2.59	30	27.4	1.10	0.74–1.56
Stomach (151)	13	22.0	0.59	0.32–1.01	7	11.7	0.60	0.24–1.24	20	33.6	0.60*	0.36–0.92
Colorectal (153–154)	67	75.6	0.89	0.69–1.13	36	37.8	0.95	0.67–1.32	103	113.3	0.91	0.74–1.10
Colon (153)	58	61.8	0.94	0.71–1.21	26	30.7	0.85	0.55–1.24	84	92.5	0.91	0.73–1.13
Rectum (154)	9	12.7	0.71	0.32–1.35	9	6.8	1.33	0.61–2.52	18	19.5	0.92	0.55–1.46
Biliary passages and liver (155–156)	15	18.3	0.82	0.46–1.35	10	7.8	1.28	0.61–2.36	25	26.1	0.96	0.62–1.42
Pancreas (157)	31	37.6	0.82	0.56–1.17	20	17.8	1.12	0.69–1.74	51	55.4	0.92	0.69–1.21
Larynx (161)	4	7.8	0.51	0.14–1.32	3	3.3	0.92	0.19–2.68	7	11.1	0.63	0.26–1.31
Bronchus, Trachea, and Lung (162)	204	239.8	0.85*	0.74–0.98	106	101.3	1.05	0.86–1.27	310	340.9	0.91	0.81–1.02
Bone (170)	0	1.7	0.00	0.00–2.19	1	0.9	1.10	0.03–6.14	1	2.6	0.39	0.01–2.15
Connective and other soft tissue (171)	3	3.8	0.78	0.16–2.29	0	1.7	0.00	0.00–2.20	3	5.5	0.54	0.11–1.59
Melanoma of skin (172)	13	11.1	1.17	0.62–2.00	4	4.2	0.95	0.26–2.43	17	15.3	1.11	0.65–1.78
Breast (174–175)	21	21.0	1.00	0.62–1.53	21	20.4	1.03	0.64–1.57	42	41.5	1.01	0.73–1.37
All uterine (females only) (179–182)	3	5.5	0.54	0.11–1.59	6	5.5	1.09	0.40–2.38	9	11.0	0.82	0.37–1.55
Cervix uteri (180)	1	2.6	0.38	0.01–2.12	2	2.5	0.78	0.10–2.83	3	5.2	0.58	0.12–1.69
Ovary and other female genital organs (183–184)	9	7.2	1.25	0.57–2.36	7	7.4	0.95	0.38–1.96	16	14.6	1.10	0.63–1.78
Prostate (Males only) (185)	47	57.4	0.82	0.60–1.09	24	24.1	1.00	0.64–1.48	71	81.4	0.87	0.68–1.10
Testes and other male genital organs (186–187)	0	1.7	0.00	0.00–2.12	0	0.7	0.00	0.00–5.32	0	2.4	0.00	0.00–1.51
Kidney (189.0–189.2)	19	17.6	1.08	0.65–1.68	8	7.4	1.08	0.47–2.13	27	25.0	1.08	0.71–1.57
Bladder and other urinary (188, 189.3–189.9)	15	19.6	0.77	0.43–1.27	9	8.8	1.02	0.47–1.93	24	28.4	0.85	0.54–1.26
Brain and central nervous system (191–192)	12	17.9	0.67	0.35–1.17	4	7.8	0.51	0.14–1.31	16	25.7	0.62	0.36–1.01
Thyroid and other endocrine glands (193–194)	2	2.2	0.90	0.11–3.26	1	1.1	0.90	0.02–5.02	3	3.3	0.90	0.19–2.63
All lymphatic tissue (200–203)	49	43.2	1.13	0.84–1.50	13	19.6	0.66	0.35–1.13	62	62.8	0.99	0.76–1.27

Continued on next page

TABLE 3
Extended.

Cause of death (ICD9)	Radiation status											
	Any radiation Number of workers = 4,977 Person–years = 202,178				No radiation Number of workers = 2,292 Person–years = 91,284				Total population Number of workers = 7,269 Person–years = 293,462			
	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
Hodgkin lymphoma (201)	3	3.6	0.84	0.17–2.45	0	1.8	0.00	0.00–2.05	3	5.4	0.56	0.12–1.63
Non-Hodgkin lymphoma (200, 202)	31	27.1	1.14	0.78–1.62	7	12.1	0.58	0.23–1.19	38	39.2	0.97	0.69–1.33
Multiple myeloma (203)	15	12.5	1.20	0.67–1.97	6	5.7	1.06	0.39–2.30	21	18.2	1.15	0.71–1.76
All leukemia and aleukemia (204–208)	21	27.6	0.76	0.47–1.16	10	12.6	0.80	0.38–1.46	31	40.2	0.77	0.52–1.10
Chronic lymphocytic leukemia (204.1)	2	6.0	0.33	0.04–1.20	3	2.9	1.05	0.22–3.07	5	8.9	0.56	0.18–1.31
Leukemia other than CLL	19	21.6	0.88	0.53–1.38	7	9.7	0.72	0.29–1.48	26	31.3	0.83	0.54–1.22
Mesothelioma, MN of pleura and peritoneum (158.8, 158.9, 163)	5	2.7	1.87	0.61–4.36	0	0.9	0.00	0.00–4.07	5	3.6	1.40	0.45–3.26
Smoking-related cancers (140–150, 157, 161–162, 188–189)	303	357.1	0.85*	0.76–0.95	167	152.9	1.09	0.93–1.27	470	509.8	0.92	0.84–1.01
AIDS (042–044, 795.8)	0	9.3	0.00*	0.00–0.40	0	2.1	0.00	0.00–1.76	0	11.4	0.00*	0.00–0.32
Diabetes (250)	58	64.5	0.90	0.68–1.16	33	29.4	1.12	0.77–1.57	91	93.9	0.97	0.78–1.19
Mental and behavioral disorders (290–319)	33	37.3	0.88	0.61–1.24	29	17.8	1.63*	1.09–2.34	62	55.1	1.13	0.86–1.44
Diseases of nervous system and sense organs (320–389)	78	78.5	0.99	0.79–1.24	47	41.8	1.12	0.83–1.50	125	120.3	1.04	0.87–1.24
Cerebrovascular disease (430–438)	131	157.9	0.83*	0.69–0.98	88	91.0	0.97	0.78–1.19	219	248.8	0.88	0.77–1.01
All heart disease (390–398, 404, 410–429)	753	935.5	0.81*	0.75–0.87	436	466.6	0.93	0.85–1.03	1,189	1,401.8	0.85*	0.80–0.90
Nonmalignant respiratory disease (460–478, 490–519)	126	175.0	0.72*	0.60–0.86	104	80.5	1.29*	1.06–1.57	230	255.4	0.90	0.79–1.03
Emphysema (492)	22	26.9	0.82	0.51–1.24	15	14.2	1.06	0.59–1.74	37	41.1	0.90	0.63–1.24
Cirrhosis of liver (571)	28	50.4	0.56*	0.37–0.80	24	20.8	1.16	0.74–1.72	52	71.1	0.73*	0.55–0.96
Nephritis and nephrosis (580–589)	25	32.4	0.77	0.50–1.14	17	14.7	1.16	0.68–1.86	42	47.1	0.89	0.64–1.21
All external causes of death (800–999)	129	170.5	0.76*	0.63–0.90	88	64.2	1.37*	1.10–1.69	217	234.6	0.93	0.81–1.06
Accidents (850–949)	72	108.7	0.66*	0.52–0.83	58	42.6	1.36*	1.03–1.76	130	151.2	0.86	0.72–1.02
Suicides (950–959)	45	40.7	1.11	0.81–1.48	24	14.5	1.66*	1.06–2.46	69	55.2	1.25	0.97–1.58
Unknown causes of death	24				49				73			

* $P < 0.05$.

TABLE 4
Observed and Expected Numbers of Deaths and Standardized Mortality Ratios (SMRs) for Mound Workers with Intakes of Radioactive Elements by Type of Radionuclide

	Radionuclide			
	Any polonium dose Number of workers = 2,295 Person–years = 97,255			
Cause of death (ICD9)	Observed	Expected	SMR	95% CI
All causes of death (001–999)	1,557	1,662.3	0.94*	0.89–0.98
All malignant neoplasms (140–208)	388	434.3	0.89*	0.81–0.99
Buccal cavity and pharynx (140–149)	7	8.8	0.79	0.32–1.63
Esophagus (150)	7	11.0	0.63	0.26–1.31
Stomach (151)	9	14.3	0.63	0.29–1.20
Colorectal (153–154)	39	46.4	0.84	0.60–1.15
Colon (153)	32	37.8	0.85	0.58–1.20
Rectum (154)	7	8.2	0.86	0.35–1.77
Biliary passages and liver (155–156)	8	10.1	0.79	0.34–1.56
Pancreas (157)	17	22.1	0.77	0.45–1.23
Larynx (161)	2	4.6	0.43	0.05–1.56
Bronchus, trachea and lung (162)	135	138.8	0.97	0.82–1.15
Bone (170)	0	1.1	0.00	0.00–3.49
Connective and other soft tissue (171)	1	2.0	0.49	0.01–2.73
Melanoma of skin (172)	7	5.8	1.20	0.48–2.47
Breast (174–175)	14	10.9	1.28	0.70–2.15
All uterine (females only) (179–182)	2	3.0	0.67	0.08–2.40
Cervix uteri (180)	1	1.4	0.73	0.02–4.04
Ovary and other female genital organs (183–184)	6	3.9	1.53	0.56–3.32
Prostate (males only) (185)	30	37.8	0.79	0.54–1.13
Testes and other male genital organs (186–187)	0	1.0	0.00	0.00–3.65
Kidney (189.0–189.2)	10	10.0	1.00	0.48–1.83
Bladder and other urinary (188, 189.3–189.9)	9	12.4	0.73	0.33–1.38
Brain and central nervous system (191–192)	7	9.8	0.71	0.29–1.47
Thyroid and other endocrine glands (193–194)	1	1.3	0.78	0.02–4.34
All lymphatic tissue (200–203)	30	25.1	1.20	0.81–1.71
Hodgkin lymphoma (201)	3	2.2	1.37	0.28–4.01
Non-Hodgkin lymphoma (200, 202)	17	15.6	1.09	0.64–1.75
Multiple myeloma (203)	10	7.3	1.37	0.66–2.52
All leukemia and aleukemia (204–208)	14	16.4	0.86	0.47–1.44
Chronic lymphocytic leukemia (204.1)	2	3.8	0.52	0.06–1.89
Leukemia other than CLL	12	12.6	0.96	0.49–1.67
Mesothelioma, MN of pleura and peritoneum (158.8, 158.9, 163)	4	1.5	2.75	0.75–7.03
Smoking-related cancers (140–150, 157, 161–162, 188–189)	187	207.8	0.90	0.78–1.04
AIDS (042–044, 795.8)	0	1.6	0.00	0.00–2.35
Diabetes (250)	39	36.3	1.08	0.76–1.47
Mental and behavioral disorders (290–319)	22	21.9	1.00	0.63–1.52
Diseases of nervous system and sense organs (320–389)	53	50.4	1.05	0.79–1.38
Cerebrovascular disease (430–438)	99	104.5	0.95	0.77–1.15
All heart disease (390–398, 404, 410–429)	547	598.2	0.91*	0.84–0.99
Nonmalignant respiratory disease (460–478, 490–519)	92	107.0	0.86	0.69–1.05
Emphysema (492)	19	17.8	1.07	0.64–1.67
Cirrhosis of liver (571)	21	27.0	0.78	0.48–1.19
Nephritis and nephrosis (580–589)	17	19.3	0.88	0.51–1.41
All external causes of death (800–999)	86	81.2	1.06	0.85–1.31
Accidents (850–949)	51	53.9	0.95	0.71–1.25
Suicides (950–959)	28	19.5	1.44	0.96–2.08
Unknown causes of death	18			

* $P < 0.05$.

or plutonium. Sixteen died of nephritis but only 7 had exposure to polonium or plutonium, and the kidney doses were below 7 mSv for all but one worker whose cumulative dose was 199 mSv.

DISCUSSION

An additional 26 years of follow-up failed to uncover any significant associations between cancer and radiation dose within the Mound workforce with the exception of

TABLE 4
Extended.

Radionuclide											
Any plutonium dose Number of workers = 837 Person–years = 35,049				Any tritium dose Number of workers = 1,125 Person–years = 45,776				Any internal dose Number of workers = 3,082 Person–years = 129,429			
Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
380	500.8	0.76*	0.68–0.84	424	591.9	0.72*	0.65–0.79	1,753	1,984.5	0.88*	0.84–0.93
105	134.7	0.78*	0.64–0.94	124	159.9	0.78*	0.65–0.93	459	524.2	0.88*	0.80–0.96
1	2.8	0.35	0.01–1.96	2	3.4	0.59	0.07–2.13	8	10.8	0.74	0.32–1.46
5	4.1	1.23	0.40–2.87	5	4.9	1.02	0.33–2.39	12	14.0	0.86	0.44–1.50
1	3.8	0.26	0.01–1.47	3	4.4	0.68	0.14–1.98	10	16.6	0.60	0.29–1.11
7	13.4	0.52	0.21–1.08	9	15.8	0.57	0.26–1.08	43	55.0	0.78	0.57–1.05
6	11.0	0.55	0.20–1.19	9	12.9	0.70	0.32–1.32	36	44.8	0.80	0.56–1.11
1	2.2	0.46	0.01–2.56	0	2.5	0.00	0.00–1.45	7	9.5	0.74	0.30–1.52
1	3.5	0.29	0.01–1.60	2	4.2	0.47	0.06–1.71	9	12.7	0.71	0.33–1.35
6	6.9	0.88	0.32–1.90	8	8.2	0.98	0.42–1.93	25	26.8	0.94	0.61–1.38
0	1.5	0.00	0.00–2.39	1	1.8	0.55	0.01–3.04	3	5.7	0.53	0.11–1.55
44	46.7	0.94	0.68–1.27	39	55.3	0.71*	0.50–0.96	157	169.9	0.92	0.79–1.08
0	0.3	0.00	0.00–13.0	0	0.3	0.00	0.00–10.9	0	1.2	0.00	0.00–2.95
1	0.7	1.42	0.04–7.92	0	0.9	0.00	0.00–4.26	1	2.6	0.39	0.01–2.16
2	2.2	0.91	0.11–3.28	3	2.7	1.11	0.23–3.24	8	7.5	1.06	0.46–2.10
0	1.0	0.00	0.00–3.66	0	1.5	0.00	0.00–2.44	14	12.3	1.14	0.62–1.91
0	0.2	0.00	0.00–16.6	0	0.3	0.00	0.00–11.0	2	3.3	0.60	0.07–2.17
0	0.1	0.00	0.00–37.0	0	0.2	0.00	0.00–22.3	1	1.5	0.65	0.02–3.61
1	0.3	3.26	0.08–18.2	2	0.4	4.47	0.54–16.1	9	4.4	2.07	0.94–3.92
4	11.2	0.36*	0.10–0.92	8	12.7	0.63	0.27–1.24	33	43.6	0.76	0.52–1.06
0	0.4	0.00	0.00–10.5	0	0.4	0.00	0.00–8.73	0	1.3	0.00	0.00–2.90
2	3.4	0.58	0.07–2.11	4	4.1	0.97	0.27–2.49	12	12.4	0.97	0.50–1.69
1	3.7	0.27	0.01–1.53	3	4.2	0.71	0.15–2.07	11	14.5	0.76	0.38–1.36
3	3.4	0.89	0.18–2.59	4	4.1	0.97	0.26–2.48	7	12.3	0.57	0.23–1.17
1	0.4	2.58	0.07–14.4	1	0.5	2.15	0.05–12.0	2	1.6	1.28	0.16–4.63
9	8.0	1.13	0.51–2.14	8	9.6	0.83	0.36–1.64	34	30.6	1.11	0.77–1.55
0	0.6	0.00	0.00–5.77	0	0.8	0.00	0.00–4.87	3	2.6	1.14	0.24–3.33
7	5.1	1.39	0.56–2.86	5	6.0	0.83	0.27–1.94	20	19.1	1.05	0.64–1.62
2	2.3	0.86	0.10–3.09	3	2.8	1.09	0.22–3.17	11	8.9	1.24	0.62–2.22
4	5.1	0.78	0.21–2.01	6	6.0	1.00	0.37–2.17	15	19.7	0.76	0.43–1.25
0	1.1	0.00	0.00–3.36	1	1.3	0.79	0.02–4.39	2	4.5	0.45	0.05–1.62
4	4.0	1.00	0.27–2.56	5	4.8	1.05	0.34–2.45	13	15.3	0.85	0.45–1.46
2	0.6	3.55	0.43–12.8	2	0.7	2.98	0.36–10.8	5	1.9	2.69	0.87–6.28
59	69.1	0.85	0.65–1.10	62	81.9	0.76	0.58–0.97	228	254.0	0.90	0.79–1.02
0	1.6	0.00	0.00–2.35	0	2.8	0.00	0.00–1.34	0	4.1	0.00*	0.00–0.90
9	11.8	0.77	0.35–1.45	11	14.2	0.78	0.39–1.39	43	44.7	0.96	0.70–1.30
10	6.6	1.52	0.73–2.80	11	7.8	1.41	0.70–2.52	26	26.3	0.99	0.65–1.45
15	13.0	1.16	0.65–1.91	15	14.9	1.01	0.56–1.66	60	58.1	1.03	0.79–1.33
19	25.7	0.74	0.45–1.15	26	29.6	0.88	0.57–1.29	107	119.1	0.90	0.74–1.09
133	169.0	0.79*	0.66–0.93	152	195.5	0.78*	0.66–0.91	604	696.7	0.87*	0.80–0.94
22	32.2	0.68	0.43–1.04	16	37.3	0.43*	0.25–0.70	101	126.2	0.80*	0.65–0.97
2	4.7	0.43	0.05–1.54	2	5.4	0.37	0.05–1.35	20	20.4	0.98	0.60–1.52
2	9.9	0.20*	0.02–0.73	2	12.2	0.16*	0.02–0.59	22	34.5	0.64*	0.40–0.97
6	5.9	1.02	0.37–2.21	4	6.9	0.58	0.16–1.48	17	23.0	0.74	0.43–1.18
21	33.9	0.62*	0.38–0.95	24	43.7	0.55*	0.35–0.82	100	110.9	0.90	0.73–1.10
10	21.4	0.47*	0.22–0.86	14	27.3	0.51*	0.28–0.86	56	72.0	0.78	0.59–1.01
8	8.2	0.98	0.42–1.93	6	10.5	0.57	0.21–1.24	35	26.5	1.32	0.92–1.84
2				3				21			

esophageal cancer based on a relatively small number of cases. Comparisons with the general population revealed a healthy workforce with overall death rates (SMR 0.83) and cancer rates (SMR 0.86) significantly low among radiation workers. Cancers of *a priori* interest, e.g., lung, leukemia, liver and kidney were not significantly associated with radiation over categories of organ dose. All occupational doses received both before and after employment at Mound were sought and additional doses were included for 36.6% of the radiation workers. Organ specific doses from

TABLE 5
Observed and Expected Numbers of Deaths and Standardized Mortality Rates (SMRs) for Mound Workers Monitored for Radiation, by Cumulative Radiation Dose[1]

	Radiation dose (mSv)							
	< 10 Number of workers = 2,539 Person–years = 97,043				10– Number of workers = 1,506 Person–years = 63,792			
Cause of death (ICD9)	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
All causes of death (001–999)	908	1,074.4	0.85*	0.79–0.90	791	964.0	0.82*	0.76–0.88
All malignant neoplasms (140–208)	265	296.2	0.90	0.79–1.01	222	256.4	0.87*	0.76–0.99
Buccal cavity and pharynx(140–149)	4	5.8	0.70	0.19–1.78	2	5.3	0.38	0.05–1.37
Esophagus (150)	8	7.8	1.03	0.44–2.02	6	7.1	0.85	0.31–1.85
Stomach (151)	6	7.9	0.76	0.28–1.65	5	7.9	0.63	0.21–1.47
Colorectal (153–154)	30	29.3	1.03	0.69–1.46	24	26.6	0.90	0.58–1.34
Colon (153)	26	24.1	1.08	0.71–1.58	20	21.7	0.92	0.56–1.42
Rectum (154)	4	4.7	0.85	0.23–2.19	4	4.6	0.88	0.24–2.25
Biliary passages and liver (155–156)	8	7.6	1.05	0.46–2.08	6	6.3	0.95	0.35–2.06
Pancreas (157)	12	15.1	0.79	0.41–1.39	12	13.1	0.92	0.47–1.60
Larynx (161)	2	2.9	0.68	0.08–2.47	1	2.8	0.36	0.01–1.99
Bronchus, trachea, and lung (162)[1]	77	95.4	0.81	0.64–1.01	81	84.2	0.96	0.76–1.20
Bone (170)	0	0.6	0.00	0.00–5.72	0	0.6	0.00	0.00–6.21
Connective and other soft tissue (171)	2	1.7	1.19	0.14–4.30	0	1.3	0.00	0.00–2.87
Melanoma of skin (172)	6	4.7	1.28	0.47–2.79	3	3.8	0.78	0.16–2.29
Breast (174–175)	12	13.6	0.89	0.46–1.55	6	5.2	1.15	0.42–2.51
All uterine (females only) (179–182)	3	3.5	0.85	0.18–2.48	0	1.4	0.00	0.00–2.65
Cervix uteri (180)	1	1.7	0.58	0.02–3.25	0	0.6	0.00	0.00–5.80
Ovary and other female genital organs (183–184)	3	4.6	0.65	0.13–1.90	5	1.8	2.74	0.89–6.38
Prostate (males only)(185)	19	18.6	1.02	0.61–1.59	19	21.0	0.90	0.54–1.41
Testes and other male genital organs (186–187)	0	0.6	0.00	0.00–5.72	0	0.6	0.00	0.00–5.93
Kidney (189.0–189.2)	10	7.0	1.42	0.68–2.61	5	6.2	0.81	0.26–1.88
Bladder and other urinary (188, 189.3–189.9)	7	7.0	1.01	0.40–2.07	5	7.1	0.71	0.23–1.65
Brain and central nervous system (191–192)	3	7.6	0.40	0.08–1.15	5	6.1	0.81	0.26–1.90
Thyroid and other endocrine glands (193–194)	1	0.9	1.08	0.03–5.99	0	0.8	0.00	0.00–4.84
All lymphatic tissue (200–203)	20	17.5	1.14	0.70–1.77	16	15.1	1.06	0.61–1.72
Hodgkin lymphoma(201)	1	1.4	0.72	0.02–4.02	1	1.3	0.80	0.02–4.44
Non-Hodgkin lymphoma (200, 202)	13	11.0	1.18	0.63–2.02	10	9.4	1.06	0.51–1.95
Multiple myeloma (203)	6	5.1	1.18	0.43–2.57	5	4.4	1.15	0.37–2.68
All leukemia and aleukemia (204–208)	10	10.8	0.92	0.44–1.70	4	9.7	0.41	0.11–1.06
Chronic lymphocytic leukemia (204.1)	1	2.2	0.46	0.01–2.54	0	2.2	0.00	0.00–1.70
Leukemia other than CLL	9	8.6	1.04	0.48–1.98	4	7.5	0.53	0.15–1.37
Mesothelioma, MN of pleura and peritoneum (158.8, 158.9, 163)	1	1.1	0.94	0.02–5.24	3	1.0	3.14	0.65–9.18
Smoking-related cancers (140–150, 157, 161–162, 188–189)	120	141.0	0.85	0.71–1.02	112	125.8	0.89	0.73–1.07
AIDS (042–044, 795.8)	0	6.1	0.00*	0.00–0.60	0	2.3	0.00	0.00–1.63
Diabetes (250)	26	27.1	0.96	0.63–1.41	17	22.1	0.77	0.45–1.23
Mental and behavioral disorders (290–319)	14	15.1	0.93	0.51–1.55	11	12.8	0.86	0.43–1.54
Diseases of nervous system and sense organs (320–389)	28	29.4	0.95	0.63–1.38	27	27.7	0.98	0.64–1.42
Cerebrovascular disease (430–438)	53	57.5	0.92	0.69–1.21	42	56.2	0.75	0.54–1.01
All heart disease (390–398, 404, 410–429)	269	341.3	0.79*	0.70–0.89	272	334.6	0.81*	0.72–0.92
Nonmalignant respiratory disease (460–478, 490–519)	40	67.4	0.59*	0.42–0.81	51	61.3	0.83	0.62–1.09
Emphysema (492)	5	9.5	0.52	0.17–1.22	11	9.6	1.14	0.57–2.04
Cirrhosis of liver (571)	11	21.4	0.52*	0.26–0.92	12	17.3	0.69	0.36–1.21
Nephritis and nephrosis (580–589)	9	12.9	0.70	0.32–1.33	13	11.2	1.16	0.62–1.99
All external causes of death (800–999)	65	76.5	0.85	0.66–1.08	40	56.8	0.70*	0.50–0.96
Accidents (850–949)	36	47.5	0.76	0.53–1.05	19	36.6	0.52*	0.31–0.81
Suicides (950–959)	24	18.1	1.33	0.85–1.98	17	13.6	1.25	0.73–2.00
Unknown causes of death	9				6			

[1] The primary dose in this table is from external (photon) exposure. Tritium dose in mGy was included. Organ doses from polonium and plutonium to the lung are included in mGy, i.e., there was no assumed radiation weighting factor, but only for the lung and not other organ doses. The external dose from neutrons was in mSv, assuming a radiation weighting factor of 10.

* $P < 0.05$.

TABLE 5
Extended.

Radiation dose (mSv)											
100– Number of workers = 703 Person–years = 30,864				500– Number of workers = 150 Person–years = 6,751				1000+ Number of workers = 79 Person–years = 3,729			
Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
399	509.9	0.78*	0.71–0.86	117	132.0	0.89	0.73–1.06	64	76.1	0.84	0.65–1.07
103	132.4	0.78*	0.64–0.94	31	33.5	0.93	0.63–1.31	11	19.0	0.58	0.29–1.04
4	2.8	1.45	0.40–3.72	1	0.7	1.42	0.04–7.92	0	0.4	0.00	0.00–9.38
5	3.6	1.40	0.45–3.25	0	0.9	0.00	0.00–4.15	0	0.5	0.00	0.00–7.62
2	4.4	0.46	0.06–1.66	0	1.1	0.00	0.00–3.21	0	0.7	0.00	0.00–5.68
9	14.0	0.64	0.29–1.22	3	3.6	0.84	0.17–2.46	1	2.0	0.49	0.01–2.72
8	11.4	0.70	0.30–1.38	3	2.9	1.04	0.21–3.03	1	1.7	0.60	0.02–3.34
1	2.5	0.41	0.01–2.26	0	0.6	0.00	0.00–5.87	0	0.4	0.00	0.00–10.2
1	3.2	0.31	0.01–1.74	0	0.8	0.00	0.00–4.85	0	0.4	0.00	0.00–8.63
5	6.8	0.74	0.24–1.73	2	1.7	1.20	0.15–4.35	0	0.9	0.00	0.00–3.92
1	1.5	0.68	0.02–3.81	0	0.4	0.00	0.00–9.60	0	0.2	0.00	0.00–17.4
29	42.9	0.68*	0.45–0.97	11	11.1	0.99	0.50–1.78	6	6.2	0.97	0.36–2.12
0	0.3	0.00	0.00–11.5	0	0.1	0.00	0.00–45.0	0	0.0	0.00	0.00–79.5
0	0.6	0.00	0.00–5.80	0	0.1	0.00	0.00–24.6	1	0.1	11.86	0.30–66.1
3	1.9	1.59	0.33–4.66	1	0.5	2.20	0.06–12.3	0	0.2	0.00	0.00–14.8
2	2.1	0.94	0.11–3.41	1	0.1	18.46	0.46–103	0	0.1	0.00	0.00–34.3
0	0.6	0.00	0.00–6.54	0	0.0	0.00	0.00–487	0	0.0	0.00	0.00–170
0	0.3	0.00	0.00–14.2	0	0.0	0.00	0.00–900	0	0.0	0.00	0.00–421
1	0.7	1.35	0.03–7.53	0	0.0	0.00	0.00–731	0	0.0	0.00	0.00–111
5	12.0	0.42*	0.14–0.97	3	3.7	0.82	0.17–2.40	1	2.1	0.48	0.01–2.68
0	0.3	0.00	0.00–11.1	0	0.1	0.00	0.00–40.0	0	0.1	0.00	0.00–72.9
2	3.2	0.63	0.08–2.29	2	0.8	2.53	0.31–9.14	0	0.4	0.00	0.00–8.39
3	3.9	0.78	0.16–2.27	0	1.1	0.00	0.00–3.46	0	0.6	0.00	0.00–6.10
4	3.0	1.32	0.36–3.37	0	0.7	0.00	0.00–5.02	0	0.4	0.00	0.00–9.05
1	0.4	2.60	0.07–14.5	0	0.1	0.00	0.00–40.4	0	0.1	0.00	0.00–71.7
11	7.7	1.43	0.71–2.56	1	2.0	0.50	0.01–2.78	1	1.1	0.91	0.01–5.06
0	0.7	0.00	0.00–5.58	1	0.2	5.72	0.14–31.8	0	0.1	0.00	0.00–37.7
8	4.8	1.67	0.72–3.29	0	1.2	0.00	0.00–3.08	0	0.7	0.00	0.00–5.44
3	2.2	1.34	0.28–3.92	0	0.6	0.00	0.00–6.57	1	0.3	3.16	0.08–17.6
5	5.0	0.99	0.32–2.31	2	1.3	1.54	0.19–5.57	0	0.7	0.00	0.00–5.00
0	1.2	0.00	0.00–3.16	1	0.3	3.17	0.08–17.7	0	0.2	0.00	0.00–20.5
5	3.9	1.29	0.42–3.01	1	1.0	1.02	0.03–5.68	0	0.6	0.00	0.00–6.62
1	0.5	2.11	0.05–11.7	0	0.1	0.0	0.00–31.0	0	0.1	0.00	0.00–58.5
49	64.5	0.76	0.56–1.00	16	16.6	0.97	0.55–1.57	6	9.2	0.65	0.24–1.41
0	0.9	0.00	0.00–4.06	0	0.1	0.00	0.00–62.8	0	0.0	0.00	0.00–178
9	11.2	0.80	0.37–1.53	4	2.7	1.50	0.41–3.84	2	1.5	1.32	0.16–4.75
6	6.6	0.91	0.33–1.97	2	1.8	1.12	0.14–4.05	0	1.0	0.00	0.00–3.72
12	15.0	0.80	0.41–1.40	7	4.0	1.74	0.70–3.58	4	2.3	1.71	0.47–4.38
26	31.5	0.83	0.54–1.21	5	8.0	0.63	0.20–1.47	5	4.8	1.04	0.34–2.42
141	182.0	0.78*	0.65–0.91	43	49.0	0.88	0.64–1.18	28	28.6	0.98	0.65–1.42
27	32.4	0.83	0.55–1.21	5	8.8	0.57	0.18–1.32	3	5.0	0.60	0.12–1.75
4	5.4	0.74	0.20–1.90	1	1.4	0.69	0.02–3.85	1	0.8	1.20	0.03–6.69
4	8.5	0.47	0.13–1.21	1	2.1	0.48	0.01–2.70	0	1.2	0.00	0.00–3.21
2	5.9	0.34	0.04–1.23	1	1.6	0.62	0.02–3.44	0	0.9	0.00	0.00–4.08
15	27.8	0.54*	0.30–0.89	8	6.1	1.31	0.57–2.59	1	3.3	0.30	0.01–1.68
11	18.2	0.61	0.30–1.08	5	4.1	1.22	0.40–2.85	1	2.2	0.45	0.01–2.48
2	6.6	0.30	0.04–1.09	2	1.5	1.32	0.16–4.78	0	0.8	0.00	0.00–4.50
5				2				2			

TABLE 6
Internal Cohort Dose-Response Analyses[1] and Hazards Ratio (HR) for Cancers of *a priori* Concern (because of Likely Polonium Deposition) Over Categories of Organ-Specific Radiation Doses[2] for Three Assumptions as to the Relative Biological Effectiveness of Polonium and Plutonium[3]

	RBE = 1 for Po and Pu				RBE = 10 for Po and Pu				RBE = 20 for Po and Pu			
Dose (mSv)	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												
<10	2,285	74	1.00	REF	1,890	51	1.00	REF	1,824	47	1.00	REF
10–	1,482	84	1.14	0.82–1.59	1,044	48	1.11	0.73–1.68	823	40	1.25	0.80–1.95
100–	683	28	0.75	0.47–1.19	935	54	1.20	0.79–1.84	971	47	1.10	0.71–1.70
500–	145	12	1.37	0.71–2.65	239	18	1.30	0.71–2.37	275	19	1.34	0.73–2.44
1,000+	77	5	1.04	0.41–2.68	564	32	0.87	0.50–1.50	779	50	1.06	0.63–1.79
P for trend			*0.42*	+			*0.45*	+			*0.45*	+
Kidney cancer												
<5	2,266	8	1.00	REF	1,848	7	1.00	REF	1,759	7	1.00	REF
5–	1,528	4	0.64	0.19–2.16	1,410	4	0.52	0.14–1.87	1,306	1	0.13	0.01–1.11
50+	878	4	1.21	0.35–4.19	1,414	5	0.60	0.16–2.22	1,607	8	0.79	0.23–2.75
P for trend			*0.34*	–			*0.47*	–			*0.48*	–
Liver cancer												
<5	2,026	8	1.00	REF	1,860	7	1.00	REF	1,795	7	1.00	REF
5–	1,378	6	0.69	0.23–2.03	1,433	6	0.64	0.20–2.03	1,415	6	0.63	0.20–2.00
50+	1,268	3	0.29	0.07–1.16	1,379	4	0.32	0.08–1.21	1,462	4	0.26	0.07–1.02
P for trend			*0.09*	–			*0.07*	–			*0.07*	–
Leukemia other than CLL												
<5	2,577	11	1.00	REF								
5–	1,386	5	0.77	0.26–2.26								
50+	709	5	1.70	0.56–5.19								
P for trend			*0.33*	+								

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[1] Model included radiation doses lagged by 10 years for solid tumors and by 2 years for leukemia. Doses were analyzed using time-dependent covariates. All models adjusted for sex, education, year of birth and year of hire. Gender was not included in the model for kidney cancer and education was not included in the model for non-CLL or liver cancer because of non-convergence. *P* value for test for linear trend in the relative risk (i.e., hazard ratio) computed for continuous organ dose. *P* values are one-sided and ''+'' denotes a positive trend and ''–'' a negative trend. REF denotes reference category.

[2] Dose categories include external radiation doses received before, during and after employment at Mound. Internal doses from the intake of radionuclides are included for all organs or tissues. For non-CLL the dose to active bone marrow was used and only an RBE = 1 for polonium and plutonium.

[3] All doses are to specific organs combining external (photon and neutron) and internal intakes of radionuclides, i.e., polonium, plutonium and tritium. For tritium the RBE is taken to be 1. For polonium and plutonium the RBE is taken to be 1, 10 and 20, as indicated. For neutrons a radiation weighting factor of 10 was assumed.

available bioassay monitoring records on polonium, plutonium and tritium intake were incorporated in the analyses. The period of observation was up to 60 years (mean, 40.4 years) and over half of the workforce had died. RRs at 100 mSv as low as 1.04 could be excluded with 95% confidence for lung cancer, 2.11 for kidney cancer, 1.32 for liver cancer and 1.99 for leukemia other than CLL. Interestingly, the RR upper confidence limit of 1.04 at 100 mSv is consistent with the central estimate of lung cancer risk among male atomic bomb survivors of 1.032 (*13*). The RR at 100 mSv for esophageal cancer (RR 1.54) was statistically significant and higher than the 1.05 estimate reported for males in the study of atomic bomb survivors (*13*).

The inclusion of females and non-white personnel increased the original study population of 4,402 by 65% to 7,269. The additional follow-up through 2009 increased the person-years of observation by nearly threefold (from 104,326 to 293,462) and the total number of deaths by over threefold (from 987 to 3,681). Among the 4,977 radiation workers, 2,295 (46%) had positive bioassays for polonium and these intakes contributed to the high total doses estimated for lung, kidney, liver and several other organs. While 776 workers had polonium doses only, they were not sufficient to analyze separately. Only 3 workers had been exposed to plutonium alone.

Low mortality rates for heart disease (SMR 0.80) and cerebrovascular disease (SMR 0.82) are often reported in occupational studies and are usually ascribed to factors associated with the selection for employment and with the ability to continue employment once hired, i.e., the ''healthy worker effect'' (*44–46*). The healthy worker effect often diminishes with time, although this was not notably apparent among the male workers previously studied where the SMR for circulatory disease was reported as 0.90 after follow-up through 1983 (*8*) and changed little (SMR 0.86) after an addition 26 years of observation through 2009.

When conducting multiple statistical tests of numerous disease endpoints, some elevated cancer risk estimates are

TABLE 7
Internal Cohort Dose-Response Analyses[1] and Hazards Ratio (HR) for Selected Cancers Over Categories of Organ-Specific Radiation Doses[2] for Three Assumptions as to the Relative Biological Effectiveness of Polonium and Plutonium[3]

	RBE = 1 for Po and Pu				RBE = 10 for Po and Pu				RBE = 20 for Po and Pu			
Dose (mSv)	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
Esophageal cancer												
<5	2,758	8	1.00	REF	2,558	7	1.00	REF	2,433	7	1.00	REF
5–	1,262	5	1.15	0.37–3.62	1,418	6	1.32	0.43–4.07	1,475	6	1.20	0.39–3.74
50+	652	6	2.46	0.75–8.03	696	6	2.37	0.70–8.0	764	6	1.99	0.59–6.73
P for trend			*0.002*	+			*0.007*	+			*0.04*	+
Colon cancer												
<5	2,753	44	1.00	REF	2,520	37	1.00	REF	2,394	34	1.00	REF
5–	1,266	29	1.42	0.87–2.31	1,443	35	1.37	0.85–2.21	1,481	36	1.31	0.80–2.13
50+	653	4	0.47	0.17–1.35	709	5	0.52	0.20–1.35	797	7	0.56	0.24–1.30
P for trend			*0.12*	–			*0.09*	–			*0.07*	–
Non-Hodgkin lymphoma												
<5	2,577	17	1.00	REF								
5 –	1,386	12	1.05	0.50–2.24								
50+	709	7	1.34	0.54–3.32								
P for trend			*0.45*	+								
Heart disease												
<5	2,758	626	1.00	REF	2,558	548	1.00	REF	2,433	508	1.00	REF
5–	1,262	294	0.95	0.82–1.10	1,418	352	0.93	0.81–1.06	1,475	366	0.86	0.75–0.99
50+	652	138	1.10	0.91–1.33	696	158	1.12	0.93–1.34	764	184	1.05	0.88–1.25
P for trend			*0.14*	+			*0.07*	+			*0.06*	+

[1] Model included radiation doses lagged by 10 years for solid tumors and by 2 years for leukemia. Doses were analyzed using time-dependent covariates. All models adjusted for gender, education, year of birth and year of hire. *P* value for test for linear trend in the relative risk (i.e., hazard ratio) computed for continuous organ dose. *P* values are one-sided and "+" denotes a positive trend and "–" a negative trend. REF denotes reference category.

[2] Dose categories include external radiation doses received before, during and after employment at Mound. Internal doses from the intake of radionuclides are included for all organs or tissues. For NHL the dose to active bone marrow was assumed as a surrogate for dose to lymphoid tissue.

[3] All doses are to specific organs combining external (photon and neutron) and internal intakes of radionuclides, i.e., polonium, plutonium and tritium. For tritium the RBE is taken to be 1. For polonium and plutonium the RBE is taken to be 1, 10 and 20.

expected to occur by chance alone and should be considered in context of findings from other studies. A significant positive trend in the RRs of esophageal cancer, for example, was seen over categories of radiation dose whereas a nearly significant negative trend in liver cancer, an *a priori* site, was also seen. Cancer of the esophagus has not been associated with radiation in other occupational studies, and the association reported in our study (RR 1.54 at 100 mSv) is 11 times higher than reported in the study of atomic bomb survivors (RR 1.048 at 100 mSv) (*13*). There are little to no data available on the possible effect of high-LET radiation on esophageal cancer risk, or on radiation interactions with other risk factors such as tobacco use or heavy alcohol consumption (*47*). The significant dose-response relationship was based on a relatively small number of cancers among workers with >50 mSv esophageal dose ($n = 6$), and there was no increase compared with general population rates (SMR 0.96). Although a causal association is supported by the data, chance could have contributed to the high risk coefficient based on the substantial number of multiple comparisons made.

There are little human data on the RBEs for high-LET radiations for specific tissues (*48, 49*), although 1 is used for red bone marrow dose and leukemia risk and higher values assumed for other tissue (*50, 51*). We assumed RBE values of 10 and 20 and conducted intra-cohort analyses, but the numbers may have been too small to discern any differences in the dose response, and none was seen.

A slight increase in leukemia excluding CLL was observed that was consistent with (but lower than) statistical predictions from other radiation studies, i.e., the RR at 100 mSv for all leukemia excluding CLL was 1.14 (95% CI 0.65–1.99). Consistent with practically all radiation studies there was no evidence for an association between radiation and CLL (SMR 0.33; $n = 2$) (*13*). A slight positive trend was seen for non-Hodgkin lymphoma and a slight negative trend was seen for cancer of the colon in the intra-cohort analyses.

There were no statistically significant dose-response trends for any cancer except for cancers of the esophagus (positive with dose) and liver (negative with dose). Polonium and plutonium are heavy metals in addition to being radioactive but there was little evidence for increased risks to nonmalignant diseases of the kidney, liver or lung where depositions would be highest.

An indirect approach was taken to evaluate whether radiation doses accrued at older ages carried a higher risk than cumulative exposures occurring at younger ages (*52, 53*). We evaluated risks by age at hire recognizing that some of the younger workers did receive exposures at ages >55 years. For lung cancer, significantly elevated SMRs were seen for radiation workers hired after age 45 years and significantly low SMRs were seen for radiation workers hired before age 45 years. However, a similar pattern was observed among nonradiation workers. Evaluations by calendar year of hire indicated that the excess lung cancer deaths were concentrated among workers hired in the 1940s and during the years of World War II. Because military personnel needs for the war were met by drafting citizens into service, there was a marked decrease in the available labor force throughout the country. Persons classified as 4F by the U.S. Selective Service as physically, psychologically or morally unfit for military duty, however, would be accepted for employment during these years despite not meeting employment requirements normally in play during peace time (*54*). Conceivably, selection factors for these early workers related to existent conditions (perhaps due to unhealthy lifestyles or behavioral problems) may have been partially responsible for the increased rates seen among those hired at older ages (*8*). Significant increases in deaths from mental disorders and suicides among nonradiation workers support the conjecture that some early workers hired may have had behavioral issues that made them unfit for military service. Further, intra-cohort dose-response analyses among radiation workers, adjusting for year of hire, did not reveal an increasing trend for lung cancer with radiation dose. There is a need for better epidemiology and statistically powerful studies to address age-at-exposure effects when exposure is received gradually over time and not acutely (*55*).

Heart Disease

There is current scientific interest in the possibility that heart disease may be related to radiation doses at levels lower than previously thought (*56–63*). Among Mound workers, dose-response analyses based on population comparisons suggested an association with heart disease which appeared related more to a very low risk among workers with <5 mSv cumulative dose than to a monotonic incremental increase with dose. Further, evidence for a dose response was not present in the intra-cohort analysis, comparing Mound workers with Mound workers over categories of dose and adjusting for important factors such as year of hire. This intra-cohort analysis also included 307 contributing causes of death from heart disease for a total number of 1,053 cases. It seems that the SMR external analyses may have been affected by the generally poorer health status of workers hired during World War II who may not have qualified for service in the military because of existing health problems (*8*). External comparisons with a general population are hampered by potential biases in selection, most notably that workers are healthier and less likely to die. Internal comparisons are expected to minimize biases associated with general population comparisons. Nonetheless, future analyses should evaluate finer categories of heart disease, such as ischemic heart disease, to more fully evaluate the potential for a low dose radiation association.

Polonium

The Mound study is the largest cohort of workers exposed to polonium that has any reasonable chance of address possible late effects (*1*). Polonium is of particular interest today because of the poisoning of the Russian national in the UK (*2, 64*), because it is a component of tobacco smoke (*7*), and because of the recent speculation that polonium poisoning may have contributed to the death of Yasser Arafat (*3*). Polonium is a unique radioactive element in that it is a soft-tissue (rather than bone-) seeking alpha-particle emitter, its health effects resemble whole-body exposure more so than a highly localized tissue deposition, and it ''creeps'' and is difficult to contain in the workplace (*5*). The previous study of Mound workers was restricted to 4,402 white males employed 1944–1972 and followed through 1983 (*8*). A nonstatistically significant increase in lung cancer had been noted among workers hired during World War II which was not related to polonium intake and possibly was due to an ''unhealthy worker effect'' (e.g., wartime selection bias also called the ''4F effect''). As discussed earlier, workers unable to qualify for military service (and classified as 4F) may have been more likely to have chronic conditions related perhaps to unhealthy lifestyles such as increased tobacco use. There was no association between total radiation dose to lung and lung cancer risk in our extended study, which included improved dose reconstructions, larger numbers of workers and intra-cohort analyses.

Plutonium

Previous studies of plutonium workers in Russia have linked increased cancers of the lung, liver and bone to relatively high levels of plutonium intake, enough so as to cause pulmonary sclerosis of the lung, a deterministic effect (*13, 16, 17, 65*). Only 32% of the Mayak plutonium workers had urine bioassays and the average number was less than two (*66*). Studies of U.S. and UK workers exposed to lower levels (lower body burdens), however, are inconsistent (*14, 15, 52, 67–72*). The number of workers with positive plutonium bioassays at Mound was relatively small, only 838 in total; lung cancer was not increased (SMR 0.94; $n = 44$) and there were no cases of bone cancers. The plutonium doses were low, e.g., only 14.3 mSv on average to lung tissue. Larger studies of workers exposed to plutonium would seem warranted to clarify the inconsistent associations seen in the low-dose domain.

Strengths and Limitations

Strengths of our occupational study include the cohort design, the long follow-up of up to 60 years, the capturing of occupational doses received both before and after employment at Mound, the computation and inclusion of organ specific doses from intakes of radionuclides from polonium, plutonium and tritium, and the inclusion of women and non-white employees. Other strengths include the low percentage of workers who were lost to follow-up (1.3%), and the low percentage of deaths for which a specific cause was not available (2.0%). The over 200,000 polonium urine bioassay samples (over 70 samples per worker) adds to the quality of the information on dose reconstruction. Linkages to identify cancer incidence and serious renal disease added extra dimensions to the mortality findings. The similarities between the cancer incidence and the mortality data were reassuring. The mortality data were statistically more powerful than the cancer incidence data because the numbers of deaths were larger: mortality covered the entire U.S. and incidence was limited to Ohio; and mortality follow-up began in 1944 whereas cancer incidence in 1996. Linkages with the U.S. Renal Data System identified workers with serious nonfatal kidney disease but there were no indications that occurrence was related to radiation dose or heavy metal exposures.

Limitations of the study include the relatively small number of workers and the incomplete knowledge of confounding factors such as smoking history. Further, for the early years of work there may have been missing or incomplete measurements of radiation doses (*73*). Although the sheer number of polonium bioassays was large, there were uncertainties associated with assumptions as to aerosol size and residence time in the lungs. Further, the default assumption that urinary polonium-210 arose only from inhaled polonium could yield sizable overestimates of lung dose to individual workers due to the potential for intake by contamination of wounds, absorption through intact skin or ingestion. Intake through exposure modes other than inhalation or intake by multiple modes including inhalation, appear to be more likely for polonium-210 than for most other radionuclides due to the tendency of polonium-210 to ''creep'' throughout a workplace as a result of alpha recoil and attachment to dust particles.

Some of the earliest reported cases of elevated intake of polonium-210 at Mound involved absorption through intact skin or intake by a puncture wound. To assess the possible impact of the uncertainty associated with the route of intake, we re-analyzed the data assuming worst case scenarios where no polonium intake was from inhalation. There were no appreciable changes in either the dose-response patterns or the estimates of risk per 100 mSv. For example, the RR per 100 mSv for lung cancer became 1.02 (95% CI 0.97–1.06) and for esophageal cancer 1.42 (95% CI 1.07–1.89) – essentially the same as the risk estimates of 1.00 (95% CI 0.97–1.04) and 1.54 (1.15–2.07), respectively, based on our best assumptions. Another important uncertainty is the level of recovery of polonium from urine samples by the technique applied at Mound.

Differences in smoking habits (*74*) may explain the significantly low risk of smoking-related cancers among radiation workers and the near normal risks seen among nonradiation workers compared with the general population. The overall SMR for smoking-related sites was significantly low at 0.85 (95% CI 0.75–0.95) for radiation workers, suggesting a low cigarette consumption compared with the general population. Adjustment was made for education in the analyses as a crude surrogate measure of socioeconomic class among radiation workers. Compared with radiation workers, the workers not monitored for radiation had higher risks of death for all causes, all cancers and most specific causes of death, which suggested differences in lifestyle factors and disease risk factors that precluded using them for direct comparisons. The study also is of mortality and not incidence of disease for which the number of events and quality of diagnoses would be expected to be higher. Most of the diseases of interest, e.g., cancers of the lung, liver, esophagus and leukemia, however, have a high fatality rate over the years of study so that mortality would be expected to reflect incidence fairly closely. Diseases that have a low fatality rate can be evaluated in mortality studies, although the statistical power to identify a significant increase in risk might be lower than for an incidence survey because of the smaller number of events.

For organs other than the lung, kidney and liver, the relatively low cumulative dose limits the ability of the study to detect an effect had there been one. Nonetheless, the mean dose from external radiation (26.1 mSv; maximum 939 mSv; percent workers >500 mSv, 4.6%) and the mean lung dose from external and all internal radiation combined of 100.1 mSv (maximum 17.5 Sv) are comparable to, if not greater than, the mean doses from the recent, albeit much larger, international study of radiation workers with mean external dose of 19.4 mSv and less than 0.1% receiving cumulative doses over 500 mSv (*75*). The mean follow-up of Mound workers (40.4 years) was also much longer than the 12.7 years in this international study. The 171,541 workers in the UK National Registry for Radiation Workers had a mean dose of 24.9 mSv (6% over 100 mSv) and mean follow-up of 22.7 years (*58*). No worker study, however, finds convincing evidence of cancer excesses occurring below about 150–200 mSv (*13, 76, 77*).

In summary, the long-term follow-up of Mound workers exposed to relatively high but nonlethal levels of polonium as early as 1944 failed to reveal significant excesses of cancers or nonmalignant diseases, with the possible exception of esophageal cancer for which the RR at 100 mSv was estimated as 1.54. Although limited by a relatively small sample size and low cumulative occupational doses, the workers were followed for up to 60 years and the cumulative occupational dose for 4.6% of the workers was greater than 500 mSv. RRs at 100 mSv of 1.04 for lung cancer, 1.99 for leukemia other than CLL, 1.32 for liver cancer and 2.11 for kidney cancer could be excluded with 95% confidence. Larger combined studies of early workers in the U.S. following similar methodologies are warranted to refine and clarify radiation risks following prolonged exposures to ionizing radiation as well as to evaluate risks from intakes of radioactive elements (*77, 78*).

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