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Cohort Profile: Four Early Uranium Processing Facilities in the US and Canada

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Abstract

Purpose: Risks of occupational radiation exposures of workers involved in uranium refining and processing ("*uranium processing workers*") may be different from risks of other workers from the nuclear fuel cycle. Pooling of individual-level data from published studies and analysis using similar dosimetry and statistical methods might provide valuable insights into risks from occupational uranium and external ionizing radiation exposures.

Methods: We pooled the data for workers from four uranium processing facilities (Fernald Feed Materials Production Center, Ohio; Mallinckrodt Chemical Works Uranium Division, Missouri; Middlesex Sampling Plant, New Jersey; and the Port Hope Radium and Uranium Refining and Processing Plant, Canada). Employment began as early as the 1930s in Canada and follow-up for vital status was as late as 2017. These facilities used similar methods to process Belgian Congo pitchblende ore which contained high concentrations of uranium, radium, and their decay products. In addition, workers were exposed to elevated levels of gamma radiation, fission product contaminants in recycled uranium and ambient radon decay products. Non-radiation exposures of industrial hygiene concern were silica dust inhalation, heavy metal toxicity from uranium, solvents, acid mists and chemicals associated with uranium processing. Exposure and outcome data were harmonized using similar definitions and dose reconstruction methods. Standardized

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mortality ratios (SMR) were estimated by comparing mortality in the pooled cohort with age-, sex- and calendar time-specific general population mortality rates for the U.S. and Canada.

Results: Over 12,400 workers will be evaluated for cancer and non-cancer mortality in relation to exposures to uranium byproducts and gamma radiation (including ~1,300 females). In total, death from 560 lung cancers, 503 non-malignant respiratory diseases, 67 renal diseases, 1,596 ischemic heart diseases, and 101 dementia and Alzheimer's diseases (AD) were detected among male workers during follow-up. Mean cumulative doses were 45 millisievert for whole-body external exposures and 172 milligray for lung dose from radon decay products. Of the 16 pooled SMRs, seven were above 1.00, none were significantly low, and only one was significantly high, i.e., dementia and AD among males (SMR=1.29; 95% confidence interval: 1.04,1.54).

Conclusions: This is the largest study to date to examine health risks in uranium processing workers (excluding uranium enrichment workers). The pooling of uranium processing worker data will address issues of importance today, specifically the concerns for cleanup workers and environmental contamination from the operation of past and present nuclear reactor and radiation facilities, reactor accidents, and possible terrorist events.

Keywords

occupational exposures; ionizing radiation; uranium; gamma radiation; uranium processing workers

Introduction

The study of low dose and low-dose-rate exposure to ionizing radiation is important to the understanding of the possible range of adverse health effects. Two major unanswered questions in radiation risk assessment relate to long-term health effects when exposures are low and protracted overtime or when exposures come from high-linear-energy-transfer (LET) alpha radiation, such as that emitted from uranium and its decay products. The radiological and chemical toxicity of uranium compounds depends on the route of exposure (inhaled, ingested, or wound) and the solubility of the compounds, with the most soluble being readily absorbed into the blood and transported to other organs such as the kidneys and bone surfaces (Leggett 1994). Other uranium target organs include lung, upper respiratory and digestive tracts, and lymphatic and hematopoietic tissues (Guseva Canu et al. 2012; Zhivin et al. 2014). Conclusions from the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) report on biological effects of uranium indicate a weak association with lung cancer risk and unclear evidence for risks of leukemia, other lymphohematopoietic malignancies, digestive system cancers, kidney and other urological cancers, and brain/central nervous system (CNS) tumors with uranium exposure (UNSCEAR 2017). Recent studies suggest a possible cardiovascular effect (Guseva Canu et al. 2012; Anderson et al. 2021) while experimental data indicate that chemically toxic soluble uranium compounds could potentially impair kidney function, as has been shown in high dose laboratory animal studies (UNSCEAR 2011; ATSDR 2013), while lower dose studies indicated only transient changes (Turner et al. 2010). Alpha radiation from radium has been found to be carcinogenic to humans (IARC 2012). In particular, exposure to high levels of radium results in an increased incidence of bone sarcomas. Intakes of radionuclides

may be capable of reaching the brain and exposing the tissue to low levels of alpha radiation (Leggett et al. 2019). There are recent suggestions that ionizing radiation, primarily gamma radiation, leads to the development of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease and dementia (Begum et al. 2012; Azizova et al. 2020).

The nuclear fuel cycle provides an opportunity for occupational exposure to uranium throughout various stages (UNSCEAR 2017). Uranium processing involves converting uranium extracted from ore into yellowcake, which is then converted to uranium oxides or uranium metal through a series of chemical and/or metallurgical processes. 'Dry' processing methods of the Belgian Congo ore in the 1930s to 1950s were associated with high dust and aerosol exposures from long-lived, alpha-emitting isotopes of uranium. The potential for exposure to external gamma radiation is also present at each stage of the nuclear fuel cycle, although workers involved in uranium refining and processing ('uranium processing workers') have the highest exposures to external radiation. Uranium processing workers also have the potential for other radiological exposures, such as radium, thorium, and radon decay products (RDP), and non-radiological exposures (e.g. silica dust and chemicals used in refinement). There is limited evidence in humans on the carcinogenicity of mixtures of uranium isotopes from the nuclear fuel cycle (Guseva Canu et al. 2010, 2011; IARC 2012; ATSDR 2013; Zhivin et al. 2014; Yiin et al. 2018). However, because of the various chemicals used in processing, the exposures of uranium processors are substantially different from those of other nuclear fuel cycle workers (i.e. uranium enrichment workers), and they should be carefully evaluated in separate studies. To date, only a few studies have conducted dose-response analyses of uranium processing workers with individual radiation doses (Dupree-Ellis et al. 2000; Guseva Canu et al. 2010; Silver et al. 2013; Zablotska et al. 2013; Gillies and Haylock 2014; Kreuzer et al. 2015; Zablotska et al. 2018; Zhivin et al. 2018; Golden et al. 2019). A limited number of these studies estimated individual doses from uranium or other radionuclides (Silver et al. 2013; Kreuzer et al. 2015; Zhivin et al. 2018; Golden et al. 2019), and study findings were constrained by relatively small sample sizes.

Of the ~500,000 North American workers involved in nuclear fuel production (Bouville and Kryuchkov 2014), only 10–15% have been involved in uranium processing. These workers have been previously described in eight North American studies (Table 1) (Dupree et al. 1987; Dupree-Ellis et al. 2000; Pinkerton et al. 2004; Boice et al. 2007, 2008; Silver et al. 2013; Zablotska et al. 2013; Golden et al. 2019). These workers are a distinct group because their cumulative external gamma exposures are 4–5 times higher than those of nuclear workers (100 millisievert (mSv) vs. 20 mSv (Richardson et al. 2015)) and their RDP exposures are 4–5 times lower than those of uranium miners (20 working level months (WLM) vs. 90 WLM (Lubin et al. 1995)). Of these eight studies, we identified four cohorts with at least two of the following exposures necessary for risk estimation in a pooled analysis: assessed individual internal uranium, radium, RDP exposures, and external radiation doses. In this pooled analysis we included the Fernald Feed Materials Production Center in Ohio (Hornung et al. 2008; Anderson et al. 2012; Silver et al. 2013), Mallinckrodt Chemical Works Uranium Division in Missouri (Dupree-Ellis et al. 2000; Golden et al. 2019), the Middlesex Sampling Plant in New Jersey (Eisenbud 1975), and the Port Hope radium and uranium refinery and processing plant in Canada (Zablotska et al. 2013, 2018).

The unifying feature of these four cohorts is that they all belonged to a network of plants that provided the uranium needed by the United States during World War II and the Cold War era (Eisenbud 1975).

In view of the potential importance of nuclear fuel cycle exposures for radiological protection of occupationally exposed North American workers, pooling of individual-level data from the Fernald, Mallinckrodt, Middlesex, and Port Hope cohorts and analysis using similar dosimetry and statistical methods will provide valuable insights into risks from occupational uranium and external ionizing radiation exposures and any differences in risk compared with other workers. Further, the pooling of worker data will address issues of importance today, specifically the concerns of cleanup worker exposure and environmental contamination from the operation of past and present nuclear reactor and fuel cycle facilities, and possible terrorist events. The pooled analysis will be the largest study to date to examine health risks in uranium processing workers (excluding uranium enrichment workers) and will guide the development of a new line of research before new and more costly studies are undertaken. In addition, this work will facilitate the preparation of a common research protocol and development of methodology for the international pooled analysis of uranium processing workers (iPAUW) (Zablotska 2019).

Cohort descriptions and published results

Fernald Feed Materials Production Center—The Fernald Feed Materials Production Center (Fernald) study included 6409 uranium processing workers employed for 30 days or more between 1951 and 1985, including female and nonwhite employees (Silver et al. 2013), with vital status determined through 2004. The dose reconstruction was comprehensive and organ/tissue-specific doses were estimated for internal intakes of uranium-based on urine samples (Anderson et al. 2012). Additionally, estimates of exposures to external ionizing radiation and RDP were included. A limitation was that the urine analyses were based on single-void samples and not on 24-h urinary excretion collections, which introduces uncertainty in estimates of uranium intakes.

Among male Fernald workers, there was a statistically significant relationship between intestinal cancer mortality (small and large intestine) and lower large intestine dose from internal uranium exposure (excess relative risk (ERR) per 100 μGy = 1.5; 95% confidence interval (CI): 0.12, 4.1) (Silver et al. 2013). Leukemia (other than chronic lymphocytic leukemia) showed a significant negative dose-response with internal uranium exposure to bone marrow (hazard ratio (HR) at 100 μGy = 0.27; 95% CI: 0.022, 0.96). No dose-response relationship was found between internal uranium dose and mortality from lung cancer or chronic obstructive pulmonary disease. Stratification by pay type (salaried and hourly) showed that male hourly workers, compared with the general population, had significant excess mortality from lung cancer (standardized mortality ratio (SMR) = 1.25; 95% CI: 1.09, 1.42), whereas male salaried workers had a significant deficit (SMR = 0.62; 95% CI: 0.46, 0.81). Since salaried workers had low exposures to radiation and are assumed to have had a lower incidence of smoking resulting in a low risk of death due to smoking-related conditions, this study provides evidence that failure to adjust for pay type (or some other measure of socioeconomic status (SES)) might produce spurious results. The Fernald study

will be especially valuable when patterns are compared and combined with the other three uranium processing facilities in the ongoing investigation.

Mallinckrodt Chemical Works—The Mallinckrodt Chemical Works (Mallinckrodt) study cohort included 2514 white male workers employed at least 30 days between 1942 and 1966, which comprises the entire period of uranium processing operations (Dupree-Ellis et al. 2000; Boice et al. 2018; Ellis et al. 2018; Golden et al. 2019). Females and nonwhite workers were excluded because of small numbers. Vital status was last determined through 2012. The facility processed pitchblende ore shipped from Middlesex and Port Hope for a significant period of its operations. Processing operations potentially exposed workers to external gamma radiation and internal radiation from inhalation and ingestion of pitchblende dust (uranium, radium, and silica). The worker roster was developed from employment records including work history and personal radiation monitoring data. Personal and area monitoring were extensive, allowing for the calculation of organ-specific doses. Personal monitoring records included film badges, uranium urinalysis, and breath radon monitoring. In addition, occupational medical chest X-rays were included in individual dose reconstructions, as were ambient levels of radon and RDP.

The recent Mallinckrodt analysis updated through 2012 (Golden et al. 2019) presented no evidence for a radiation dose-response for lung cancer mortality. These findings suggested that chronic radiation exposures, including intakes of radionuclides that provide high-LET dose to lung tissue, are not associated with a detectable increase of lung cancer mortality risk in the range of radiation doses received (HR at 100 mGy = 0.95; 95% CI: 0.81, 1.12), providing some additional evidence that low-dose radiation exposures to the lung experienced over a period of years may be much less carcinogenic than doses received all at once and at a high level (Golden et al. 2019). However, the number of workers and the range of organ-specific dose estimates limit the strength of conclusions that might be drawn. A significant association with radiation was found for kidney cancer mortality (HR at 100 mGy = 1.73; 95% CI: 1.04, 2.79) and an association was suggested for mortality from nonmalignant kidney diseases (HR at 100 mGy = 1.30; 95% CI: = 0.96, 1.76). A non-radiation etiology could not be discounted, however, because of the possible renal toxicities of uranium, a heavy metal, and silica, a component of pitchblende dust.

Middlesex Sampling Plant—The Middlesex Sampling Plant (Middlesex) operated from 1943 through 1955, during which workers handled pitchblende, a high-grade uranium ore containing significant amounts of radium (Milder et al. 2018). The pitchblende was subsequently shipped to Mallinckrodt and Fernald Feed Materials Production Center for processing. Workers inhaled pitchblende ore dust and concomitant silica and were otherwise exposed to gamma radiation, radium, and RDP (Mears and Engel 1945; Cahalane 1958; DOE 1997). As this site has not been studied before, the cohort was assembled from original job history and radiation monitoring records. Of the 830 workers identified, 489 have sufficient identifying information for vital status tracing to be included in the study cohort, after excluding individuals who had missing hire and termination dates or worked less than 30 days. This number includes 35 females and at least 75 nonwhite individuals, though records of race are incomplete (122 of 489 workers have any information on race),

and separating workers by race was not possible. Vital status was determined through 2014. Workers were monitored for potential exposure to radiation using film badges and pocket chambers, uranium and radium urine bioassays, radon breath measurements, and ambient dust level monitoring. Of these measurements, only film badges, pocket chambers, and uranium urinalysis records provided enough information to contribute to exposure reconstruction. The number of workers at this facility is small, but the unique exposure and long-term follow-up add value to the analyses of pitchblende-derived uranium toxicity and silica exposures on lung and kidney disease risks when combined with uranium processing facilities with similar exposure circumstances. Results from this pooled cohort will be the first report of any findings for Middlesex.

Port Hope Radium and Uranium Refining and Processing Plant—The Port Hope Radium and Uranium Refining and Processing Plant (Port Hope) study in Canada included 3000 male and female uranium processing workers first employed during 1932–1980 and alive at the start of follow-up in 1950 (Zablotska et al. 2013, 2018). Mortality follow-up data were obtained through the end of 1999 from the Canadian national reporting of vital statistics data. The workers processed pitchblende and were exposed to external gamma-rays, dust, and inhaled or ingested uranium and radium. Exposure assessment for this cohort was based on film badge doses and area-level monitoring of radon. Cancer mortality from a variety of causes was evaluated, with most analyses focused on the 2645 male workers. Organ doses from uranium and dust exposures are currently being reconstructed and will be available for this pooled analysis.

The Port Hope workers provided some indication of a relationship between lung cancer mortality and RDP exposure in non-mining, male workers (ERR per 100 WLM = 0.21; 95% CI: < −0.45, 1.59); this association was significant when limited to non-mining, male workers primarily exposed to uranium (ERR per 100 WLM = 0.39; 95% CI: < −1.22, 4.52) (Zablotska et al. 2013). A unique feature of this study is the availability of mortality complete during the period of follow-up from 1950–1999 for the whole cohort. There was no indication of a dose-response relationship between mortality from any other causes with either exposure to RDP or to external gamma radiation. While the ERR estimate for the association between gamma-ray dose and colon cancer was high the confidence interval was wide (ERR per 1 gray = 1.65, 95% CI: < −2.16, 23.45). Due to the small size of the cohort, power was likely too low to detect a significant risk from any mortality outcomes. Although small, this is one of the oldest studies with exposures dating back to 1932, and with complete ascertainment of mortality during the period of follow-up; it will make a valuable contribution to the pooled assessment.

Objectives of the pooled cohort study

There are three specific goals of this pooled study. First, radiation exposure assessment will be completed and updated for all uranium processing facilities and harmonized across studies, including individual doses from external ionizing radiation, internally-deposited uranium, and RDP, where adequate measurements exist. Silica dust exposures will also be estimated where appropriate and available. Second, radiation-related risks of mortality from site-specific cancers and nonmalignant causes of death will be examined, in particular the

possible risk of lung and kidney diseases resulting from chronic radiation exposures. Third, the risk of mortality from dementia, AD, Parkinson's disease, and motor neuron disease associated with exposure of the brain to alpha-emitting radionuclides will be evaluated. This paper presents the first of this pooled cohort series. In this paper, the Fernald, Mallinckrodt, Middlesex, and Port Hope cohorts are profiled in terms of their vital status and exposures received, and both individual and pooled standardized mortality ratios are reported.

The pooled analysis will bring clarity to questions of radiation health effects from inhalation of uranium, radium, and RDP because of the combined population size (n = 12,403), long period of follow-up, individual dose assessments for both external and internal radiation exposures, and similarity in radiation exposures across the four cohorts. Study findings will be uniquely relevant to workers employed in the uranium processing industry and will be generalizable to workers and the public with exposures related to the environmental cleanup of previous radiologically contaminated areas (Wakeford 2012). Astronauts exposed to cosmic radiation on long, interplanetary missions are another group for which high-LET exposures to lung and brain tissue are of particular importance (Boice 2017; Cekanaviciute et al. 2018).

Methods

Human subjects research approval was received from the Central Department of Energy Institutional Review Board (IRB), the Vanderbilt University IRB, the National Institute for Occupational Safety and Health (NIOSH) Human Subjects Review Board, and the University of California, San Francisco IRB.

Harmonization of cohort vital status and outcomes

Cohort-specific vital status tracing is described fully in the original research articles: Fernald (Silver et al. 2013); Mallinckrodt (Mumma et al. 2019; Golden et al. 2019); and Port Hope (Zablotska et al. 2013). Tracing for the previously unstudied Middlesex cohort was performed similarly as described for Mallinckrodt.

Briefly, for the Fernald cohort, vital status through 1989 was obtained from a previous study (Cragle et al. 1995) where death was ascertained by searching the Social Security Administration (SSA), state death indices, Pension Benefits, Inc, and the National Death Index (NDI). Death certificates were retrieved for that study and coded to the eighth revision of the International Classification of Diseases (ICD). For the latest Fernald cohort study, mortality was updated through 2004 using the SSA Death Master File and the NDI. Cause of death was coded to the ICD revision at the time of death using the underlying cause of death (Silver et al. 2013). The NIOSH Fernald data set shared with the pooled study consisted of anonymized, aggregated person-time tables with cell sizes of five or greater. Nine Fernald workers had a work history that either overlapped with or occurred previously at Mallinckrodt, so it was determined that these workers would be excluded from the Fernald cohort for the pooled analyses. Thus, 6400 Fernald workers are included in the pooled study, as opposed to the 6409 reported by Silver et al.

The Mallinckrodt and Middlesex cohorts were traced using extensive resources available within the Million Person Study (Mumma et al. 2019). Briefly, vital status as of 2012–2014 for the workers was determined from linkages of the study rosters with multiple sources including the NDI; various state mortality files; the SSA Death Master File; and the SSA Epidemiological Vital Status Service (which confirms alive status). Corrections to in-house files were made to maximize linkages using the Transunion TLOxp database, which is an online information service provider (https://www.tlo.com/). Additionally, 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 (Campbell et al. 2008). The underlying cause of death was determined from the NDI for deaths that occurred after 1978 and were determined from death certificate information for those who died prior to 1979 when the NDI began.

The nominal roll file for Port Hope was linked to the Canadian Mortality Data Base (CMDB) and to the Canadian Cancer Data Base (CCDB) to ascertain mortality from 1950 to 1999. Data in the CMDB are obtained through the vital statistics system for national reporting of vital statistics data (Zablotska et al. 2013). Since the registration of deaths is a legal requirement through the Vital Statistics Acts (or equivalent legislation) in each Canadian province and territory, reporting is virtually complete. The ‘alive’ follow-up (1984–1999) was completed via deterministic linkage of the nominal roll with the Historic Tax Summary file using the social insurance number (SIN) or probabilistic linkage with the CMDB and the CCDB. The remaining subjects were considered lost to follow-up and had their termination date at work as the last date alive.

Each worker contributed person-years at risk from the later of the date of hire or the start date of follow-up, to the exit or date of death, or the last date known alive defined as the date of last employment or contact, whichever occurred later, as previously described for each cohort (Silver et al. 2013; Zablotska et al. 2013; Mumma et al. 2019; Golden et al. 2019). Data processing and preparation for analyses were conducted using SAS 9.4 (SAS Institute Inc 2018) and Stata Version 15 statistical software (StataCorp 2017).

For this pooled analysis, the data on mortality outcomes were harmonized by re-categorizing into 16 outcomes of interest, taking into account the differences between U.S. and Canadian rates (Supplemental Table 1). As a result, the number of observed outcomes in this analysis for some cohorts might differ from original publications. Overall pooled estimates of the SMR, together with associated 95% CI, were obtained using random-effects meta-analysis, calculated from the observed (O) and expected (E) deaths in individual cohorts, as SMR = O/E and its 95% CI = SMR ± 1.96√O/E, weighted by study population size.

Harmonization of cohort exposure assessments

Radiation dose assessments have been described for the four uranium processing facilities previously (Anderson et al. 2012; Zablotska et al. 2013; Dauer et al. 2018; Ellis et al. 2018). For each cohort, annual organ-specific doses resulting from all external and internal radiation exposures were estimated using available personal and area monitoring data. This comprehensive dosimetric approach follows methods outlined by the National Council on

Radiation Protection Scientific Committee 6–9 for the Million Worker Study (Dauer et al. 2018).

External exposure—Exposure to external ionizing radiation at all facilities was estimated using film badge (Mallinckrodt, Middlesex, and Port Hope) and pocket chamber data (Middlesex). For Fernald, external dose data were obtained from the facility exposure database. These data were assumed to represent the deep dose equivalent (Hp(10)) due to gamma radiation exposure. For Fernald, Mallinckrodt, and Middlesex, additional external dose data were obtained from the DOE Radiation Exposure Monitoring System (REMS) for facilities other than workers' respective primary sites. Likewise, three additional sources of film badge data were included for the Mallinckrodt cohort, as previously described (Golden et al. 2019). Neutron dose measurements were not available as there was little potential for exposure to neutrons at these sites. The Mallinckrodt cohort also had data available for occupational medical chest X-rays, primarily conventional chest radiography. Thus, these contributions to the external dose estimate for Mallinckrodt study subjects were separated out so that sensitivity analyses could be run with and without that component. The Middlesex cohort is currently missing film badge doses between the years 1949 and 1952; these annualized doses were singly imputed from the mean of each individual's previous and later annual doses, weighted by the number of days worked in each year. For individuals who only worked during 1949–1952 and therefore had no prior or later film badge records, doses were singly imputed from means of all other workers' exposures during that year if they had any evidence of exposure (from bioassay records, etc.).

Radon progeny (RDP) exposure—Estimates of exposure to airborne radon and its short-lived progeny were based on radon measurements in work areas where radium-containing materials were handled or stored, together with estimated exposure times in these areas based on job titles for Mallinckrodt and Port Hope. For Fernald, RDP exposure was estimated using a radon exposure matrix (Hornung et al. 2008) based on a Gaussian plume dispersion model coupled with source term information for the on-site silos where radium-bearing residues were stored. To harmonize Fernald and Port Hope radon progeny exposure with Mallinckrodt (Ellis et al. 2018) (radon progeny exposures not estimated at Middlesex), estimates of radon progeny exposure in terms of WLM were converted to lung absorbed dose by multiplying by 8.19 mGy WLM−1. This absorbed dose conversion factor was based on the following assumptions (Ellis et al. 2018) and reference values from ICRP Publication 137 (ICRP 2017): an equilibrium factor of 0.4; unattached, nucleated, and accumulation fractions of 0.08, 0.184, and 0.736, respectively; and particle sizes for unattached, nucleated, and accumulation modes of 0.001, 0.06, and 0.5 μm activity median aerodynamic diameter (AMAD).

Internal exposure—For the pooled study, it was necessary to harmonize available annual organ doses estimated in previous studies. For the pooled study, the organs of interest include lung, brain, heart, kidney, colon, and red bone marrow. Fernald, Mallinckrodt, and Middlesex all used urine uranium concentration data in combination with ICRP 60 (ICRP 1990), ICRP 66 (ICRP 1994), and ICRP 69 (ICRP 1995) dosimetric and biokinetic models assuming the aerosols were Type M (moderate absorption to the blood) uranium compounds

with either a 5-μm AMAD particle size (Mallinckrodt, Middlesex, and Port Hope) or 10-μm AMAD particle size (Fernald, based on site data). All sites have estimated organ doses for lungs, kidneys, and red bone marrow, however, Mallinckrodt and Middlesex organ data also include heart, brain, and colon dose. For the purpose of harmonization, the Fernald lower large intestine dose will be used as a surrogate for colon dose, and pancreas dose will be used to represent heart and brain dose. Organ doses from internal exposure to uranium were not evaluated for Port Hope. The radium body burden was estimated for Mallinckrodt, and similarly for Middlesex, from radon breath analyses as previously described (Ellis et al. 2018). However, calibration for radon breath analyses at Middlesex was performed too irregularly for these records to inform dosimetry for that site. Because Mallinckrodt is the only site with this dosimetry component, it was separated from the internal estimate component such that sensitivity analyses could be performed in comparison to the complete dose complement estimated in the Mallinckrodt study (Ellis et al. 2018; Golden et al. 2019).

Results

Descriptive characteristics of the four individual cohorts and the pooled dataset are presented in Table 2. Overall, the pooled cohort of 12,403 workers (11,059 males and 1344 females) with approximately half a million years of follow-up (409,686 and 49,520, males and females, respectively) more than doubles the number of workers and person-years of Fernald, the largest of the four individual cohorts. The variation among the cohorts in the length of follow-up, year of birth, and year of hire is presented separately for participating four cohorts by sex and reflects the variation in the start of and length of operations at the four facilities. The years of birth and hire at Middlesex and Mallinckrodt, which both began operations in the 1940s, were at least a decade earlier than Fernald and Port Hope, which began operations in the 1950s. Both males and females started work around 30 years old. The differences in the mean duration of employment by cohort also reflect the length of operations at the different facilities. While all cohorts were followed for at least 30 years, the average length of follow-up exceeded 40 years, up to over 70 years for both Middlesex and Mallinckrodt. As a result of the long follow-up, over half of the males in the pooled cohort are deceased as are nearly a quarter of the females. Vital status is known for 98.6% of the pooled cohort, as is the cause of death for those known to be deceased.

Although all sites processed uranium, the type and quantity of exposure data available to estimate dose for the organs of interest varied. Bioassay monitoring was rudimentary during WWII which is reflected in the mean number of bioassay samples per worker for Middlesex and Mallinckrodt compared to Fernald, which began operations post-war. Bioassay data are available for Port Hope and organ doses are in the process of being estimated. All sites had doses assessed for external ionizing radiation and RDP. For the three facilities with estimated organ dose from internal exposure to uranium, Mallinckrodt had the highest estimated mean organ doses, whereas Fernald had the lowest (Table 2). Fernald had the highest mean lung dose from exposure to radon progeny resulting from the emanation of radon from the silos used to store radium residues onsite during the entire period of operation. Port Hope had the highest mean dose from external ionizing radiation exposure. The temporal variation in annual external gamma radiation dose by cohort is presented in Figure 1. Exposure trends are similar for all four facilities, with higher exposures recorded

for earlier years. For Fernald and Mallinckrodt, elevated external exposure prior to the start of study facility operations is due to the ascertainment of exposures from other facilities being included in the facility exposure records, as described in the methods.

Observed and expected deaths and SMRs for 16 selected outcomes by sex are shown in Tables 3–7 for each of the four cohorts and for the pooled cohort. For outcomes of interest, pooling resulted in substantial numbers of observed deaths in males: 560 lung cancers, 503 nonmalignant respiratory diseases, 67 renal diseases (nephritis and nephrosis), 1596 ischemic heart diseases, and 101 dementia and AD. Statistically significant deficits of deaths compared to sex- and the age-specific general population was observed for all causes of death in males from all cohorts with the exception of Port Hope, a likely indication of a healthy worker effect. Statistically significant excesses for all cancer and dementia and AD were observed in Fernald males; for CNS cancers in Mallinckrodt males; and for ischemic heart disease in Port Hope males. The only significant increase that persisted in the pooled analysis was dementia and AD among males (n = 101, Table 7). No other statistically significant increased SMRs were observed in the pooled analysis.

Using radiation risk estimates for lung cancer and nonmalignant respiratory diseases from the International Nuclear Workers Study (INWORKS) (Gillies et al. 2017; Richardson et al. 2018) and pooled analysis of uranium miners (Lubin et al. 1995), statistical power to detect radiation associations with the pooled study was estimated. Using NCI's Power V3.0 software (Garcia-Closas and Lubin 1999), assuming a type I error at 5% and distribution of gamma-ray doses in all four cohorts, statistical power to detect a significant increase in excess relative risk of lung cancer >0.51/Sv is projected at greater than 90% power while the power to detect radiation risks of nonmalignant respiratory disease >0.13/Sv is substantially lower at 30% (Figure 2(a)). More than 90% power is projected to detect RDP-associated risks of lung cancer >0.50/Gy and nonmalignant respiratory diseases >0.50/Gy (Figure 2(b)). There are no published estimates of risks of dementia and AD, but we project that we will have 82% power to exclude radiation risks of dementia and AD ≥0.75/Sv (not shown). Thus, the pooled study should have sufficient statistical power to detect significant increase in risk for main outcomes of interest.

Discussion

In this paper, we present cohort characteristics of the pooled analysis of uranium processing workers from four facilities in the U.S. and Canada. This study will be the largest study to date to examine health risks in this group of workers involved in uranium processing and refining (excludes uranium enrichment workers). While a substantial body of epidemiologic literature on occupational cohorts exposed to ionizing radiation exists, few have directly estimated dose-response associations for internal exposure with individual doses. The majority of these studies reported increases, though often not statistically significant, in radiation risks of lung cancer among workers with exposures to processed uranium (Chan et al. 2010; Boice et al. 2011; Silver et al. 2013; Zablotska et al. 2013; Kreuzer et al. 2015; Zhivin et al. 2018; Golden et al. 2019). While several studies reported increased risk of kidney cancer from RDP exposure, uranium or uranium/external exposures (Boice et al. 2011; Silver et al. 2013; Zablotska et al. 2013; Yiin et al. 2018; Golden et al. 2019),

many were not statistically significant due to low statistical power, primarily related to small numbers of kidney cancers. Likewise, risks of nonmalignant respiratory and renal diseases were increased but not statistically significant (Boice et al. 2011; Yiin et al. 2018; Golden et al. 2019). As has been previously reviewed (Guseva Canu et al. 2008), the findings of the individual studies were generally limited by low statistical power, primarily due to small cohort size or low total doses from radiation exposures.

Because the Fernald, Mallinckrodt, Middlesex, and Port Hope cohorts share many similarities in occupational exposures (due to similarities in uranium processing methods), dose reconstruction approaches, and study design, there is a strong rationale to conduct a pooled study in order to overcome limitations related to low statistical power. The pooled cohort described here will be the largest study to date to examine health risks from uranium processing and provides the opportunity to refine and clarify radiation risks reported in the individual studies. As demonstrated, the pooled cohort size (n = 12,403), long follow-up period (large summary person-years at risk), and large numbers of deaths (particularly for lung cancer) should provide sufficient statistical power to evaluate radiation effects in the low dose range. While the numbers of deaths do not reach the magnitude of those reported in other pooled studies of occupational cohorts (Hamra et al. 2015; Rage et al. 2020), it is the only pooled cohort focused on uranium processing workers that have data available for evaluating intake of uranium and RDP exposure for individuals. Previous analyses of the three published cohorts suggested an increased risk of kidney (Golden et al. 2019) and colon cancer mortality (Silver et al. 2013; Zablotska et al. 2013). A larger sample size of the pooled analysis would allow us to conduct more in-depth analyses of these outcomes as well as present an unparalleled opportunity to directly evaluate radiogenic risks of non-Hodgkin lymphoma and nonmalignant respiratory, cardiovascular, and renal diseases, which have been evaluated in studies of nuclear workers but have not been analyzed previously in uranium processing workers. Further, large-scale population studies are urgently needed to measure the potential radiation risks of AD, dementia, and other neurodegenerative disorders, such as, for example, the recently reported results for Parkinson's disease (Azizova et al. 2020); see also (Boice 2017, 2019). One of the major concerns of NASA in space missions to Mars is the effect of high-LET radiation on brain tissue and the possibility of cognitive dysfunction and dementia related to long-term missions (Cekanaviciute et al. 2018). As uranium and radium emit high-LET alpha particles and intakes of these radionuclides by workers are known to reach the brain (Leggett et al. 2019), the uranium processing cohorts provide a close, albeit imperfect, human analog to circumstances in deep space (Boice 2017, 2019). Results presented in this paper from pooled SMR calculations for AD and dementia provide a tentative signal (SMR = 1.29; 95% CI: 1.04, 1.54) that will be further examined using internal dose-response analyses in the pooled cohort. It is noted, however, that for Mallinckrodt workers there was no evidence for a dose-response for the combined categories of dementia, AD, Parkinson's and motor neuron disease (ERR at 100 mGy = −0.13; 95% CI: −0.28, 0.02; n = 93) (Golden et al. 2019).

Strengths and limitations of the pooled studies of US and Canadian workers

Strengths of this pooled evaluation of four uranium processing facilities include the long follow-up and high mortality, up to 70 years of follow-up and over 50% of males and

20% of females deceased; the similarities in cohort design and facility operations; the comprehensive dose reconstruction that includes available data on external and internal doses from multiple sources of exposure; and unique methodological approaches for evaluating contribution to risk from varying exposure components and sensitivity analyses for confounding and effect modification.

The pooled analysis will expand and improve upon the previous studies through several innovative aspects. While primary analyses will focus on the pooled cohort of ~11,000 males, exploratory analyses of ~1300 females involved in uranium processing will be evaluated for all cancers, lung cancer, and CVD. Dose-response analyses not previously conducted for females and sex-specific risks have only recently begun to be evaluated in occupational cohorts. Pooled SMR analyses presented in Table 7 suggest an elevation of lung cancer among female uranium processing workers above the general population (SMR = 1.34; 95% CI: 0.87, 1.81) compared to no increased rate in males (SMR= 1.04; 95% CI: 0.95, 1.12), though not statistically significant. On the other hand, studies of uranium miners typically show statistically significant increases in SMRs/SIRs for lung cancer compared to the general population in males, for example, (Richardson et al. 2020), although the difference in lung cancer risk between this pooled analysis and uranium miners is likely due to the differences in exposures between the two cohorts. Specific or sex-adjusted dose-response analyses may aid in further elucidation of any differences in lung cancer risk among females and males.

While not all four facilities have complete exposure information, all have some information on intakes for either uranium or RDP, which represents specific strengths related to dose reconstruction:

1. Greater statistical power than other existing studies of uranium processing workers because of larger numbers, but mean organ doses remain in the low-dose range (below 100 mGy) even when combined with internal exposure estimates.
2. Occupational external radiation doses received both before and after employment at the specific uranium processing facility are captured.
3. Organ/tissue-specific doses from intakes of uranium and/or RDP are available. The availability of urine bioassay samples adds to the quality of the information on dose reconstruction.
4. Organ/tissue-specific doses from occupational medical X-rays required for employment and radon breath analyses are available for one cohort, allowing for evaluation with and without these components.
5. Dust measurements from pitchblende, including uranium, radium, and silica, are available in at least two cohorts for stratification of risks, where appropriate.

Because of the quality of dosimetry information available and the similarity of facility operations, harmonization of data from each cohort was achieved in order to estimate risks from RDP exposure, external radiation dose, and uranium organ doses (Table 2). The broad distribution of doses across the varying components, but predominantly in the low dose range, offers the opportunity to evaluate the contributions to risk from different

exposures separately, as was previously done in two cohorts (Silver et al. 2013; Zablotska et al. 2013), and then together as total radiation contribution from all exposures, as in the Mallinckrodt analyses (Golden et al. 2019). The analyses of the separate dose components, while adjusting for other sources of radiation, allows for more direct comparison with prior studies and can provide insight into the potential relationship between some outcomes and non-radiogenic, chemical properties of uranium. To further examine the robustness of radiation risk estimates to different analytical strategies, analyses with different lag intervals and dose weighting factors for high-LET contributions of uranium intakes will be evaluated, but, as seen previously (Golden et al. 2019), are not expected to affect risk estimates.

While limitations exist for studies of uranium processing workers, the pooled study described here utilizes methodological approaches to identify and address potential biases through sensitivity and other comparative analyses as part of planned dose-response evaluations. Likely due to low statistical power, most prior studies of uranium processing workers did not investigate possible effects from confounders or other modifying factors with the possible exception of adjusting for measures of SES as a surrogate for smoking and other lifestyle confounders. Leveraging the pooled large sample size and wide ranges of age, calendar time, and exposures, planned dose-response analyses will include stratifications for examining potential confounding and effect modification of various variables, such as age at risk, calendar-year at risk, total duration of employment, age at first exposure, cumulative exposure, and years since first exposure.

A major limitation of the individual studies, and thus the pooled analysis, is the incomplete knowledge of lifestyle factors, such as diet and smoking, and family history. This is a frequent limitation for most retrospective studies of occupational cohorts where demographic and exposure information are based on past occupational records and registries and often do not include medical or personal history. When smoking data are often not available, SES such as pay type (salaried/hourly) is frequently used in occupational studies as a surrogate adjustment factor for smoking and other lifestyle factors (Boice et al. 2006) as is education (Cohen et al. 2019). In previous studies, the mortality of tobacco-related cancers was similar to the general population, suggesting that smoking was not substantially elevated relative to the general population (Zablotska et al. 2013; Golden et al. 2019). Both Fernald and Mallinckrodt analyzed SMRs separately by pay type, with similar results: salaried workers had significant low SMRs for ischemic heart disease and lung cancer, whereas hourly workers had significant (Silver et al. 2013) or near-significant (Golden et al. 2019) elevated SMRs for lung cancer, indirectly supporting the likelihood that the payment type is a good proxy for smoking history in these cohorts. Thus, pay type (hourly, salary) was harmonized across detailed job data for all four cohorts of the pooled analyses and is expected to be an important adjustment factor for lung cancer and CVD. Additionally, past Fernald analyses imply pay type may be an important adjustment factor in its own right, regardless of its relationship with smoking status (Silver et al. 2013).

Other limitations include misclassification of dose caused by the possibility of missing or incomplete dosimetry and bioassay data, the assumptions of aerosol particle size and solubility of uranium compounds to which workers were exposed, and the precision of available data for internal radiation exposures. The Middlesex cohort has particular

uncertainty due to the imputations needed for missing film badge data from 1949 to 1952 for all workers. Since Middlesex was only open from 1943 to 1954, the missing time period accounts for a third of the time the plant operated. While the imputation allows the use of more information, more accuracy, and more precision than excluding that time period, results for this cohort add additional uncertainty but the magnitude and direction of any systematic bias are unclear (Harrell 2015). However, the Middlesex population accounts for less than 4% of the pooled cohort, so these uncertainties are not expected to have an appreciable impact on the pooled results. The missing data are currently being sought and if obtained, would allow for validation of the assumption of limited impact on overall study results. Difficulties in evaluating internal dose are common limitations of studies of cancer risk in nuclear workers (Guseva Canu et al. 2008) which is why many prior studies have excluded workers with potential for internal exposure or attempted to adjust for internal intakes as a categorical or indicator variable. Uncertainty in RDP exposure estimates was introduced by modeling parameters such as plant inventories of radium-bearing materials, measurement or modeling of radon emanation rates from various materials, building volumes and estimated air exchange rates, and meteorological data. Further, concomitant intakes of radionuclides such as actinium, protactinium, and contaminant radionuclides in recycled uranium feed, as well as non-radiological exposures (including solvents and other laboratory chemical exposures), were not available or able to be harmonized for all cohorts. Some qualitative assessment is available for other types of exposures for Fernald, Mallinckrodt, and Port Hope (Anderson et al. 2012; Silver et al. 2013; Zablotska et al. 2013; Ellis et al. 2018; Golden et al. 2019) and uncertainties associated with radiation dose evaluations are expected to be cohort-specific. Care will be taken in pooled dose-response analyses to examine modifications to the associations between radiation and various outcomes by using indicator variables for facility/cohort effects and exposures to dust, other types of radiation, chemicals, etc.

Despite these limitations, the construction of this pooled cohort of four uranium processing facilities will contribute considerable knowledge to dose-response relationships among nuclear workers with internal exposures to radiation, particularly uranium, radium, and radon and its decay progeny. This pooled cohort represents a step forward in maximizing the ability to assess the health effects of chronic, low-dose radiation on a population with greater statistical power to estimate the significance of effects because of its size, long follow-up, and breadth of individual dose assessments. Additionally, this work will facilitate the preparation of a common research protocol and the verification of the feasibility of the international pooled analysis of uranium processing workers (iPAUW) to bring clarity to our understanding of the long-term health effects of prolonged exposure to low doses of ionizing radiation (Zablotska 2019).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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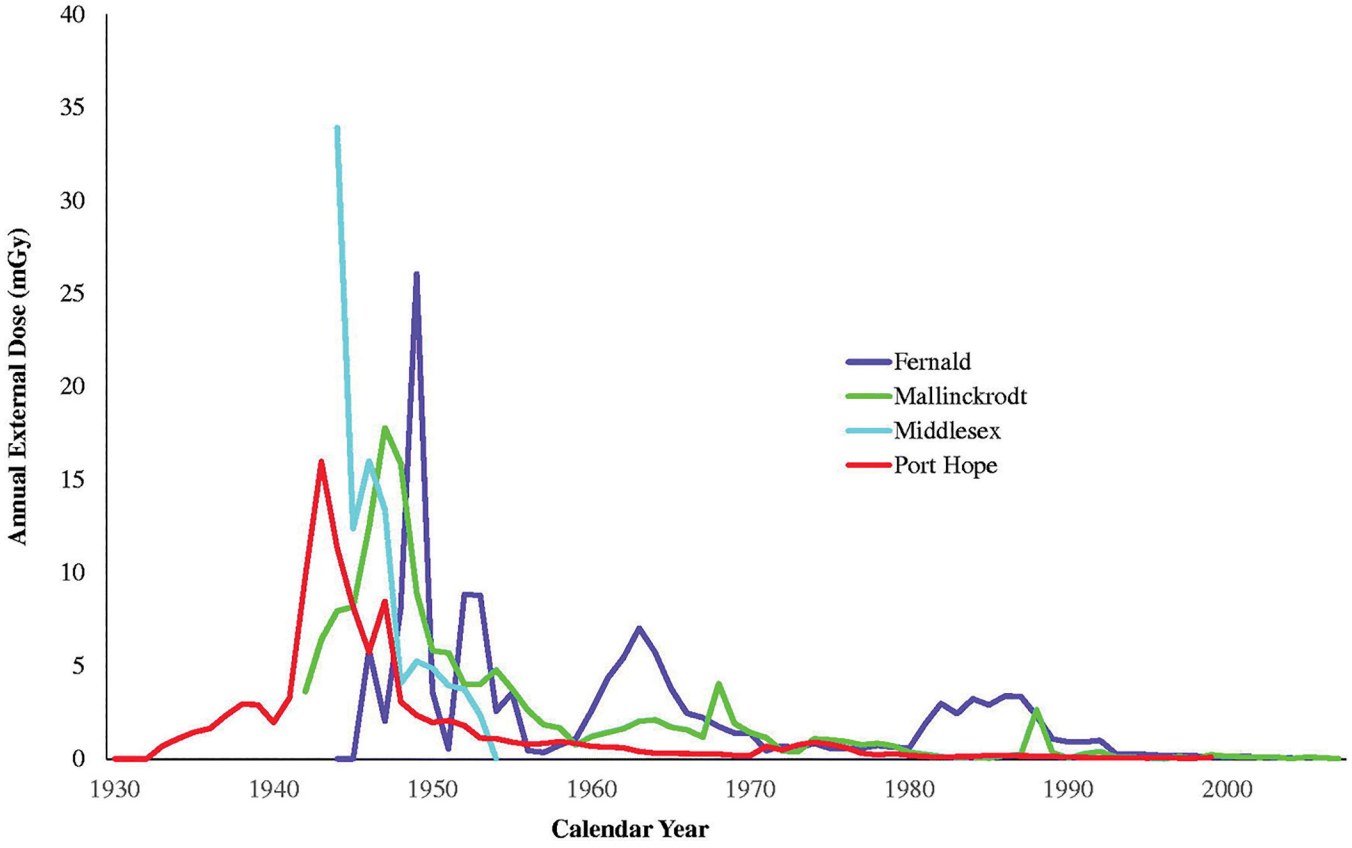

Figure 1.
Mean Annual External Dose by Individual Study.

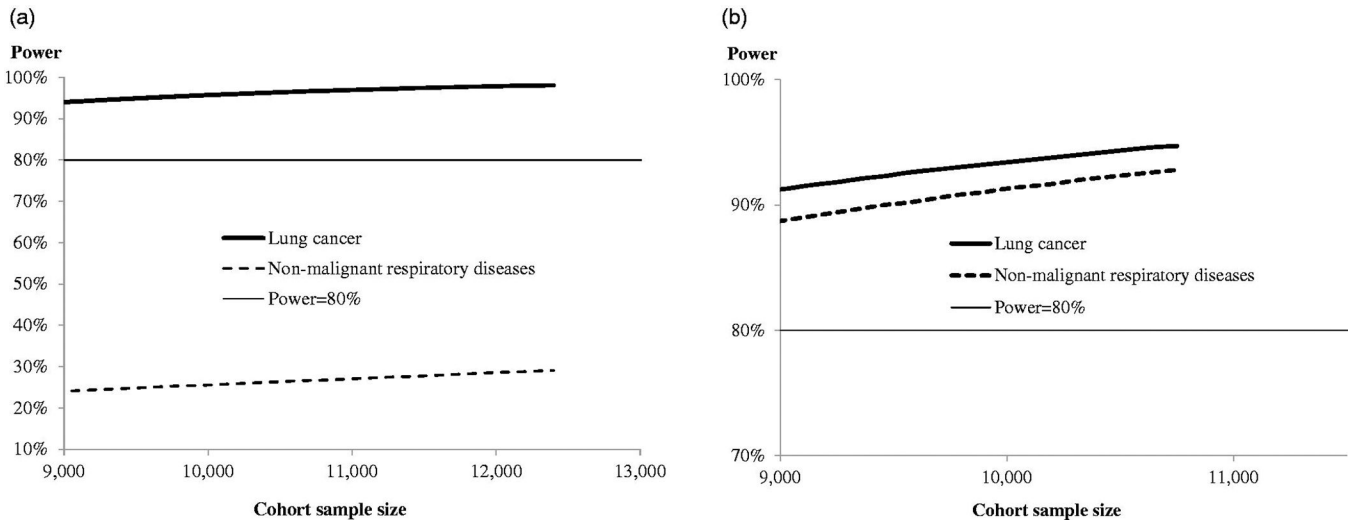

Figure 2.

Power projections for analyses of mortality risks from (a) gamma-ray radiation and (b) RDP exposures.

Table 1.

Published studies of North American workers involved in uranium milling, refining and processing.

Cohort	Reference	Cohort size	Availability of individual dosimetry
Colorado Plateau	(Pinkerton et al. 2004)	1484	No
Fernald Feed	(Silver et al. 2013)	6409	Yes
Grants, NM	(Boice et al. 2008)	718	No
Linde Air	(Dupree et al. 1987)	995	Yes, but dosimetry is limited and no current plans to update it
Mallinckrodt	(Dupree-Ellis et al. 2000), (Golden et al. 2019)	2514	Yes
Middlesex			Yes, but need to calculate from badge and urine analyses data (computerized) and breath radon (computerized, but calibration too irregular to calculate dose accurately)
Port Hope	(Zablotska et al. 2013)	3000	Yes
Uravan, CO	(Boice et al. 2007)	622	No

Blank values represent employment records available but have never been analyzed and published.

Table 2.

Descriptive statistics for individual studies and the pooled cohort.

Descriptive Characteristic	Fernald[a]		Mallinckrodt	Middlesex		Port Hope		Pooled	
	Male	Female	Male	Male	Female	Male	Female	Male	Female
Number	5,446	954	2,514	454	35	2,645	355	11,059	1,344
Person-years at risk	200,707	35,587	107,919.80	18,339.7	1,834.4	82,753	12,103	409,720	49,524
Mean years of follow-up (SD)	36.9 (12.9)	37.3 (12.6)	42.9 (15.2)	40.4 (17.8)	52.4 (14.4)	33.8 (13.7)	36.4 (14.2)		
Mean year of birth (SD)	1929 (13)	1938 (14)	1921 (11.7)	1913 (12)	1918 (10)	1928	1932		
Mean year of hire (SD)	1960 (11)	1965 (13)	1946 (3)	1946 (3)	1946 (3)	1957	1960		
Mean age at hire (SD)	30.7 (8.8)	27.1 (8.5)	32.1 (11.2)	32.6 (11.2)	26.7 (8.1)	29.7	27.3		
Mean years of employment (SD)	10.1 (10.4)	7.6 (9.4)	5.6 (5.5)	2.1 (2.1)	2.6 (1.7)	6.4 (9.3)	4.8 (7.5)		
Mean number of bioassay samples per worker	40.7	14.9	20.5	0.6 (1.7)	0[b]	0	0		
Mean cumulative organ dose from internal uranium, mGy (SD)									
Lung	1.1 (3.3)	0.24 (2.5)	10.5 (12.7)	6.2 (7.2)	NA	NE	NE	3.54 (8.14)	0.24 (2.47)
Kidney	0.098 (0.28)	0.022 (0.22)	0.63 (0.76)	1.7 (1.7)	NA	NE	NE	0.24 (0.52)	0.02 (0.22)
Colon	0.012 (0.035)	0.0031 (0.033)	0.060 (0.075)	0.17 (0.16)	NA	NE	NE	0.025 (0.053)	0.0031 (0.0327)
Red Bone Marrow	0.034 (0.097)	0.0079 (0.081)	0.17 (0.20)	2.5 (2.1)	NA	NE	NE	0.073 (0.204)	0.0079 (0.0814)
Mean cumulative external dose, mGy (SD)	14.6 (29.5)	1.3 (4.6)	32.6 (62.7)	64.3 (146.3)	34.6 (48.3)	116.3 (312.3)	36.1 (69.8)	45.01 (164.98)	11.36 (40.02)
Mean cumulative lung dose from RDP, mGy (SD)	240.3 (686.1)	34.1 (59.5)	18.2 (21.7)	NE	NE	109.3 (376.2)	40.2 (79.0)	171.76 (564.18)	35.79 (65.37)
Vital status[c]									
Alive (%)	2,850 (52.3)	755 (79.1)	598 (23.8)	52 (11.5)	10 (71.4)	1,548 (58.5)	276 (77.8)	5,048 (45.6)	1,041 (77.5)
Dead (%)	2,566 (47.1)	199 (20.9)	1,895 (75.4)	398 (87.7)	25 (28.6)	1,097 (41.5)	79 (22.2)	5,956 (53.9)	303 (22.5)
Unknown (%)	30 (0.6)	0 (0)	21 (0.8)	4 (0.9)	0	0	0	55 (0.50)	0.0 (0.0)
Cause of death known	2,549	197	1,879	346	23	1,097	79	5,871	299

Abbreviations: mSv, millisievert; mGy, milligray; NA, not applicable (workers were not monitored); NE, not estimated (workers were monitored but estimates of exposures are not available); SD, standard deviation.

[a]Number of Fernald Workers is excluding nine workers who overlapped with the Mallinckrodt cohort.

[b]0 - zero dose or below the limit of detection.

[c]Vital status follow-up differs for each cohort: Fernald – start of employment-2004; Mallinckrodt – start of employment-2012; Middlesex – start of employment-2014; Port Hope – 1950–2000.

Table 3.

Standardized mortality ratios for males and females in the Fernald Feed cohort.

	Fernald[a]									
	Male					Female				
Cause of Death	**Observed**	**Expected**	**SMR**	**95% CI lower**	**95% CI upper**	**Observed**	**Expected**	**SMR**	**95% CI lower**	**95% CI upper**
All Causes of Death	2,517	2,671.38	0.94	0.91	0.98	199	214.72	0.93	0.80	1.06
All Malignant Neoplasms	779	712.91	1.09	1.02	1.17	74	71.92	1.03	0.81	1.29
Cancer of Bronchus Trachea Lung	272	257.46	1.06	0.93	1.19	22	17.50	1.26	0.79	1.90
Cancer of Bone	<5	1.54				<5	0.14			
Cancer of Kidney	14	18.32	0.76	0.42	1.28	<5	1.18			
Cancer of Biliary Passages and Liver	17	16.86	1.01	0.59	1.61	<5	1.42			
Cancer of Large Intestine	64	61.36	1.04	0.80	1.33	7	5.94	1.18	0.47	2.43
Cancer of Central Nervous System	21	18.72	1.12	0.69	1.71	<5	1.90			
Non-Hodgkin Lymphoma	30	26.85	1.12	0.75	1.60	<5	2.56			
Leukemia and Aleukemia	31	26.42	1.17	0.80	1.67	<5	2.20			
Multiple Myeloma	19	11.87	1.60	0.96	2.50	<5	1.11			
Nonmalignant Respiratory Disease	193	224.46	0.86	0.74	0.99	21	18.35	1.14	0.71	1.75
Nephritis and Nephrosis	20	24.76	0.81	0.49	1.25	<5	2.26			
Ischemic Heart Disease	626	751.57	0.83	0.77	0.90	28	37.99	0.74	0.49	1.07
Cerebrovascular Disease	107	131.71	0.81	0.67	0.98	8	13.67	0.59	0.25	1.15
Dementia and Alzheimer’s Disease	42	26.79	1.57	1.13	2.12	5	3.67	1.36	0.44	3.18

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

Blank values are not calculated due to small numbers (<5 outcomes).

[a]SMRs were based on U.S. mortality rate files that began in 1960. As a result, person-time and 49 deaths occurring before 1960 were excluded.

Table 4.

Standardized mortality ratios for males in Mallinckrodt cohort.

	Mallinckrodt				
Cause of Death	**Observed**	**Expected**	**SMR**	**95% CI lower**	**95% CI upper**
All Causes of Death	1,894	2,024.50	0.94	0.89	0.98
All Malignant Neoplasms	488	502.50	0.97	0.89	1.06
Cancer of Bronchus Trachea Lung	157	171.10	0.92	0.78	1.07
Cancer of Bone	<5	1.10			
Cancer of Kidney	13	12.50	1.04	0.55	1.77
Cancer of Biliary Passages and Liver	6	12.10	0.50	0.18	1.08
Cancer of Large Intestine	46	42.20	1.09	0.80	1.45
Cancer of Central Nervous System	22	11.90	1.85	1.16	2.80
Non-Hodgkin Lymphoma	25	18.60	1.34	0.87	1.98
Leukemia and Aleukemia	23	20.00	1.15	0.73	1.73
Multiple Myeloma	6	8.50	0.71	0.26	1.54
Nonmalignant Respiratory Disease	176	187.30	0.94	0.81	1.09
Nephritis and Nephrosis	31	24.40	1.27	0.86	1.80
Ischemic Heart Disease	521	567.00	0.92	0.84	1.00
Cerebrovascular Disease	114	110.30	1.03	0.85	1.24
Dementia and Alzheimer’s Disease	50	42.40	1.18	0.88	1.55

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

Blank values are not calculated due to small numbers (<5 outcomes).

Table 5.

Standardized mortality ratios for males in Middlesex cohort.

	Middlesex									
	Male					Female				
Cause of Death	**Observed**	**Expected**	**SMR**	**95% CI lower**	**95% CI upper**	**Observed**	**Expected**	**SMR**	**95% CI lower**	**95% CI upper**
All Causes of Death	398	456.99	0.87	0.79	0.96	25	34.51	0.72	0.47	1.07
All Malignant Neoplasms	100	98.26	1.02	0.83	1.24	7	6.86	1.02	0.41	2.10
Cancer of Bronchus Trachea Lung	32	30.43	1.05	0.72	1.48	<5	1.38			
Cancer of Bone	<5	0.27				<5	0.01			
Cancer of Kidney	<5	2.31				<5	0.12			
Cancer of Biliary Passages and Liver	<5	2.16				<5	0.16			
Cancer of Large Intestine	6	8.83	0.68	0.25	1.48	<5	0.74			
Cancer of Central Nervous System	<5	2.04				<5	0.14			
Non-Hodgkin Lymphoma	<5	3.48				<5	0.28			
Leukemia and Aleukemia	6	4.02	1.49	0.55	3.25	<5	0.25			
Multiple Myeloma	<5	1.60				<5	0.12			
Nonmalignant Respiratory Disease	42	42.67	0.98	0.71	1.33	<5	3.21			
Nephritis and Nephrosis	6	5.87	1.02	0.37	2.22	<5	0.48			
Ischemic Heart Disease	91	138.25	0.66	0.53	0.81	7	7.92	0.88	0.35	1.82
Cerebrovascular Disease	18	30.46	0.59	0.35	0.93	<5	3.06			
Dementia and Alzheimer’s Disease	<5	11.32				<5	2.36			

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

Blank values are not calculated due to small numbers (<5 outcomes).

Table 6.

Standardized mortality ratios for males and females in Port Hope cohort.

	Port Hope									
	Male					Female				
Cause of Death	**Observed**	**Expected**	**SMR**	**95% CI lower**	**95% CI upper**	**Observed**	**Expected**	**SMR**	**95% CI lower**	**95% CI upper**
All Causes of Death	1,097	1,054.73	1.04	0.98	1.10	79	87.47	0.90	0.70	1.10
All Malignant Neoplasms	266	279.02	0.95	0.84	1.07	26	28.06	0.93	0.57	1.28
Cancer of Bronchus Trachea Lung	99	89.28	1.11	0.89	1.33	7	4.52	1.55	0.40	2.69
Cancer of Bone	<5	0.92				<5	0.07			
Cancer of Kidney	7	6.82	1.03	0.27	1.79	<5	0.47			
Cancer of Biliary Passages and Liver	<5	5.30				<5	0.61			
Cancer of Large Intestine	23	26.35	0.87	0.52	1.23	<5	3.16			
Cancer of Central Nervous System	5	7.58	0.66	0.08	1.23	<5	0.74			
Non-Hodgkin Lymphoma	7	8.54	0.82	0.21	1.43	<5	0.90			
Leukemia and Aleukemia	6	9.41	0.64	0.13	1.15	<5	0.85			
Multiple Myeloma	<5	4.30				<5	0.44			
Nonmalignant Respiratory Disease	92	79.46	1.16	0.92	1.39	<5	5.83			
Nephritis and Nephrosis	10	12.53	0.80	0.30	1.29	<5	1.22			
Ischemic Heart Disease	358	240.44	1.49	1.33	1.64	22	16.93	1.30	0.76	1.84
Cerebrovascular Disease	71	67.33	1.05	0.81	1.30	9	7.58	1.19	0.41	1.96
Dementia and Alzheimer’s Disease	5	5.13	0.98	0.12	1.83	<5	1.04			

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

Blank values are not calculated due to small numbers (<5 outcomes).

Table 7.

Standardized mortality ratios for males and females in the pooled cohort.

	Pooled									
	Male					Female				
Cause of Death	**Observed**	**Expected**	**SMR**	**95% CI lower**	**95% CI upper**	**Observed**	**Expected**	**SMR**	**95% CI lower**	**95% CI upper**
All Causes of Death	5,906	6,207.59	0.96	0.94	0.99	303	336.70	0.92	0.81	1.02
All Malignant Neoplasms	1,633	1,592.69	1.03	0.98	1.08	107	106.84	1.00	0.81	1.19
Cancer of Bronchus Trachea Lung	560	548.27	1.04	0.95	1.12	31	23.40	1.34	0.87	1.81
Cancer of Bone	<5	3.83				<5	0.21			
Cancer of Kidney	37	39.95	0.91	0.62	1.21	<5	1.78			
Cancer of Biliary Passages and Liver	29	36.42	0.83	0.53	1.13	<5	2.19			
Cancer of Large Intestine	139	138.74	1.00	0.83	1.16	10	9.84	1.09	0.41	1.76
Cancer of Central Nervous System	49	40.24	1.15	0.83	1.47	<5	2.78			
Non-Hodgkin Lymphoma	64	57.47	1.07	0.81	1.34	<5	3.74			
Leukemia and Aleukemia	66	59.84	1.05	0.80	1.31	<5	3.30			
Multiple Myeloma	29	26.27	1.11	0.71	1.52	<5	1.68			
Nonmalignant Respiratory Disease	503	533.90	0.95	0.87	1.04	22	27.38	0.86	0.50	1.22
Nephritis and Nephrosis	67	67.56	0.92	0.70	1.14	8	3.96	1.96	0.60	3.32
Ischemic Heart Disease	1,596	1,697.26	1.00	0.95	1.05	57	62.84	0.89	0.66	1.12
Cerebrovascular Disease	310	339.80	0.91	0.81	1.01	17	24.31	0.73	0.38	1.08
Dementia and Alzheimer’s Disease	101	85.63	1.29	1.04	1.54	6	7.07	0.98	0.20	1.76

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

Blank values are not calculated due to small numbers (<5 outcomes).