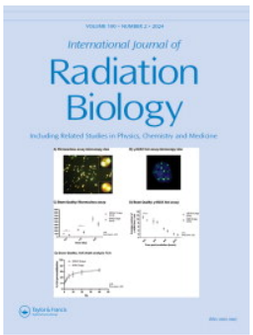

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ORIGINAL ARTICLE

Third mortality follow-up of the Mallinckrodt uranium processing workers, 1942–2019

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ABSTRACT

Introduction: Mallinckrodt Chemical Works was a uranium processing facility during the Manhattan Project from 1942 to 1966. Thousands of workers were exposed to low-dose-rates of ionizing radiation from external and internal sources. This third follow-up of 2514 White male employees updates cancer and noncancer mortality potentially associated with radiation and silica dust.

Materials and methods: Individual, annualized organ doses were estimated from film badge records (n monitored = 2514), occupational chest x-rays ($n = 2514$), uranium urinalysis ($n = 1868$), radium intake through radon breath measurements ($n = 487$), and radon ambient measurements ($n = 1356$). Silica dust exposure from pitchblende processing was estimated ($n = 1317$). Vital status and cause of death determination through 2019 relied upon the National Death Index and Social Security Administration Epidemiological Vital Status Service. The analysis included standardized mortality ratios (SMRs), Cox proportional hazards, and Poisson regression models.

Results: Vital status was confirmed for 99.4% of workers (84.0% deceased). For a dose weighting factor of 1 for intakes of uranium, radium, and radon decay products, the mean and median lung doses were 65.6 and 29.9 mGy, respectively. SMRs indicated a difference in health outcomes between salaried and hourly workers, and more brain cancer deaths than expected [SMR: 1.79; 95% confidence interval (CI): 1.14, 2.70]. No association was seen between radiation and lung cancer [hazard ratio (HR) at 100 mGy: 0.93; 95%CI: 0.78, 1.11]. The relationship between radiation and kidney cancer observed in the previous follow-up was maintained (HR at 100 mGy: 2.07; 95%CI: 1.12, 3.79). Cardiovascular disease (CVD) also increased significantly with heart dose (HR at 100 mGy: 1.11; 95%CI: 1.02, 1.21). Exposures to dust $\geq$23.6 mg/m^3-year were associated with nonmalignant kidney disease (NMKD) (HR: 3.02; 95%CI: 1.12, 8.16) and kidney cancer combined with NMKD (HR: 2.46; 95%CI: 1.04, 5.81), though without evidence of a dose-response per 100 mg/m^3-year.

Conclusions: This third follow-up of Mallinckrodt uranium processors reinforced the results of the previous studies. There was an excess of brain cancers compared with the US population, although no radiation dose-response was detected. The association between radiation and kidney cancer remained, though potentially due to few cases at higher doses. The association between levels of silica dust $\geq$23.6 mg/m^3-year and NMKD also remained. No association was observed between radiation and lung cancer. A positive dose-response was observed between radiation and CVD; however, this association may be confounded by smoking, which was unmeasured. Future work will pool these data with other uranium processing worker cohorts within the Million Person Study.

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Radiation; epidemiology; occupational exposures; uranium; uranium processing workers

Introduction

To develop the world's first nuclear weapons, the Manhattan Project in the United States required 40 tons of uranium oxide and 6 tons of uranium metal to initiate a sustainable, controlled nuclear reaction (USACE 1996). To create the needed uranium stockpile, Arthur Holly Compton, director of the Metallurgical Laboratory at the University of Chicago, successfully recruited the existing pharmaceutical company Mallinckrodt Chemical Works ('Mallinckrodt') in St. Louis, MO to the project in 1942 because of the company's ability

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to handle the volatile substances required for processing. Within eight months, Mallinckrodt produced the large amount of uranium needed for the world's first controlled nuclear reaction (USACE 1996). Mallinckrodt's St. Louis site continued to process uranium through 1957, at which time, the operation moved to Weldon Spring, MO until the plant was shut down in 1966 (Golden, Ellis, et al. 2022).

Two previous mortality studies have been conducted of the White male Mallinckrodt workers (Dupree-Ellis et al. 2000; Golden, Ellis, et al. 2022). The first followed workers through 1993 and only included external ionizing radiation exposures in the dosimetric calculations. The authors did not report significantly increased mortality in the cohort compared with the general US population from any specific outcome of death or from overall mortality, but they did detect a significantly increased dose response for kidney cancer [excess relative risk (ERR)/Sv: 10.5, 90% confidence interval (CI): 0.6, 57.4] (Dupree-Ellis et al. 2000). The authors opined that the elevated risk of kidney cancer may have resulted from chance, internal radiation, or chemical exposures not considered.

The second study increased follow-up through 2012, and they improved organ/tissue-specific dosimetry through biokinetic models for radium and uranium and incorporated occupational medical X-ray doses, doses received at other facilities, and radon-associated doses (ICRP) (ICRP 1994, 1995, 2006, 2010, 2017) (Ellis et al. 2018; Golden, Ellis, et al. 2022). Among all workers together, standardized mortality ratios (SMRs) were elevated for cancers of the brain and central nervous system (CNS). Golden, Ellis, et al. (2022) observed a significantly increased risk of kidney cancer with increasing kidney dose [hazard ratio (HR) at 100 mGy: 1.73; 95% CI: 1.07, 2.79]. They also observed an increased but not statistically significant risk for nonmalignant kidney disease (NMKD; HR: 1.30 at 100 mGy; 95% CI: 0.96, 1.76). (Golden, Ellis, et al. 2022). This study additionally conducted dose-response analyses for silica dust exposures on lung and kidney outcomes, which showed no association with selected outcomes for continuous dust exposure but did show increased risk of lung cancer and nonmalignant respiratory disease (NMRD) combined in a categorical analysis (Golden, Ellis, et al. 2022).

The current study is one of four uranium processing worker studies included in the broader Million Person Study (MPS) of radiation workers and veterans (Boice, Cohen, et al. 2022). This analysis enabled data preparation for the Mallinckrodt component of future pooled analyses of US and international uranium processing cohorts (Golden, Ellis, et al. 2021). Individually, this study expands the mortality follow-up of the Mallinckrodt cohort by an additional 7 years through 2019, which adds 218 deaths for a total of 2113 (84.0%) deceased cohort members. Small changes to dosimetry annualization are introduced that improve upon previous approaches. Similar to the previous study (Golden, Ellis, et al. 2022), we examine the associations between radiation and kidney cancer and NMKD using both underlying cause of death (UCOD) alone and underlying plus contributing causes of death (CCOD). We evaluate other organs and tissues of interest consistent with the studies referenced above. In addition to radiation, uranium and silica dusts were present in high amounts particularly in the 1940s and 50s (Eisenbud 1975), which could increase rates of cancer and noncancer kidney and lung disease (Golden, Ellis, et al. 2022). We conduct dust analyses for lung and kidney outcomes, both for UCOD and UCOD combined with CCOD.

Materials and methods

Human subjects research approval

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

Cohort definition

The study population was described previously by Golden et al. and Dupree-Ellis et al. (Dupree-Ellis et al. 2000; Golden, Ellis, et al. 2022). Briefly, we included 2514 White male employees who worked for at least 30 days between 1 January 1942 and 31 December 1966 at the Mallinckrodt Chemical Works Uranium Division in St. Louis and/or Weldon Springs, MO. Only White males were studied because work history records and interviews with former workers confirmed other groups were unlikely to have had meaningful external radiation exposures (Dupree-Ellis et al. 2000).

Job title was used to assign a pay code of either hourly or salaried as a measure of socioeconomic status (SES) using a job spreadsheet that incorporated identifying keywords such as 'manager' or 'rigger' (Golden, Ellis, et al. 2022).

Vital status and outcome determination

Vital status tracing methods and cause of death coding have been previously described (Dupree-Ellis et al. 2000; Golden, Ellis, et al. 2022; Mumma et al. 2022). Vital status was updated through 2019 using the Social Security Administration Epidemiological Vital Status Service, National Death Index (NDI), and state mortality files, confirming 387 (15.4%) of workers were alive and 2113 (84.0%) of workers were deceased at the end of 2019 (Table 1). The International Classification of Diseases (ICD) code from the ICD revision at time of death was available directly from the NDI for both UCOD and CCODs for deaths occurring in 1979 or later; death certificates were obtained for earlier deaths prior to 1979 so that a trained nosologist could determine the appropriate UCOD and CCODs. Cause of death was determined for 2098 (99.3%) of deceased workers; only 15 (0.7%) deceased employees did not have cause of death identified (Table 1). The 14 workers lost to follow-up (0.6%) were censored at their last known alive date (from tracing activities) or their last known day of work at Mallinckrodt.

Table 1. Demographic and occupational characteristics for 2514 Mallinckrodt Chemical Works workers employed for at least 30 days, 1942–1966 and followed through 2019.

	White Males	
	N	%
All employees	2,514	100.0
Pay code at hire		
Hourly	2,076	82.6
Salaried	438	17.4
Decade of birth		
1870–1889	16	0.6
1890–1900	108	4.3
1900–1909	264	10.5
1910–1919	619	24.6
1920–1929	858	34.1
1930–1939	561	22.3
1940–1949	88	3.5
Year of hire		
1942–1949	906	36.0
1950–1956	912	36.3
1957–1966	696	27.7
Years of follow-up		
<20	226	9.0
20–29	294	11.7
30–39	395	15.7
40–49	512	20.4
50–59	623	24.8
60–69	433	17.2
≥70	31	1.2
Vital status as of 12/31/2019		
Alive	387	15.4
Dead	2,113	84.0
Unconfirmed	14	0.6
Cause of death known		
Known	2,098	99.3
Unknown	15	0.7

Radiation dosimetry

Occupational radiation dosimetry methods for the Million Person Study have been described in detail (Boice, Cohen, et al. 2006; Boice, Leggett, et al. 2006; Boice et al. 2014; NCRP 2018) and were summarized in the last Mallinckrodt cohort assessment (Ellis et al. 2018; Golden, Ellis, et al. 2022). In brief, external dosimetry was ascertained from personal film badges at Mallinckrodt, occupation-required medical chest X-ray records, and individual film badge records from other workplaces prior to or following Mallinckrodt employment. Dose imputation was conducted from 1942 through the first half of 1945, when film badges were first assigned (Dupree-Ellis et al. 2000; Ellis et al. 2018). Organ and tissue-specific doses were calculated using the deep dose equivalent for film badges considering the photon energy of the radiation source, the organ/tissue-specific conversion coefficients from the photon energy (ICRP 2010), and the geometry of the exposure of the worker to the radiation source based on job groupings that estimated percentage of time the worker was oriented anteriorly or posteriorly to the source (Ellis et al. 2018; Golden, Ellis, et al. 2022). External thoracic lymph node dose was estimated indirectly as the red marrow photon dose plus the red marrow occupation-related medical X-ray dose divided by 0.22. The number of posterior-anterior (PA) and lateral (LAT) positions and associated dose equivalents for the organ/tissue of interest were considered when calculating these medical X-ray organ doses (Thomas 2011). Additional dosimetry information for 55 (2.2%) workers, 43 (1.7%) with additional doses greater than zero, was obtained from the Department of Energy (DOE) Radiation Exposure Monitoring System (REMS); the Oak Ridge Institute for Science and Education (ORISE)-maintained data from other DOE workplaces not available in REMS; the Nuclear Regulatory Commission Radiation Exposure Information and Reporting System (REIRS); the Landauer, Inc. dosimetry company; and the Nuclear Test Personnel Review Program for military veterans involved in the atmospheric nuclear tests between 1944 and 1962 or the Hiroshima and Nagasaki occupation forces. All photon organ-specific doses were annualized for each worker.

Internal dosimetry incorporated uranium urine samples (1868, 74.3% workers), radon breath measurements (487, 19.4% workers), and radon ambient measurements (1356, 53.9% workers). Radium body burdens were estimated from radon breath analysis, and lung dose associated with breathing radon and radon progeny decay was estimated from radon ambient measurements. Workers without records for uranium, radium, or radon decay product exposures were assumed unexposed. The dosimetric and biokinetic models used for organ/tissue dose estimation from internal radiation exposure were those published by the ICRP in publications 68, 71, 100, 116, and 137 (ICRP 1994, 1995, 2006, 2017). Thoracic lymph node dose was calculated based on ICRP models and dosimetry systems, using red bone marrow dose to approximate thoracic lymph node dose (ICRP 1994, 2006). Internal thoracic lymph node dose was estimated as 4 times the red marrow internal radium dose plus 9 times the red marrow internal uranium dose plus the red marrow internal radon dose. All uranium and ^{226}Ra intakes were assumed to have been of moderately soluble (Type M) material. As with external doses, all organ-specific internal doses were annualized for each worker.

Dust exposure

Uranium and silica dusts were present in high concentrations in Mallinckrodt, particularly in the 1940s-50s (Eisenbud 1975). Mallinckrodt employed general air and breathing zone sampling for dust frequently during the years 1942–1952, and worker-specific estimates were recorded and available in dust monitoring worksheets. Using these estimates, job-specific daily time-weighted average dust exposures were calculated for 1091 of the 1362 workers employed during these years. Dust exposures were imputed for an additional 267 workers during that period of time (Ellis et al. 2018; Golden, Ellis, et al. 2022). Therefore, a total 1358 of workers who worked between 1942 and 1952 had estimated dust exposure information, excluding 4 individuals with bad linkage to dust data and/or no job or building information useful for imputation. Cohort members hired after 1952 were considered unexposed; i.e. negligibly exposed.

Statistical methods

We used several methods to analyze the data. For all analyses, person-time accrual began 30 days after hire date and ended at date of death, age 95, date lost to follow-up, or 31 December 2019, whichever occurred first. The 15 employees who were deceased but had no known cause of death were flagged as having died and included only in the 'all causes of death' category.

We calculated SMRs as the ratio of observed deaths, using underlying cause of death (UCOD), to the expected number of deaths in the general US population based on rates for individuals of the same sex (male), race (White), and five-year age and calendar time category. *A priori* SMR outcomes (Supplemental Table 4) were selected from prior knowledge of uranium and radium deposition and possible health effects as mentioned in the introduction. As a sensitivity analysis, we calculated SMRs fully stratified by pay type.

We used Cox proportional hazards and Poisson regression models for internal dose-response analyses. Outcomes with at least 10 deaths in the Mallinckrodt cohort were selected from an *a priori* list compiled from observations in prior cohorts including Fernald Feed Materials Production Center, Mallinckrodt, and the Life Span Study of atomic bomb survivors (Supplemental Table 1) (Preston et al. 2007; Silver et al. 2013; Ozasa et al. 2017; Golden, Ellis, et al. 2022). We used UCOD for the main analyses, and we used UCOD plus CCOD for sensitivity analyses in case we missed cases when using UCOD alone. When workers had both lung cancer and NMRD as underlying or contributing causes, we only counted the lung cancer. Similarly, when workers had both kidney cancer and NMKD, we only counted the kidney cancer (Golden, Ellis, et al. 2022). Additionally, when cancer was the UCOD, cancers that were listed as CCOD were not included. ICD codes used for each dose-response outcome are shown in Supplemental Table 1.

We conducted Cox regression with attained age as the time scale to assess risks across categorical and continuous organ dose (per 100 mGy) (Cox 1972). We used the dose categories selected for the previous Mallinckrodt analysis: 0–<10, 10–<50, 50–<100, 100–<250, and ≥250 mGy, with the 0–<10 mGy group as the referent (Golden, Ellis, et al. 2022). When there were fewer than 5 deaths in a category, higher dose categories were collapsed until there were at least 5 deaths per category. Continuous and categorical dose were both considered time-dependent and represented the annualized cumulative dose to date from summed external and internal exposures. The main analyses used a dose weighting factor (DWF) of 1 for internal uranium and radium intakes and radon progeny; sensitivity analyses considered DWFs of 10 (5 for red bone marrow) and 20. An additional sensitivity analysis censored individuals at age 85 instead of 95 to assess a potential loss in mortality data quality at older ages (Boice et al. 2023). A 10-year lag (2-year lag for red bone marrow) was applied to cumulative dose to account for a potential latency period between accrual of dose and outcome occurrence. Cox regression and SMR analyses were conducted using Stata version 17 (StataCorp LLC, College Station, TX, USA).

Past models assessing radiation risk have frequently used Poisson regression to estimate ERRs. Although Cox and Poisson models produce comparable results (Golden, Cohen, et al. 2022), for ease of comparison to the literature, we conducted Poisson regression analyses to estimate ERRs at 100 mGy using the AMFIT program in Epicure, with person-time defined using calendar time (Preston et al. 2015). We used the DATAB program in Epicure to create person-tables tabulated over SES (salaried vs hourly), organ dose (23 categories with cut points at 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 200, 250, 300, 350, 400, 450, and 500 mGy), five year attained age group (14 categories with cut points at 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, and 80 years), five year age at hire group (8 categories with cut points at 20, 25, 30, 35, 40, 45, and 50 years), and five year calendar time group (16 categories with cut points at 1945, 1950, 1955, 1960, 1965, 1970, 1975, 1980, 1985, 1990, 1995, 2000, 2005, 2010, and 2015). Five-year follow-up time categories began on 1 January 1942, but included any doses received in other occupational roles prior to that date. The person-table allowed time-varying variables (i.e. attained age, organ dose, calendar time) to increase over time.

Two directed acyclic graphs (DAGs) were constructed to determine potential confounders to include in regression models. DAGs are visual representations of a potential relationship between a presumed cause and an outcome of interest. In a DAG, forward facing arrows symbolize a direct or indirect causal pathway between variables. Non-causal pathways show the effects of confounders and other relevant variables; confounding is demonstrated when a series of arrows can be followed either backwards or forwards from the exposure to the outcome without constituting a direct or indirect effect of the exposure on the outcome. These confounding paths are called 'backdoor paths' (Greenland et al. 1999; Glymour and Greenland 2008). DAGs are therefore useful as a variable selection tool that can visually show both causal and non-causal pathways of variables, and they have been shown to increase the accuracy of estimating exposure-outcome relationships in explanatory models compared with other variable selection methods (Weng et al. 2009). Figure 1(A) (DAG A) represents the potential effect of radiation on lung cancer, kidney cancer, NMRD, NMKD, and colorectal cancer; Figure 1(B) (DAG B) represents that effect on the other outcomes of interest. The only difference between these DAGs is that dust exposure is included in DAGs with lung, kidney, and colorectal outcomes. These DAGs were informed by past analyses of radiation workers including the previous Mallinckrodt analysis and a previous analysis of uranium processors at the Fernald Feed Materials Production Center (Silver et al. 2013; Golden, Ellis, et al. 2022). Colorectal cancer was included in the DAG with dust exposures based on an assessment of *a priori* non-radiological risks such as coal and general building dust included in the Supplementary Tables of the Fernald study (Silver et al. 2013). DAG B shows that all backdoor paths (i.e. confounding paths) can be closed by adjusting for job type and

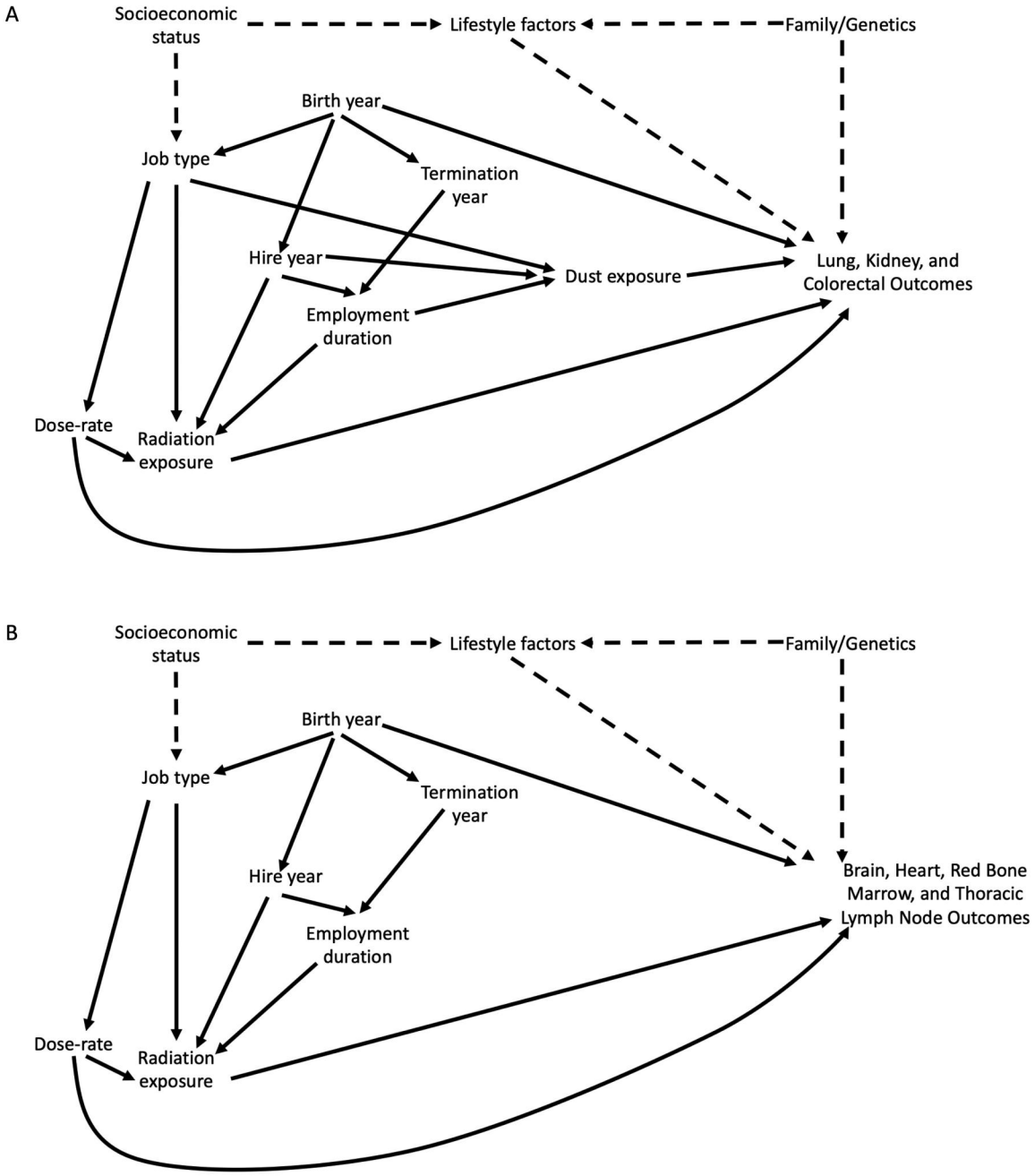

Figure 1. Directed acyclic graphs (DAGs) representing the effect of radiation exposure on outcomes of interest in Mallinckrodt Chemical Works employees. Variables at the base of solid lines represent measured or partially measured factors in each cohort; variables at the base of dashed lines represent unmeasured factors. DAG a presents lung, kidney, and colorectal outcomes. Colorectal outcomes were included in the DAG with dust exposures based on a previous analysis of coal and building dust in the Fernald cohort (Silver et al. 2013). DAG B presents all other outcomes of interest. DAG A includes dust exposures as a confounder between the potential radiation-outcome relationship, while DAG B does not include dust exposures.

year of birth. Accordingly, pay type and continuous year of birth (centered at 1920) were considered traditional confounders and included as covariates in all Cox and Poisson regression analyses. In DAG A, dust exposure must additionally be included in the model to close all backdoor paths. Therefore, in Cox and Poisson regression analyses with lung, kidney, and colorectal outcomes, dust exposure (per 100 mg/m^3-year) was included. Poisson analyses were additionally adjusted for log of age (centered at 50) because person-time in these models was defined using calendar time. All Poisson analyses adjusted for covariates in the baseline rate function. Race and sex were not considered as adjustment factors because the Mallinckrodt cohort includes only White males.

Analyses of the impact of cumulative dust exposure on lung cancer, NMRD, kidney cancer, and NMKD were also of interest. In analyses of colorectal cancer, we adjusted for dust exposure; however, we did not include colorectal cancer in dust analyses. Dust appeared to have no impact in models assessing radiation and colorectal cancer, and the colon was not considered an organ of interest for dust analyses in the past (Golden, Ellis, et al. 2022). Dust analyses were conducted using Cox regression, with cumulative dust exposure treated both categorically and continuously (per 100 mg/m^3-

year). As with dose, we used the dust tertile categories selected for the previous analysis of the Mallinckrodt cohort: 0–<3.77, 3.77–23.6, and ≥23.6 mg/m^3-year (Golden, Ellis, et al. 2022). Dust exposures were not lagged but did accumulate annually in the same manner as radiation doses. DAG A was still considered valid when dust was the exposure of interest rather than radiation; therefore, in all dust analyses, we adjusted for pay type, birth year (centered at 1920), and radiation dose (per 100 mGy) lagged 10 years. As per the radiation analyses, UCOD was used as the outcome for the main dust analysis, and a sensitivity analysis was conducted using UCOD plus CCOD.

We tested proportional hazards assumptions for all main Cox regression models using the Schoenfeld residuals test. When proportional hazards assumptions were not met for a particular variable, we simplified the variable if appropriate (e.g. categorical, dichotomous) or stratified baseline hazards by the variable.

Results

Mallinckrodt worker vital status is shown in Figure 2, and demographic information is shown in Table 1. The cohort consisted of 2514 White males, of whom 2076 (82.6%) were hourly workers. Fewer than one third were hired after the plant moved from St. Louis to Weldon Spring in 1957 (696, 27.7%). Mean duration of employment in the company's uranium division could not be calculated due to lack of information on employment termination date, but was expected to be identical to 5.2 years as reported in the previous follow-up because no additional employment time was accrued (Golden, Ellis, et al. 2022). Most workers were born between 1910 and 1940 (2038, 81.1%), and median age at start of follow-up was 28.4 years with a range from 16.2 to 65.4 years. Median length of follow-up was 46.5 years, with a range from 42 to 75 years. Vital status was known for 99.4% of the population, and cause of death was known for 99.3% of those who died.

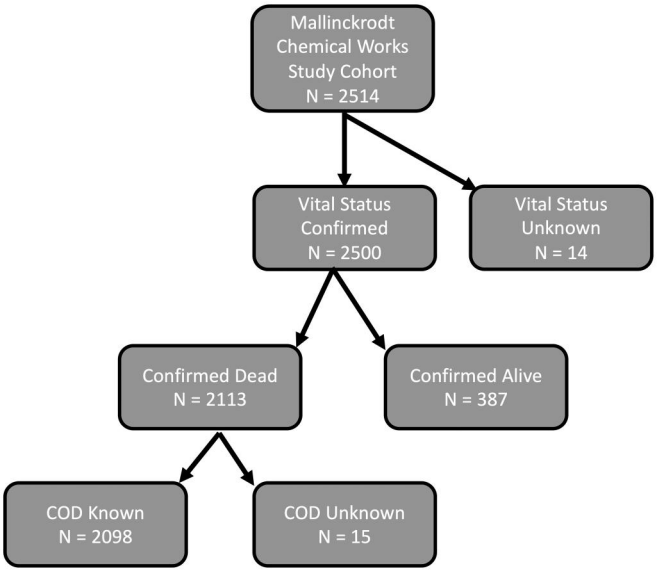

Figure 2. Cohort definition and vital status tracing for the main cohort of 2514 Mallinckrodt workers with at least 30 days of employment. COD denotes cause of death.

Radiation and dust monitoring status are shown in Supplemental Table 2. All employees had some measured radiation dose. The majority of the cohort had measurable external doses (2458, 97.8%). Internal measurements were available for 2160 (85.9%) cohort members, of whom 1855 had positive uranium assays, 423 had positive estimated radium doses >0 mGy (from radon breath measurements), and 1356 had estimated radon inhalation doses >0 mGy based on ambient radon measurements. Dust measurements or imputations were available for 1358 (54.0%) employees, of whom 1317 (97.0%) had a positive measurement.

Supplemental Table 3 shows dust exposure and organ dose descriptive statistics for job-related external dose (from Mallinckrodt and other facilities), occupation-related medical X-ray dose, internal dose, and total dose with DWFs of 1, 10, and 20 for uranium, radium, and radon decay products. For red bone marrow, DWFs of 1 and 5 are displayed. The greatest mean external (33.8 mGy), internal (21.7 mGy), and total dose occurred in the lungs (65.6 mGy with a DWF of 1; 474.4 weighted-mGy with a DWF of 20). With a DWF of 1, the heart had the second highest total dose (44.6 mGy) related to the mean medical x-ray dose of 11.1 mGy, but with a DWF of 10 or 20, thoracic lymph node dose was greater than heart dose (60.3 weighted-mGy and 80.2 weighted-mGy, respectively). Internal absorbed dose to the heart was trivial (mean: 0.1 mGy). Doses are slightly different than those reported in the previous analysis of this cohort; a coding error was found that duplicated doses for some workers in some years that was corrected for this analysis. While this correction does not particularly impact doses with a DWF of 1, lung and thoracic lymph node doses with DWFs of 10 and 20 are lower than in the previous analysis. For instance, the mean lung cancer dose with a DWF of 20 was 474.4 weighted-mGy in this analysis and 508.0 weighted-mGy in the previous analysis (Golden, Ellis, et al. 2022).

External analysis

SMRs for outcomes with at least 5 cases for the overall cohort, salaried employees, and hourly employees are presented in Supplemental Tables 4–6, respectively. Overall mortality was significantly decreased among all employees (SMR: 0.92; 95% CI: 0.88, 0.96, $n = 2113$) compared with the White male US population. Among salaried employees, mortality was much lower than the corresponding White male US population (SMR: 0.69; 95% CI: 0.62, 0.77, $n = 340$), while for hourly employees it was the same as the population (SMR: 0.99; 95% CI: 0.94, 1.03, $n = 1773$). This pattern of decreased mortality in salaried workers but similar-to-expected mortality among hourly workers was observed for many outcomes, including all heart disease, IHD, and smoking-related cancers. The only significantly elevated SMR among all employees occurred for brain and CNS cancers (SMR: 1.79; 95% CI: 1.14, 2.70, $n = 23$).

Table 2. Hazard ratios for selected causes of death for categorical and continuous organ-specific doses for 2514 Mallinckrodt employees employed for at least 30 days, 1942–1966 and followed through 2019.

	Number of workers	Number of cases	Categorical Hazard ratio	95% CI	*p* for categorical trend*	Cont. (at 100 mGy) Hazard ratio	95% CI
Lung cancer	2514	162				0.93	0.78, 1.11
0–<10 mGy [ref]	710	47					
10–<50 mGy	889	42	0.74	0.48, 1.12			
50–<100 mGy	421	38	1.15	0.75, 1.78			
100–<250 mGy	354	28	1.04	0.64, 1.70			
≥250 mGy	140	7	0.62	0.27, 1.40	0.99		
NMRD	2514	139				0.97	0.81, 1.17
0–<10 mGy [ref]	710	36					
10–<50 mGy	889	49	0.93	0.60, 1.43			
50–<100 mGy	421	29	0.88	0.54, 1.44			
100–<250 mGy	354	16	0.60	0.32, 1.11			
≥250 mGy	140	9	0.74	0.33, 1.64	0.15		
Lung cancer & NMRD	2514	301				0.95	0.84, 1.08
0–<10 mGy [ref]	710	83					
10–<50 mGy	889	91	0.83	0.61, 1.12			
50–<100 mGy	421	67	1.02	0.73, 1.41			
100–<250 mGy	354	44	0.82	0.56, 1.20			
≥250 mGy	140	16	0.69	0.39, 1.21	0.31		
Brain & CNS cancer	2514	23				0.65	0.20, 2.13
0–<10 mGy [ref]	1076	13					
≥10 mGy	1438	10	0.70	0.30, 1.64	0.41		
Kidney cancer	2514	16				2.07	1.12, 3.79
0–<10 mGy [ref]	892	5					
≥10 mGy	1622	11	1.37	0.46, 4.11	0.57		
NMKD	2514	36				1.21	0.70, 2.10
0–<10 mGy [ref]	892	9					
10–<50 mGy	1091	19	1.50	0.67, 3.34			
≥50 mGy	531	8	1.13	0.41, 3.12	0.73		
Kidney cancer & NMKD	2514	52				1.47	0.99, 2.20
0–<10 mGy [ref]	892	14					
10–<50 mGy	1091	27	1.45	0.76, 2.78			
50–<100 mGy	310	5	0.84	0.30, 2.41			
≥100 mGy	221	6	1.79	0.63, 5.11	0.48		
Colorectal cancer	2514	59				1.02	0.70, 1.48
0–<10 mGy [ref]	1162	25					
10–<50 mGy	860	20	0.97	0.54, 1.75			
50–<100 mGy	254	7	0.92	0.39, 2.19			
≥100 mGy	238	7	1.15	0.46, 2.87	0.89		
CVD	**2514**	716				1.11	1.02, 1.21
0–<10 mGy [ref]	815	179					
10–<50 mGy	1055	305	1.31	1.09, 1.58			
50–<100 mGy	361	117	1.12	0.88, 1.42			
100–<250 mGy	221	92	1.66	1.29, 2.15			
≥250 mGy	62	23	1.35	0.87, 2.08	0.00		
IHD	2514	563				1.10	1.00, 1.21
0–<10 mGy [ref]	815	137					
10–<50 mGy	1055	245	1.44	1.16, 1.78			
50–<100 mGy	361	89	1.15	0.87, 1.50			
100–<250 mGy	221	76	1.82	1.37, 2.41			
≥250 mGy	62	16	1.23	0.73, 2.07	0.01		
Dementia, Alzheimer's, Parkinson's, & MND	2514	102				0.87	0.57, 1.33
0–<10 mGy [ref]	1076	39					
10–<50 mGy	955	42	1.09	0.70, 1.70			
50–<100 mGy	262	15	1.36	0.73, 2.54			
≥100 mGy	221	6	0.83	0.34, 2.03	0.82		
Leukemia (excl. CLL)	2514	21				0.41	0.09, 1.91
0–<10 mGy [ref]	1144	11					
≥10 mGy	1370	10	0.73	0.30, 1.78	0.49		
Non–Hodgkin lymphoma	2514	25				1.36	0.87, 2.10
0–<10 mGy [ref]	849	6					
10–<50 mGy	1062	13	1.65	0.62, 4.39			
≥50 mGy	603	6	1.54	0.46, 5.15	0.44		

Cases reflect underlying cause of death only. All models estimated using Cox proportional hazards methods, adjusting for year of birth (continuous) and pay code (dichotomous). All analyses used a dose weighting factor of 1 for exposures to uranium, radium, and radon. Lung, NMRD, kidney, NMKD, and colorectal models additionally adjusted for cumulative dust exposure. Lung dose was used for lung cancer and nonmalignant respiratory disease; brain dose was used for brain cancer and dementia, Alzheimer's, Parkinson's, and MND; kidney dose was used for kidney cancer and nonmalignant kidney disease; colon dose was used for colorectal cancer; heart dose was used for all cardiovascular disease and ischemic heart disease; red marrow dose was used for non-CLL leukemia, and thoracic lymph node dose was used for non-Hodgkin lymphoma.

*Wald test for trend over dose category conducted using 1 degree of freedom.

Abbreviations: Cont: continuous; CI: confidence interval; NMRD: nonmalignant respiratory disease (excluding flu and pneumonia); CNS: central nervous system; NMKD: nonmalignant kidney disease; CVD: cardiovascular disease; IHD: ischemic heart disease; MND: motor neuron diseases; CLL: chronic lymphocytic leukemia.

Internal analysis

Results from categorical and continuous dose-response Cox analyses using UCOD as the outcome variable are shown in Table 2. Significantly elevated HRs occurred for kidney cancer, CVD, and IHD, and non-significantly elevated HRs were seen for NMKD, kidney cancer with NMKD, and non-Hodgkin lymphoma. No significantly negative HRs were observed. No trend with dose was observed for risk of either lung cancer (HR at 100 mGy: 0.93; 95% CI: 0.78, 1.11) or NMRD (HR at 100 mGy: 0.97; 95% CI: 0.81, 1.17), despite the highest doses overall occurring in the lung. On the other hand, both CVD and IHD had narrow CIs in the continuous analysis and significant tests for trend over increasing dose categories in the categorical analysis. Most CVD cases were IHD cases (563 of 716), and their HR and CIs were nearly identical (CVD HR at 100 mGy: 1.11; 95% CI: 1.02, 1.21; IHD HR at 100 mGy: 1.10; 95% CI: 1.00, 1.21). While the liver was a site of uranium and radon deposition, the number of deaths, only 6, precluded any meaningful analyses. Supplemental Tables 7 and 8 display the results from sensitivity analyses with DWFs of 10 (5 for red bone marrow) and 20 for alpha particle absorbed doses; results did not change appreciably with these different DWFs. The dose distributions changed only for those organs with meaningful deposition of alpha particle emitting nuclides, i.e. the lung and the thoracic lymph nodes. For the lung, the estimate of risk increased slightly whereas for NHL the estimate of risk decreased somewhat when the DWF was increased.

Supplemental Table 9 shows HRs from the main analysis when censoring individuals at age 85 instead of 95. Findings were very similar to the main analysis.

Supplemental Table 10 reports HRs from continuous Cox regression analyses for outcomes including both UCOD and CCOD. Compared with the main analysis based only on UCOD (Table 2), 205 NMRD and 108 NMKD CCOD outcomes were added, as well as an additional 58 dementia, Alzheimer's, Parkinson's, and MND outcomes. The HR estimate at 100 mGy for both NMRD and NMKD were essentially the same as in the UCOD-only analysis. The dementia, Alzheimer's, Parkinson's, and MND estimate increased non-significantly from 0.87 (95% CI: 0.57, 1.33) to 1.04 (95% CI: 0.79, 1.38).

ERRs from Poisson regression analyses are presented in Table 3. Due to a relatively small number of deaths over a long follow-up period, maximum likelihood estimate CIs were wide, and lower bounds frequently could not be estimated. Nonetheless, ERR estimates were generally consistent with HRs from Cox regression.

Table 4 reports HRs from Cox regression analyses for continuous and categorical dust exposure estimates using UCOD. The HR for all analyses at 100 mg/m^3-year was approximately 1, albeit with slightly elevated effect estimates for NMRD (HR: 1.10; 95% CI: 0.97, 1.25) and lung cancer with NMRD (HR: 1.08; 95% CI: 0.99, 1.17). However, categorical analyses indicated increased risk for kidney cancer combined with NMKD comparing dust exposures of greater than 23.6 mg/m^3-year with exposures less than 3.77 mg/m^3-year (HR for kidney cancer combined with NMKD: 2.46; 95% CI: 1.04, 5.81). NMKD on its own also had an elevated hazard at dust exposures greater than 23.6 mg/m^3-year (HR: 3.02; 95% CI: 1.12, 8.16), and the test for trend over increasing dust exposure categories was significant ($p = 0.04$), though the continuous model did not provide evidence for a dose-response. Supplemental Table 11 shows the results of continuous dust analyses including both UCOD and CCOD. HRs remained approximately 1 with CIs that overlapped unity.

Discussion

An additional seven years of observation were added for this third follow-up of 2514 White male Mallinckrodt Chemical Works employees who worked between 1942 and 1966. As

Table 3. Excess relative risks for selected causes of death using continuous organ doses for 2514 Mallinckrodt workers employed for at least 30 days, 1942–1966 and followed through 2019.

	Number of cases	ERR at 100 mGy	95% CI (MLE)	LRT *p*-value
Lung cancer	162	−0.10	< −0.16, 0.08	0.22
NMRD	139	0.01	< −0.13, 0.25	0.89
Lung cancer & NMRD	301	−0.04	< −0.13, 0.09	0.09
Brain & CNS cancer	23	−0.13	< −0.25, 0.87	0.49
Kidney cancer	16	1.60	< −0.39, 27.57	0.09
NMKD	36	0.34	< −0.57, 3.06	0.46
Kidney cancer & NMKD	52	0.60	< −0.22, 2.81	0.13
Colorectal cancer	59	0.16	< −0.39, 1.26	0.58
All CVD	716	0.14	0.02, 0.29	0.02
IHD	563	0.13	0.00, 0.31	0.06
Dementia, Alzheimer's, Parkinson's, and MND	102	−0.13	< −0.47, 0.34	0.41
Non-CLL leukemia	21	No convergence		
Non-Hodgkin lymphoma	25	0.79	< −0.30, 5.61	0.16

Cases reflect underlying cause of death only. All models estimated using Poisson regression, using a dose weighting factor of 1 for exposures to uranium and radon. Lung dose was used for lung cancer and nonmalignant respiratory disease, and heart dose was used for all cardiovascular disease and ischemic heart disease. All models adjusted using stratification in baseline rates for pay type, year of birth (centered at 1920), and log(age/50). Lung, NMRD, kidney models, NMKD, and colorectal models additionally adjusted for dust exposure in the log-linear term.

Abbreviations: CI: confidence interval; CLL: chronic lymphocytic leukemia; CNS: central nervous system; CVD: cardiovascular disease; ERR: excess relative risk; IHD: ischemic heart disease; LRT: Likelihood ratio test; MLE: maximum likelihood estimation; MND: motor neuron disease; NMKD: nonmalignant kidney disease; NMRD: nonmalignant respiratory disease.

Table 4. Hazard ratios for selected causes of death for categorical and continuous dust levels for 2514 Mallinckrodt employees employed for at least 30 days, 1942–1966 and followed through 2019.

	Number of cases	Categorical Hazard ratio	95% CI	p for categorical trend*	Cont. (at 100 mg/m^3-year) Hazard ratio	95% CI
Lung cancer	162				1.05	0.94, 1.18
0–<3.77 mg/m^3–year [ref]	91					
3.77–<23.61 mg/m^3–year	43	1.55	1.03, 2.33			
≥23.61 mg/m^3–year	28	1.06	0.62, 1.80	0.55		
NMRD	139				1.10	0.97, 1.25
0–<3.77 mg/m^3–year [ref]	87					
3.77–<23.61 mg/m^3–year	27	0.98	0.61, 1.58			
≥23.61 mg/m^3–year	25	1.03	0.57, 1.84	0.95		
Lung cancer & NMRD	301				1.08	0.99, 1.17
0–<3.77 mg/m^3–year	178					
3.77–<23.61 mg/m^3–year	70	1.27	0.93, 1.73			
≥23.61 mg/m^3–year	53	1.04	0.71, 1.55	0.61		
Kidney cancer	16				0.90	0.42, 1.92
0–<3.77 mg/m^3–year [ref]	11					
3.77–<23.61 mg/m^3–year	1	0.47	0.05, 4.07			
≥23.61 mg/m^3–year	4	1.53	0.27, 8.84	0.77		
NMKD	36				0.95	0.62, 1.46
0–<3.77 mg/m^3–year [ref]	20					
3.77–<23.61 mg/m^3–year	5	1.01	0.35, 2.91			
≥23.61 mg/m^3–year	11	3.02	1.12, 8.16	0.04		
Kidney cancer & NMKD	52				0.93	0.64, 1.36
0–<3.77 mg/m^3–year [ref]	31					
3.77–<23.61 mg/m^3–year	6	0.82	0.32, 2.10			
≥23.61 mg/m^3–year	15	2.46	1.04, 5.81	0.07		

Cases reflect underlying cause of death only. All models estimated using Cox proportional hazards methods, adjusting for year of birth (continuous), decade of hire (categorical), and radiation dose. Dust data were not lagged. Lung cancer and nonmalignant respiratory disease models adjusted for lung dose, and cardiovascular disease and ischemic heart disease models adjusted for heart dose.

*Wald test for trend over dust category conducted using 1 degree of freedom.

Abbreviations: Cont: continuous; CI: confidence interval; NMRD: nonmalignant respiratory disease (excluding flu and pneumonia); NMKD: nonmalignant kidney disease.

of 31 December 2019, most of the workers had died (84.0%) and cause of death was available for 99.3%. The previous study updated dosimetry to include organ/tissue-specific estimates of uranium, radium, and radon decay products, as well as quantifying dust exposure among employees (Golden, Ellis, et al. 2022). This study improved upon the methods for dose annualization and used DAGs to inform multivariable model building.

Across causes of death, SMRs were marginally lower than those reported in the previous assessment of the Mallinckrodt cohort, and interpretations were similar (Golden, Ellis, et al. 2022). The slight decrease in SMRs overall shows that individuals in this cohort continue to reflect the healthy worker effect and live longer on average compared with those of similar age and birth cohort in the general US population. This paper added to the previous analysis by evaluating pay type for all SMR outcomes. While salaried workers had lower mortality than the general population, hourly workers generally had population-equivalent mortality. Therefore, the observed healthy worker effect in the overall cohort appeared limited to the salaried workers, which is consistent with a sensitivity analysis in the previous follow-up (Golden, Ellis, et al. 2022). This difference in SMRs by pay code may be attributable to the lower SES of hourly compared with salaried workers, which implies pay type may be a reasonable surrogate for SES in this cohort. One exception to the pay code difference was brain and CNS cancers, which had an elevated SMR for both hourly and salaried workers (though was only significant for salaried workers). This finding might be due to radiation exposure including depositions of alpha-particle emitting radionuclides in the brain (Leggett et al. 2022), to unknown confounding carcinogens (e.g. workplace chemical exposures), or simply to chance when making so many multiple comparisons. The dose-response analyses do not support an associate between radiation dose to brain and brain cancer.

The elevated HR in radiation analyses for kidney cancer and NMKD at increasing doses in this cohort is consistent with the previous analysis but remains unexplained (Golden, Ellis, et al. 2022). Golden, Ellis, et al. (2022) have previously discussed these findings in detail. Briefly, most assessments of uranium processing workers have not reported an association between radiation exposure and kidney disease (UNSCEAR 2017), and 21 of the 22 kidney cancer deaths (UCOD and CCOD) were cancers of the kidney parenchyma (ICD-9 code 189.0), which has only been associated with radiation at high therapeutic doses (UNSCEAR 2008a; Ozasa et al. 2012; Golden, Ellis, et al. 2022). However, the International Agency for Research on Cancer (IARC) lists x- and gamma-radiation as two of only a few known causes of kidney cancer (IARC 2023). Additionally, there is some evidence of a kidney cancer dose-response following uranium exposure at gaseous diffusion plants, although the exposure profile is different from the present study (which also included radium) and results were not statistically significant (Yiin et al. 2017, 2018). It is unlikely renal toxicity from uranium intake caused kidney cancer mortality: only transient damage to the kidneys has been reported in studies to date, with no known deaths in humans (Kathren and Burklin 2008). Silica dust is associated with pitchblende exposures and could have caused mortality due to kidney disease; however, it has only been linked to NMKD and not

kidney cancer (Thun et al. 1985; Osorio et al. 1987; Calvert 1997; Rapiti et al. 1999; Steenland 2005; IARC 2012). Our dust analyses were mostly consistent with this previous finding: although the hazard ratios per increasing dust exposure levels were fairly flat for all outcomes, a significant elevation was found in the highest dust category versus the lowest for NMKD and for kidney cancer combined with NMKD. To reduce potential confounding, we adjusted for silica dust exposures in the radiation analyses. Therefore, it is plausible the association between radiation and kidney cancer in these analyses is causal. However, the dose-response is driven by three cases with doses over 100 mGy, and there is considerable uncertainty in these estimates.

Also consistent with the previous analysis is the lack of association found between radiation or dust exposure and lung cancer, NMRD, and their combination. Although studies of atomic bomb survivors exposed briefly to external radiation and uranium miners exposed to underground concentrations of radon and radon progeny have reported significantly increased lung cancer risks (Lubin et al. 1995; Cahoon et al. 2017; Zablotska, Richardson, et al. 2022), there have been inconsistent findings regarding radiation exposure and lung cancer risk in non-mining uranium workers and other nuclear workers. Non-significantly increased risks have been observed in a few uranium worker cohorts (Zablotska et al. 2013; Kreuzer et al. 2015), and significantly increased risks have been observed in the INWORKS pooled cohort of nuclear workers and the National Registry for Radiation Workers (NRRW), whose sub-cohorts overlap those of INWORKS to some extent (Muirhead et al. 2009; Richardson et al. 2018). In others, there have been no measurable dose responses between uranium dose and lung cancer (Grellier et al. 2017) or between radiation dose overall and lung cancer (Dupree-Ellis et al. 2000; Pinkerton et al. 2004; Boice et al. 2008, 2011; Silver et al. 2013; Leuraud et al. 2017; UNSCEAR 2017; Golden, Ellis, et al. 2022). Evidence is minimal for NMRD risk following radiation exposure (UNSCEAR 2017; Milder et al. 2022). There is evidence of silica dust exposure increasing risk of NMRD (Osorio et al. 1987; Calvert 1997; ASTDR 2019). However, there was no evidence in this follow-up of increased risk of lung cancer, NMRD, or their combination in either the categorical or the continuous dust analyses.

A small increase in risk of both CVD and IHD mortality was associated with increasing radiation dose to the heart primarily from external exposures. The magnitude of the IHD HR was similar in this analysis and the previous one, and the IHD and CVD HRs were nearly identical in the present analysis (the previous analysis did not conduct dose-response analyses for CVD). Canadian, French, and German uranium processing worker analyses have reported increases in risk similar to that of the present analysis (Guseva Canu et al. 2012; Zablotska et al. 2013, 2018; Zhivin et al. 2018), and similar effect estimates have been observed in the INWORKS cohort (Gillies et al. 2017). Two studies of uranium workers reported risks specifically associated with increasing internal uranium dose as well as external photon dose, though estimates were imprecise and not significant in each of these studies (Zhivin et al. 2018; Anderson et al. 2021). On the other hand, US cohorts of uranium workers have not historically reported increased CVD risk (Pinkerton et al. 2004; Boice et al. 2008; Silver et al. 2013), including several large MPS studies that have shown flat or even inverse dose-responses for IHD (Boice, Quinn, et al. 2022). Heart doses in Mallinckrodt were predominantly from photon exposures and not from internal uranium uptake; the mean heart dose from internal exposures was 0.07 mGy. Due to the low doses received in the heart and the lack of consistent evidence for an association of uranium with CVD risk (UNSCEAR 2017), the previous study of this cohort suggested SES or tobacco use may have confounded the dose-response relationship and resulted in the increased risk (Golden, Ellis, et al. 2022). In this follow-up study, we used DAG B to determine what adjustment factors to include in multivariable analyses. In this DAG, SES and family and genetic factors contribute to lifestyle factors such as smoking because smoking is a lifestyle factor impacted by genetics (Loukola et al. 2014), and therefore smoking is a confounder of the dose-response relationship through SES. Pay type has been shown to at least partially represent smoking use (Sorensen et al. 2004; Boice, Cohen, et al. 2006), and pay type as a surrogate for smoking is further supported by the differential smoking-related cancer SMRs in the salaried and hourly Mallinckrodt workers reported in Supplemental Tables 5 and 6. If confounding by smoking were not adequately controlled, a relationship would likely have been observed between radiation and NMRD, which includes highly smoking-relevant outcomes such as chronic obstructive pulmonary disease. No association was detected, suggesting confounding by smoking may be unlikely. Assuming confounding is adequately controlled, it is possible the relationship seen between radiation dose to the heart and CVD represents a true increase in risk following radiation exposure, as seen in studies of atomic bomb survivors, many occupational cohorts, and comprehensive systematic reviews, albeit frequently at higher doses and with some inconsistencies (Little et al. 2012; Little 2016; Ozasa et al. 2017; Little et al. 2023; Schöllnberger et al. 2023).

The previous analysis of the Mallinckrodt cohort reported an ERR/100 mGy for non-CLL leukemia that was not significantly elevated (Golden, Ellis, et al. 2022). The Poisson model for non-CLL leukemia in our analysis, however, did not converge in part because of small numbers (only 21 deaths) and a narrow dose range, and we were unable to compute an ERR/100 mGy. We were able to compute the HR at 100 mGy based on the Cox model, in part because parameter estimates for an exponential model (Cox) are generally known to have better asymptotic properties than those for a comparative linear model (Poisson) as well as a more robust convergence process. Indeed, after re-running this analysis using the Peanuts module of Epicure (Cox regression), we found similar results to the previous study albeit with a slightly wider CI (ERR at 100 mGy: −0.15; Wald 95% CI: −0.85, 0.40). Nonetheless, our results confirm the previous analysis in finding no association between

radiation dose to red bone marrow and leukemia excluding CLL.

Although the CI was wide, a nonsignificant increased HR at 100 mGy was observed for non-Hodgkin lymphoma among Mallinckrodt workers, which was similar to the HR seen in the last follow-up (Golden, Ellis, et al. 2022).

None of the additional Cox or Poisson analyses indicated a dose-response relationship. Brain and CNS cancer were of interest because of past associations reported in studies of atomic bomb survivors and patients who received therapeutic radiation (UNSCEAR 2008b; Brenner et al. 2020). Neurodegenerative outcomes including dementia, Alzheimer's disease, Parkinson's disease, and MND were of interest because of evidence that uranium and radium can deposit in the brain (Avtandilashvili et al. 2015; Dinocourt et al. 2015; UNSCEAR 2017; NCRP 2022). While there is increasing evidence of a radiation relationship with Parkinson's disease, only limited evidence exists for dementia, Alzheimer's, and MND in humans (Yamada et al. 2009; Boice, Quinn, et al. 2022; Zablotska, Zupunski, et al. 2023; Srivastava et al. 2023). In this study, brain and CNS cancers had an elevated SMR, but internal analyses showed no association with radiation. Similarly, a non-significantly decreased dose response was observed for the combined neurodegenerative conditions when using UCOD that increased to a flat dose-response when including CCOD. Although not evidence for increased risk of neurodegenerative disorders in uranium workers, this change in effect magnitude with CCOD reflects a potential problem of death certificate misclassification seen in epidemiological studies (Linet et al. 2020), particularly with regards to neurodegenerative diseases such as Parkinson's (Moscovich et al. 2017; Harding et al. 2019; Shi and Counsell 2021). Others, however, have reported that Parkinson's as a CCOD may only reflect serious cases (Mappin-Kasirer et al. 2020), and therefore using CCOD may distort a true mortality dose-response. Future studies should consider using both underlying causes of death alone and underlying with contributing cause of deaths to avoid under-ascertainment of these diseases. Better yet would be studies of the incidence of Parkinson's disease as envisioned in the MPS (Boice, Quinn, et al. 2022; Dauer et al. 2023).

This study was subject to a number of limitations, such as incomplete dose and dust measurements. External photon measurements were limited to years in which film badges were assigned, with imputation required for 20.8% of working years at Mallinckrodt (Ellis et al. 2018). Additionally, dust measurements were only available for a set number of years, and no imputation was conducted outside of that time frame. It is likely employees had some dust exposure after 1952, even if it was considerably reduced. Assumptions regarding aerosol size and residence time in the lungs were required for internal dosimetry, which may have had inaccuracies. Additionally, concomitant radionuclide intakes (e.g. actinium, protactinium) could not be estimated. Residual uncontrolled confounding was likely present from SES and other behavioral, lifestyle, and medical factors. Although unmeasured, chemical exposures were recorded at Mallinckrodt, such as nitric acid, hydrofluoric acid, and sulfuric acid, which may also have contributed to confounding for some outcomes. Likewise, smoking information was not available. Results from this study may have been confounded by the inability to control for these factors; namely, the positive dose-response seen for CVD may have decreased to some extent with better control for smoking (Muirhead et al. 2009; Golden, Ellis, et al. 2022). Smoking is also an important effect modifier for lung cancer in studies of atomic bomb survivors; an effect modification analysis with smoking would likely contribute information to our lung cancer and possibly to our NMRD findings (Furukawa et al. 2010; Cahoon et al. 2017). Further, the relatively small cohort size combined with a limited dose range diminished power to detect associations in this cohort (Golden, Ellis, et al. 2022). Past analyses of gaseous diffusion workers and nuclear fuel cycle workers have shown nonsignificant relationships between internal dose from uranium and both kidney cancer and CVD that we were unable to assess due to the low power in our cohort (Zhivin et al. 2016; Yiin et al. 2017, 2018; Anderson et al. 2021). Relatively low total radiation doses and narrow dose ranges, combined with small numbers of deaths for cancer sites thought to be associated with radiation, limited the power to detect effects in this population.

Strengths of this study include the long duration of follow-up, with over 99% confirmation of both mortality and cause of death. Thorough dosimetry was conducted for a wide range of radiation sources, including occupational photon exposures from Mallinckrodt and other workplaces, occupation-required medical X-rays, and internal intakes of uranium, radium, and radon decay products. Organ/tissue-specific absorbed doses were estimated from these data, contributing to more relevant dose-response analyses than had film badge dose [i.e. personal dose equivalent, $H_p(10)$] been used alone. The DAG-based approach to modeling provided an *a priori* method for variable selection in multivariable analyses, showing that dust might be considered as a confounding factor in radiation dose-response analyses with lung, kidney, and colorectal outcomes, and that both pay type (salaried vs hourly) and birth year are necessary to limit confounding due to SES and technological improvements (e.g. in radiation protection and medicine) over time.

Conclusions

This third follow-up of 2514 White male Mallinckrodt workers employed from 1942 to 1966 provided up to 77 years of study and 111,230 person-years of observation. The workers received exposures to job-related external photon radiation; occupation-required medical X-rays; internal alpha particle radiation from intakes of uranium, radium, and radon decay products; and silica dust inhalation. An increased SMR was observed for brain and CNS cancer in both salaried and hourly workers, though no radiation dose-response was detected. Consistent with previous analyses of this cohort, no indication of a lung cancer dose response was seen in this follow-up period although missing information on

smoking precludes definitive conclusions. Leukemia other than CLL similarly was not increased. Increased risks for kidney cancer, NMKD, CVD, and IHD were seen with increasing radiation dose. Kidney disease was associated with silica dust exposure in categorical models. This cohort will contribute to future pooled analyses of uranium processing workers (Golden, Ellis, et al. 2021), where these risks will be assessed with additional power to detect associations.

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Disclosure statement

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Data availability statement

The datasets generated during and/or analyzed during the current study will be available in the Comprehensive Epidemiologic Data Resource (CEDR) repository, https://oriseapps.orau.gov/cedr/.

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