ORIGINAL ARTICLE

Mortality and ionising radiation exposures among workers employed at the Fernald Feed Materials Production Center (1951–1985)

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ABSTRACT

Objectives To examine mortality patterns and dose-response relations between ionising radiation and mortality outcomes of a priori interest in 6409 uranium workers employed for at least 30 days (1951–1985), and followed through 2004.

Methods Cohort mortality was evaluated through standardised mortality ratios (SMR). Linear excess relative risk (ERR) regression models examined associations between cause-specific mortality and exposures to internal ionising radiation from uranium deposition, external gamma and x-ray radiation, and radon decay products, while adjusting for non-radiologic covariates.

Results Person-years at risk totalled 236 568 (mean follow-up 37 years), and 43% of the cohort had died. All-cause mortality was below expectation only in salaried workers. Cancer mortality was significantly elevated in hourly males, primarily from excess lung cancer (SMR=1.25, 95% CI 1.09 to 1.42). Cancer mortality in salaried males was near expectation, but lymphohaematopoietic malignancies were significantly elevated (SMR=1.52, 95% CI 1.06 to 2.12). A positive dose-response relation was observed for intestinal cancer, with a significant elevation in the highest internal organ dose category and a significant dose-response with organ dose from internal uranium deposition (ERR=1.5 per 100 μGy, 95% CI 0.12 to 4.1).

Conclusions A healthy worker effect was observed only in salaried workers. Hourly workers had excess cancer mortality compared with the US population, although there was little evidence of a dose-response trend for any cancer evaluated except intestinal cancer. The association between non-malignant respiratory disease and radiation dose observed in previous studies was not apparent, possibly due to improved exposure assessment, different outcome groupings, and extended follow-up.

What this paper adds

- Information on the risks from occupational exposures to uranium is limited.
- Earlier studies of workers exposed to soluble and insoluble uranium compounds while employed at the Fernald Feed Materials Production Center in Ohio, United States, were limited by short follow-up periods and the exclusion of female and non-Caucasian employees.
- We expanded the cohort to include all workers employed for 30 days or more (1951–1985) and extended vital status follow-up by 15 years.
- Consistent with previous studies, the healthy worker effect was observed only for salaried employees, and elevated all-cancer mortality was observed only for hourly employees.
- In regression analyses evaluating the relations between increasing dose from assimilated uranium (as estimated from available bioassay information) and mortality from outcomes of a priori interest, we only observed significant elevations in the risk of intestinal cancer.

INTRODUCTION

The Fernald Feed Materials Production Center (FMPC) operated as a United States Department of Energy (US DOE) uranium processing facility from 1951 through 1989. The facility's primary mission was to produce high-purity uranium metal necessary for nuclear weapons production and other defence missions. Operations involving storage and handling of radioactive materials began in 1951. By 1954, all main production plants, comprising a wide array of uranium fuel cycle chemical and metallurgical processes were fully operational. In addition to ionising radiation hazards typically associated with uranium production, subgroups of FMPC employees were potentially exposed to other sources, such as radon, thorium and low-level transuranic contamination. Non-radiologic hazards, such as acid gases (acids), solvents and dusts, were also present. The facility was operated by National Lead of Ohio (NLO) from 1951 to 1985. Production then slowed, and ceased in 1989.

Canu *et al*[1], in an extensive literature review, found limited evidence of increased mortality from respiratory, lymphatic and haematopoietic cancers in workers occupationally exposed to uranium at a variety of facilities, including FMPC, and cited inadequate assessment of internal dose from uranium as a limitation of these studies. Several studies have examined health outcomes specifically among Caucasian male FMPC workers.[2–5] These

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studies suggest increased risk of chronic non-malignant respiratory disease (NMRD) in relation to internal, and possibly external, radiation dose, and present equivocal results with respect to the relations between radiation dose and mortality from cancers of the lung, kidney, bladder and digestive tract.

The current study expanded the FMPC cohort to include all workers, added 15 years of vital status follow-up, and recalculated internal organ dose. Malignant and non-malignant respiratory and renal disease, cancers of the bladder, stomach and intestine (small intestine and colon, but not rectum), and lymphohaematopoietic cancers were of a priori interest based on the findings of previous studies of uranium production plant workers.[1–6] Idiopathic pulmonary fibrosis (IPF) was examined based on previous findings of elevated risks associated with exposures to densely ionising radiation and metal dusts.[7–10] Associations between these outcomes and internal ionising radiation from uranium deposition, gamma and x-ray radiation from external sources, and radon progeny were evaluated while adjusting for non-radiologic covariates.

METHODS

Cohort development

This research complied with the requirements of the Federal Policy for Protection of Human Subjects (10CFR745 or, where applicable, 45CFR46), and was reviewed by the National Institute for Occupational Safety and Health (NIOSH) Human Subjects Review Board to ensure that the rights and welfare of study subjects were protected.

The study population consisted of NLO workers employed 30 days or more at the FMPC from 1951 to 1985. The minimum employment criterion was used to prevent inclusion of occasional visitors and prospective hires who never actually worked at the site. The roster was developed from three sources of records, prioritised as follows: (1) the NLO Employee Database; (2) data from the original cohort assembled by Cragle *et al*[3] and expanded by NIOSH using FMPC employment records and (3) the site's Health Physics Information System (HIS-20). Information on site, medical and security databases was used to resolve inconsistencies among the primary sources. Work histories included employment dates, job title, organisation and building assignments.

Ascertainment of vital status

Vital status was previously determined by Cragle *et al*[3] through 1989, using searches conducted by the Social Security Administration (SSA), Pension Benefits, Inc, and the National Death Index (NDI). Death certificates for that study were retrieved and coded to the eighth revision of the International Classification of Diseases (ICD), Adapted for Use in the United States.

For the current study, mortality was updated through 2004 by searches of the SSA's death master file and NDI; cause of death coding was to the ICD revision in effect at time of death. Underlying cause of death was used for all analyses.

Exposure assessment

The exposure assessment is described in detail in Anderson *et al*[11] and briefly here. The exposure assessors were blinded to case status.

Radiation exposures

Ionising radiation exposure from uranium and its by-products was of primary interest; the critical source term and exposure pathway varied by outcome. Multiple radiation sources were examined; because of known differences in biological effectiveness between radiation types, heterogeneous sources of ionising radiation exposure were not combined into a single exposure metric.

The current effort improved on the internal dose assessments used by previous studies of this cohort[2–5] by using urine uranium concentration data from 1952 forward, and the latest uranium biokinetic and dosimetric models in combination with the most recent respiratory tract model to estimate exposures from internally deposited uranium compounds.[12 13] The Internal Dose Evaluation Program (InDEP, SENES Oak Ridge, Inc, Center for Risk Analysis, Oak Ridge, Tennessee, USA) was used to calculate individual intakes and corresponding organ absorbed doses (hereafter referred to as 'organ dose') from urine bioassay obtained from HIS-20. Five target organs were selected for internal dose assessment based on the outcomes of a priori interest: lung, pancreas, lower large intestine, kidney and red bone marrow. Due to the large number of individual dose assessments required, some outcomes were analysed using doses calculated for similar or nearby target tissue. All intakes were assumed due to chronic inhalation of a moderately insoluble natural uranium aerosol, with activity median aerodynamic diameter of 10 μm.

External radiation exposure was quantified primarily using penetrating whole-body 'dose' values reported in HIS-20. Most penetrating exposure resulted from photons of energies between 30 and 1000 keV and anterior-to-posterior, or isotropic exposures geometries. Under these conditions, the recorded values provided reasonable approximations of whole-body equivalent dose.[14 15] It was further assumed that the equivalent dose approximated tissue-absorbed dose in this analysis, although body attenuation would result in a moderate reduction in absorbed dose to 'deep' tissues (eg, red bone marrow). Exposure data were available in annual increments prior to 1981 and monthly thereafter. Information on external dose accrued at other facilities was abstracted from HIS-20 and the DOE Radiation Exposure Monitoring System. When records from these two sources conflicted, HIS-20 data were prioritised.

Radon decay products (RDP) exposure was estimated based on an exposure matrix developed and described by Hornung *et al*[16] that used employment information to spatially and temporally locate workers in a matrix of RDP concentrations estimated by dispersion modelling. The estimation process included a Gaussian plume model and opportunistic dosimetry methods using legacy glass to develop radon source terms and estimate transport. Briefly, working-level months (WLM) were assigned to each worker based on his or her proximity over time to radium-bearing source terms.

Thorium exposures were qualitatively assessed by examination of work assignments, site process records and available air and bioassay data. Dichotomous assignments indicating exposure potentials were made for each work history segment, based on whether the subject's work assignment (dates, job and location) coincided with thorium activities as evidenced by process records and limited monitoring data.

Non-radiologic exposures

All division, department, plant/building and job title combinations were enumerated and related to qualitative exposure potentials. Site process records, available industrial hygiene monitoring records and institutional knowledge were used to evaluate exposure potentials (ever/never) for chemicals potentially related to outcomes of a priori interest: asbestos, coal dust, acids (hydrofluoric acid, nitric acid, nitrogen dioxide), machining fluids (also called cutting fluids), miscellaneous dusts,

miscellaneous laboratory chemicals, trichloroethylene, other solvents, vehicle exhausts and welding fumes (see online supplementary table S1).[17 18]

Socioeconomic status

Pay code (salaried vs hourly) was of interest because of risk differences seen in earlier studies, and because it can be associated with lifestyle factors, like smoking, that can confound exposure-response relations.[19–21] Pay code was noted on most work history records in the employee database. The earliest pay code encountered in each worker's employment history was used; only 5.7% of workers changed pay status while employed at Fernald.

Statistical methods

Mortality was evaluated using the NIOSH Life Table Analysis System (LTAS.NET.[22] Person-years at risk (PYAR) began on the latest of on 1 January 1951, the date cohort inclusion criteria (including 30 days of employment) were met, and the comparison rate file begin date. PYAR ended at the earlier of date of death and the study end date. A small number of workers lost to follow-up (n=30) were assumed to be alive at study end. PYAR were stratified by gender, race, age (in 5-year categories) and calendar year (in 5-year categories). US mortality rates (1940–2004) were used to estimate the expected numbers of deaths for all causes, all cancers and 92 cause-of-death categories.[23] The standardised mortality ratio (SMR) was calculated as the ratio of the observed to the total number of expected deaths. Confidence limits were estimated based on a Poisson distribution for the observed deaths,[24] with exact limits for outcomes with 10 or fewer deaths. Several outcomes for which rates were not available in the 1940–2004 file (IPF,[25] asbestosis and silicosis) were evaluated using mortality rates from the US population (1960–2004). Since the FMPC was located in Ohio, mortality rates for Ohio (1960–2004) were also used. Directly standardised rate ratios (SRR) were used to ascertain differences by pay code.

Regression models were used to evaluate the relations between exposure and mortality from specific causes, adjusting for potential confounders. Only Caucasian males were included in these models because there were few workers (and deaths) from other demographic groups. Risk sets were defined using incidence density matching based on attained age.[26] Within risk sets, exposure data were truncated at a cut-off date defined as the death date for cases and the date the worker reached the case's death age for controls. Model parameters were estimated using conditional logistic regression based on the full risk sets, which is equivalent to a Cox proportional hazards analysis.[27]

For each outcome, regression models estimated the excess relative risk (ERR) associated with the radiologic exposures. Linear ERR models, which are often used to describe the effects of low-dose ionising radiation exposure, were preferred. Dose-response was further explored using categorical and natural (restricted cubic) spline models. Exposure categories (5 for outcomes with at least 50 cases; 3 otherwise) were based on the exposure distribution among the cases. Spline models placed knots at the 10th, 50th and 90th percentiles of the exposure distribution across all risk sets. Model fit was assessed using Akaike's Information Criterion (AIC).[28] All models were adjusted for birth year (using natural splines[29]) and pay code.

Univariate models examined radiation terms separately. To allow independent evaluation of the effects of each type of radiation exposure, multivariable models included terms for both organ dose and external radiation dose (and RDP exposure in WLM for models of lung cancer and chronic obstructive pulmonary disease (COPD)). For example, a multivariable ERR model (adjusted for pay code and birth year) was given by:

$$h(t|X) = h_o(t)e^{(\alpha 1(\text{paycode=salary})+\alpha_2(\text{birthyear}-1930)+\alpha_2(\text{birth year spline term}))} \times (1+\beta(\text{organ dose}(t))+\gamma(\text{external dose}(t)) + \delta(\text{RDP exposure}(t)))$$

where t represents attained age, h_0 (t) is the (unspecified) baseline hazard function (for unexposed hourly workers born in 1930), α_1 is the log HR for salaried workers relative to hourly workers, α_2 and α_3 are spline parameters for birth year, and β, γ, and δ are the (age-, birth year- and pay code-adjusted) ERRs associated with one unit of organ dose, external dose and RDP exposure, respectively. In some models, the ERR was inestimable because either the dose parameter fell on the parameter space boundary (−1/maximum dose), or the model lacked convergence. In the former, the parameter estimate was assigned the lowest value that generated a non-negative HR, and a lower bound was not estimated; in the latter, no solution was reported. Consequently, log-linear models, which approximate linear models in the low-dose range, were considered and HRs reported. Because continuous linear trend estimators can be sensitive to outlying observations when exposure distributions are highly skewed,[30] we assessed the impact of outliers using trimmed analyses that excluded risk set members with at least one exposure exceeding the exposure-specific 99th percentile.

For models of non-leukaemia outcomes, exposure lag periods of 0, 10 and 15 years were evaluated; however, when the number of cases was sparse, only a 10-year lag was evaluated because of the biological implausibility of a zero lag and the diminishing number of cases available at greater lags. For leukaemia models, chronic lymphocytic leukaemia was excluded because of possible differences in aetiology and latency and lags of 0, 2 and 5 years were assessed; however, deaths from lymphatic leukaemia not further specified were retained. The lag period was applied to all exposures in the model.

Assessment of selected potential non-radiologic confounders was included in univariate and multivariable modelling for outcomes with at least 30 cases (see online supplementary table S1). For agents to which at least 25% of the cohort was exposed, exposure duration to the agent was trichotomised as unexposed, low-duration (≤median exposure duration for exposed workers), and high-duration (the remainder of exposed workers). Less common exposures were dichotomised (ever/never to the cut-off date). Thorium, with only 150 workers assessed as exposed, was evaluated for potential confounding only in models of lung cancer and COPD. Potential confounders were added to the log-linear term in the base model one at a time, and confounding was evaluated by comparing dose coefficients from models including and excluding the potential confounding variables. Any variable resulting in more than a 20% change in the parameter estimate for one of the radiation terms was considered a confounder and retained in the model.

All regression modelling was performed using SAS (SAS Institute Inc, Cary, North Carolina, USA) based on recently published methods for modifying the Cox proportional hazards regression model to fit a linear ERR model using the NLMIXED procedure.[31 32] Finally, diagnostics were run for lung cancer and COPD to assess collinearity among the three radiation terms (organ, external and RDP).

RESULTS

The study cohort comprised 6409 workers employed by NLO for at least 30 days (table 1). Collectively, there were 236 568 PYAR, for an average follow-up of 37 years. The cohort was largely male (85%) and Caucasian (95%). Workers' mean age at first hire was 30.1 years. Results excluded six workers for whom pay code could not be determined. Although 40% of all workers were salaried, this ranged from 83% of Caucasian women to 20% of non-Caucasian men. Through 2004, a total of 2771 workers (43%) had died, with 860 of these deaths due to malignancies. Organ dose, external dose and RDP exposure distributions for the full cohort are summarised in table 1 and described in-depth in Anderson *et al*.[11] A total of 348 workers had dose records at other facilities; the collective dose added from this offsite component was 1.29 person-Gy.

Mortality results

For the full cohort, all-cause mortality was below expectation (SMR 0.91, 95% CI 0.88 to 0.95, n=2771) based on US population rates. However, all-cancer mortality was slightly elevated (SMR 1.06, 95% CI 0.99 to 1.14, n=860). All-cause and all-cancer mortality differed by race, sex and pay code (see online supplementary table S2). As there were few deaths among non-Caucasian workers, cause-specific mortality is reported by sex and pay code only (a priori outcomes, table 2; all outcomes, see online supplementary tables S3 and S4). Results were similar when Ohio referent rates were used (data not shown).

Males

Among hourly males (see online supplementary table S3), all-cause mortality was as expected (SMR=0.98, 95% CI 0.94 to 1.03, n=1892) but mortality from all cancers combined was elevated (SMR=1.15, 95% CI 1.06 to 1.24, n=575), primarily due to excess mortality from cancers of the lung (SMR=1.25, 95% CI 1.09 to 1.42, n=223) and digestive tract (SMR=1.21, 95% CI 1.03 to 1.43, n=148).

In salaried males, all-cause mortality was below expectation (SMR=0.77, 95% CI 0.71 to 0.83, n=678), with significant deficits in mortality from lung cancer (SMR=0.62, 95% CI 0.46 to 0.81, n=52), heart disease (SMR=0.69, 95% CI 0.60 to 0.79, n=209), and COPD (SMR=0.43, 95% CI 0.25 to 0.69, n=17). Mortality from all cancers was not elevated (SMR=0.90, 95% CI 0.79 to 1.03, n=211); however, mortality from lymphatic and haematopoietic tissue neoplasms was significantly elevated (SMR=1.52, 95% CI 1.06 to 2.12, n=35). Stomach cancer was not significantly elevated (SMR=1.77, 95% CI 0.91 to 3.09, n=12).

The SMR for the category encompassing cancers of the 'peritoneum and other and unspecified digestive tract' was significantly elevated among male workers, with nine deaths (SMR=3.51, 95% CI 1.61 to 6.67). Four of these were from peritoneal/retroperitoneal cancers and the remainder comprised miscellaneous digestive malignancies. Only one case of mesothelioma and one case of asbestosis were observed, both among hourly workers.

SRRs were significantly elevated for hourly compared with salaried males for a few causes of a priori interest: all cancers (SRR=1.29, 95% CI 1.10 to 1.52), including lung cancer (SRR=2.05, 95% CI 1.51 to 2.79); and COPD (SRR=2.37, 95% CI 1.40 to 4.00). Non-significantly elevated SRRs of at least 1.5 were seen for several a priori outcomes including Hodgkin's disease and malignancies of the oesophagus, intestine, peritoneum and unspecified parts of the digestive system, and kidney, as well as a group of outcomes comprising pneumoconiosis and miscellaneous respiratory diseases. A non-significant twofold elevation was seen for brain cancer, not an outcome of a priori interest. Among non-cancer outcomes, the SRRs for ischaemic heart disease (SRR=1.38, 95% CI 1.16 to 1.64) and accidents (SRR=1.84, 95% CI 1.20 to 2.82) were significantly elevated.

Table 1 Cohort demographics and exposures by sex, race, and pay code*

	Male				Female			
	Caucasian†		Non-Caucasian		Caucasian‡		Non-Caucasian	
Metric	Hourly	Salaried	Hourly	Salaried	Hourly	Salaried	Hourly	Salaried
Number	3440	1771	193	47	153	731	30	38
Person-years at risk	125338	67615	6337	1487	4641	28839	912	1150
Years of follow-up (mean, SD)	36.4 (13.1)	38.2 (12.4)	32.8 (12.2)	31.6 (9.7)	30.3 (11.9)	39.4 (12.3)	30.4 (6.6)	30.3 (7.1)
Percent deceased	52.8	37.9	38.3	12.8	28.8	19.6	13.3	15.8
Mean year of birth	1928	1931	1935	1946	1938	1936	1951	1947
Mean year of hire	1959	1960	1965	1971	1970	1963	1973	1973
Age at hire (mean, SD)	31.6 (8.6)	29.4 (8.9)	29.7 (9.4)	25.2 (5.9)	32.1 (9.9)	26.3 (7.8)	22.0 (7.1)	25.9 (9.5)
Years of employment (mean, SD)	10.2 (9.9)	8.53 (9.9)	10.2 (9.4)	4.69 (6.4)	8.48 (8.6)	7.19 (8.8)	2.64 (5.4)	3.42 (5.1)
Number of bioassay samples per worker (mean, SD)	52.1 (57.1)	18.3 (25.3)	50.0 (50.4)	12.7 (21.4)	39.4 (51.9)	10.5 (16.8)	9.5 (20.3)	5.4 (10.7)
Mean cumulative organ dose (μGy)								
Lung	1552	388	965	138	67.9	296	34.5	154
Kidney	133	33.9	80.6	12.1	5.97	26.3	3.02	13.5
Red bone marrow	45.4	11.9	27.1	4.15	2.13	9.63	1.00	4.64
Lower large intestine	16.3	4.45	9.84	1.48	0.81	3.80	0.33	1.64
Pancreas	9.36	2.73	5.54	0.861	0.51	2.49	0.18	0.96
Mean cumulative external dose (mGy)	20.7	3.05	13.6	2.16	5.51	0.53	0.77	0.21
Mean cumulative RDP (working level months)	39.1	12.0	19.4	6.46	2.91	4.59	3.54	0.81

*Workers employed at the Fernald Feed Materials Production Center at least 30 days between 1951–1985.
†Results exclude four Caucasian males with unknown pay code (two of these were known to be deceased).
‡Results exclude two Caucasian females with unknown pay code (both were deceased).
FMPC, Feed Materials Production Center; PYAR, Person-years at risk; RDP, radon decay products.

Table 2 Observed deaths and standardised mortality ratios for all causes, all cancers and a priori outcomes by sex and pay code*, Fernald Feed Materials Production Center Cohort, 1951–2004†

	Males (n=5451)						Females (n=952)					
	Hourly (n=3633)			Salaried (n=1818)			Hourly (n=183)			Salaried (n=769)		
Cause‡	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All causes	1892	0.98	0.94 to 1.03	678	0.77	0.71 to 0.83	48	1.05	0.77 to 1.39	149	0.83	0.70 to 0.98
All cancers	575	1.15	1.06 to 1.24	211	0.90	0.79 to 1.03	13	1.05	0.56 to 1.79	59	0.97	0.74 to 1.25
MN stomach	18	1.15	0.68 to 1.82	12	1.77	0.91 to 3.09	0	0.00	0.00 to 13.2	2	1.93	0.23 to 6.96
MN intestine	50	1.16	0.86 to 1.53	14	0.71	0.39 to 1.18	2	1.66	0.20 to 6.00	4	0.82	0.22 to 2.09
MN trachea, bronchus, lung	223	1.25	1.09 to 1.42	52	0.62	0.46 to 0.81	5	2.01	0.65 to 4.68	17	1.13	0.66 to 1.81
MN kidney	12	0.95	0.49 to 1.66	3	0.49	0.10 to 1.44	0	0.00	0.00 to 18.2	3	2.99	0.62 to 8.75
MN bladder and other urinary organs	15	1.15	0.64 to 1.89	6	1.00	0.37 to 2.17	0	0.00	0.00 to 23.7	3	5.13	1.06 to 15.0
Non-Hodgkin's lymphoma	18	0.97	0.58 to 1.54	12	1.33	0.69 to 2.32	2	4.41	0.53 to 16.0	0	0.00	0.00 to 1.71
Hodgkin's disease	5	1.81	0.59 to 4.22	1	0.76	0.02 to 4.23	0	0.00	0.00 to 70.1	0	0.00	0.00 to 13.0
Leukaemia	17	0.92	0.54 to 1.48	15	1.71	0.95 to 2.81	0	0.00	0.00 to 9.23	3	1.61	0.33 to 4.70
Multiple myeloma	12	1.44	0.75 to 2.52	7	1.82	0.73 to 3.75	0	0.00	0.00 to 17.7	0	0.00	0.00 to 3.96
Chronic obstructive pulmonary disease	87	1.01	0.81 to 1.25	17	0.43	0.25 to 0.69	0	0.00	0.00 to 2.15	11	1.29	0.64 to 2.31
Idiopathic pulmonary fibrosis	11	1.77	0.88 to 3.17	3	1.01	0.21 to 2.94	1	7.40	0.19 to 41.2	0	0.00	0.00 to 6.10
Chronic and unspecified nephritis and renal failure	13	0.83	0.44 to 1.41	6	0.85	0.31 to 1.85	1	2.29	0.06 to 12.8	1	0.61	0.02 to 3.41

*Four men and two women of unknown paycode were excluded.
†Based on US population rates 1940–2004 for all outcomes except idiopathic pulmonary fibrosis (based on US population rates 1960–2004).
‡ICD codes were mapped to cause of death categories as described by Robinson and colleagues[23] and as described on the NIOSH website (http://www.cdc.gov/niosh/ltas/rates.html).
COPD, chronic obstructive pulmonary disease; FMPC, Feed Materials Production Center; IPF, Idiopathic pulmonary fibrosis; MN, malignant neoplasm; Obs, observed number of deaths; SMR, standardised mortality ratio.

Females

Among hourly females (see online supplementary table S4), all-cause mortality (SMR=1.05, 95% CI 0.77 to 1.39, n=48) and all-cancer mortality were as expected (SMR=1.05, 95% CI 0.56 to 1.79, n=13). In salaried females, all-cause mortality was reduced (SMR=0.83, 95% CI 0.70 to 0.98, n=149), mostly from a significant deficit of heart disease (SMR=0.55, 95% CI 0.35 to 0.82, n=24); mortality from cancers of the urinary tract was the only cause of a priori interest that was significantly elevated (SMR=3.78, 95% CI 1.39 to 8.23, n=6), with three deaths from kidney cancer and three from bladder cancer. Sparse deaths among hourly females precluded statistical comparison of standardised rates between hourly and salaried females.

Regression analyses

For each outcome, the lagged distributions of radiation metrics within risk sets are provided in online supplementary table S5. Untrimmed distributions were highly skewed. Maximum values were reduced in 1% trimmed risk sets, but the trimmed distributions remained quite skewed. Diagnostics indicated a low degree of collinearity among the three radiation terms for both lung cancer (maximum condition index 2.76) and COPD (maximum condition index 2.82).

For COPD and intestinal cancer, models with 10-year lags fit best, as determined by the AIC (data not shown). For lung cancer, the unlagged model fits slightly better than the model with a 10-year lag; however, a 10-year lag was selected because of biological plausibility. Similarly, leukaemia exposures were lagged 2 years, although unlagged models had a slightly improved fit.

Estimates from the univariate and multivariable regression models are displayed in tables 3 and 4, respectively, for outcomes with at least 25 cases, and in online supplementary tables S6 and S7, respectively, for other outcomes of a priori interest. Point estimates from dose-response analyses were scaled according to the observed range of internal exposure for cases and controls; therefore, effects from internal deposition are reported in units smaller than those used for external radiation.

The categorical, spline and linear (untrimmed) models for outcomes with at least 50 cases are graphically displayed in figure 1. Graphs were truncated at the 95th percentile because data were sparse above that point, and distributions highly right-skewed.

In the categorical univariate and multivariable models, only for intestinal cancer did any organ dose category differ significantly from baseline, with an elevation in the highest category (>36 μGy). This finding was echoed by a positive, significant relation between organ dose and intestinal cancer in the univariate linear model (ERR=1.5 per 100 μGy, 95% CI 0.12 to 4.1); no solution was found for the multivariable linear model, but a positive, significant relation was seen for the multivariable log-linear model. Although no strong monotonic trend was evident, the linear model provided a reasonably good fit (evaluated using the AIC) for the relation between intestinal cancer and organ dose (figure 1). No other significant positive associations were observed. The only other statistically significant result was a negative relation between leukaemia and organ dose that was limited to the univariate and multivariable log-linear models.

A number of potential confounders were examined in the linear models. For both lung cancer and COPD, exposure to acids (trichotomised duration of exposure to hydrofluoric acid, nitric acid and/or nitrogen dioxide) was a confounder. Both trichloroethylene and laboratory chemicals were confounders for non-Hodgkin's lymphoma; as the model would not converge with both terms included, trichloroethylene, which had the larger effect, was retained. No other non-radiologic exposure met the threshold for inclusion in the final models.

DISCUSSION

This update of the FMPC cohort extended follow-up and improved exposure characterisation. Overall mortality outcomes

Table 3 Summary of univariate Cox proportional hazards regression models for Caucasian male Fernald workers (mortality through 2004) for outcomes of a priori interest with at least 25 cases

	Organ dose (μGy)*				External dose (mGy)				Radon decay products (WLM)			
Outcome	**Model†**		**EST**	**PL 95% CI‡**	**Model**		**EST**	**PL 95% CI‡**	**Model**		**EST**	**PL 95% CI‡**
MN lung	U1	Unexposed (25)§	Ref		U1	Unexposed (94)	Ref		U1	0.0–0.51 (53)	Ref	
		>0.0–14 (61)	0.047	(−0.33 to 0.68)		>0.0–2.0 (31)	−0.047	(−0.36 to 0.39)		>0.51–5.4 (54)	−0.21	(−0.45 to 0.13)
		>14–170 (61)	−0.16	(−0.46 to 0.34)		>2.0–9.0 (54)	−0.13	(−0.37 to 0.19)		>5.4–20 (54)	−0.33	(−0.53 to −0.034)
		>170–1500 (61)	−0.34	(−0.58 to 0.053)		>9.0–40 (46)	−0.26	(−0.48 to 0.049)		>20–42 (55)	−0.22	(−0.46 to 0.13)
		>1500 (61)	−0.094	(−0.42 to 0.45)		>40 (44)	0.019	(−0.30 to 0.47)		>42 (53)	−0.25	(−0.49 to 0.089)
	U2	ERR (per 100 μGy)	0.0021	(−0.00062 to 0.0064)	U2	ERR (per 100 mGy)	0.17	(−0.18 to 0.68)	U2	ERR (per 10 WLM)	−0.0061	(−0.013 to 0.0046)
	U3	ERR (per 100 μGy), 1%¶	0.00087	(−0.0034 to 0.0071)	U3	ERR (per 100 mGy), 1%	0.12	(−0.32 to 0.74)	U3	ERR (per 10 WLM), 1%	0.00062	(−0.011 to 0.020)
	U4	HR (at 100 μGy)	1.002	(0.999 to 1.005)	U4	HR (at 100 mGy)	1.2	(0.79 to 1.7)	U4	HR (at 10 WLM)	0.993	(0.98 to 1.005)
COPD	U1	0.0–24 (20)	Ref		U1	Unexposed (27)	Ref		U1	0.0–4.3 (20)	Ref	
		>24–150 (21)	0.64	(−0.092 to 2.0)		>0.0–2.0 (12)	0.20	(−0.40 to 1.3)		>4.3–14 (20)	0.67	(−0.084 to 2.1)
		>150–650 (21)	0.46	(−0.20 to 1.7)		>2.0–16 (24)	−0.094	(−0.48 to 0.57)		>14–30 (21)	0.60	(−0.12 to 1.9)
		>650–2100 (19)	0.58	(−0.15 to 1.9)		>16–49 (20)	0.15	(−0.38 to 1.1)		>30–45 (21)	1.1	(0.16 to 2.9)
		>2100 (21)	0.54	(−0.17 to 1.9)		>49 (19)	0.62	(−0.15 to 2.0)		>45 (20)	0.42	(−0.23 to 1.6)
	U2	ERR (per 100 μGy)	−0.0018	(NE to 0.0027)	U2	ERR (per 100 mGy)	0.48	(−0.17 to 1.6)	U2	ERR (per 10 WLM)	−0.011	(−0.013 to 0.0068)
	U3	ERR (per 100 μGy), 1%	0.0015	(−0.0056 to 0.014)	U3	ERR (per 100 mGy), 1%	0.58	(−0.24 to 2.0)	U3	ERR (per 10 WLM), 1%	−0.017	(−0.017 to 0.012)
	U4	HR (at 100 μGy)	0.997	(0.99 to 1.002)	U4	HR (per 100 mGy)	1.4	(0.79 to 2.3)	U4	HR (at 10 WLM)	0.989	(0.96 to 1.01)
MN intestine	U1	0.0–0.01 (12)	Ref		U1	Unexposed (19)	Ref					
		>0.01–0.98 (12)	−0.28	(−0.68 to 0.65)		>0.0–3.0 (9)	−0.077	(−0.60 to 1.0)				
		>0.98–4.4 (13)	0.21	(−0.46 to 1.8)		>3.0–9.1 (12)	0.36	(−0.37 to 1.8)				
		>4.4–36 (11)	−0.22	(−0.67 to 0.86)		>9.1–28 (10)	0.28	(−0.44 to 1.8)				
		>36 (13)	1.7	(0.16 to 5.3)		>28 (11)	0.13	(−0.50 to 1.5)				
	U2	ERR (per 100 μGy)	1.5	(0.12 to 4.1)	U2	ERR (per 100 mGy)	−0.31	(NE to 0.82)				
	U3	ERR (per 100 μGy), 1%	2.1	(0.13 to 5.7)	U3	ERR (per 100 mGy), 1%	−0.30	(−0.75 to 1.3)				
	U4	HR (at 100 μGy)	1.7	(0.92 to 2.7)	U4	HR (at 100 mGy)	0.74	(0.23 to 1.8)				
MN pancreas	U1	0.0–0.13 (14)	Ref		U1	0.0–<2.0 (20)	Ref					
		>0.13–1.5 (13)	0.49	(−0.32 to 2.2)		2.0–<7.0 (11)	0.37	(−0.37 to 1.8)				
		>1.5 (14)	0.25	(−0.44 to 1.9)		≥7.0 (1)	−0.31	(−0.70 to 0.50)				
	U2	ERR (per 100 μGy)	−0.42	(NE to 2.6)	U2	ERR (per 100 mGy)	−0.31	(NE to 0.82)				
	U3	ERR (per 100 μGy), 1%	0.87	(−1.6 to 8.5)	U3	ERR (per 100 mGy), 1%	−0.78	(NE to 0.39)				
	U4	HR (at 100 μGy)	0.5	(0.011 to 3.2)	U4	HR (at 100 mGy)	0.57	(0.10 to 1.8)				
NHL	U1	0.0–0.26 (9)	Ref		U1	Unexposed (10)	Ref					
		>0.26–7.2 (10)	0.25	(−0.52 to 2.4)		>0.0–9.9 (10)	0.16	(−0.55 to 2.1)				
		>7.2 (11)	0.32	(−0.52 to 2.7)		>9.9 (10)	0.39	(−0.52 to 3.1)				
	U2	ERR (per 100 μGy)	0.33	(−0.065 to 1.6)	U2	ERR (per 100 mGy)	0.0010	(−0.31 to 3.0)				
	U3	ERR (per 100 μGy), 1%	−0.24	(−0.25 to 1.2)	U3	ERR (per 100 mGy), 1%	−0.78	(NE to 2.6)				
	U4	HR (at 100 μGy)	1.2	(0.88 to 1.5)	U4	HR (at 100 mGy), 1%	1.0	(0.19 to 3.0)				
Leukaemia (excluding CLL)	U1	0.0–0.22 (10)	Ref		U1	Unexposed (14)	Ref					
		>0.22–2.8 (8)	−0.042	(−0.64 to 1.5)		>0.0–7.0 (7)	−0.50	(−0.81 to 0.24)				
		>2.8 (10)	−0.38	(−0.76 to 0.64)		>7.0 (7)	−0.42	(−0.80 to 0.55)				
	U2	ERR (per 100 μGy)	−0.061	(NE to 0.25)	U2	ERR (per 100 mGy)	0.33	(−0.27 to 2.8)				
	U3	ERR (per 100 μGy), 1%	−0.23	(NE to 0.26)	U3	ERR (per 100 mGy), 1%	−0.72	(NE to 1.4)				

Continued

Table 3 Continued

Outcome	Organ dose (μGy)*				External dose (mGy)				Radon decay products (WLM)			
	Model†		EST	PL 95% CI‡	Model		EST	PL 95% CI‡	Model		EST	PL 95% CI‡
	U4	HR (at 100 μGy)	0.27	(0.022 to 0.96)	U4	HR (at 100 mGy)	1.8	(0.54 to 4.2)				
MN stomach	U1	0.0–0.05 (9)	Ref		U1	0.0–1.0 (9)	Ref					
		>0.05–6.2 (9)	−0.32	(−0.75 to 0.87)		>1.0–3.0 (8)	1.2	(−0.19 to 5.2)				
		>6.2 (10)	0.65	(−0.41 to 3.8)		>3.0 (11)	0.33	(−0.50 to 2.7)				
	U2	ERR (per 100 μGy)	0.38	(−0.20 to 5.7)	U2	ERR (per 100 mGy)	1.1	(−0.31 to 5.9)				
	U3	ERR (per 100 μGy), 1%	−0.80	(NE to 7.6)	U3	ERR (per 100 mGy), 1%	0.39	(−0.81 to 5.1)				
	U4	HR (at 100 μGy)	1.2	(0.21 to 2.6)	U4	HR (at 100 mGy)	1.8	(0.45 to 4.7)				

*Target organ varied by outcome (see online supplementary table S5); estimates of cumulative exposure incorporate a 10-year lag period for non-leukaemia outcomes (2-year lag period for leukaemia excluding CLL).
†All univariate models are adjusted for pay code (hourly/salaried) and birth year (spline terms) and consider one radiologic exposure at a time. Model U_1 is linear ERR with a categorical treatment of exposure; model U_2 is linear ERR with continuous treatment of exposure; model U_3 is like model U_2, but incorporates a 1% trim; and model U_4 is log-linear with a continuous treatment of exposure. Models of lung cancer and COPD are additionally adjusted for occupational exposure to acids (external dose model only); the organ dose model of NHL is additionally adjusted for occupational exposure to trichloroethylene.
‡Profile likelihood 95% CIs.
§Number of cases in parentheses.
¶1% denotes a 1% trimmed model which excluded risk sets for which the case exceeded the 99th percentile and all controls that exceed the 99th percentile.
CLL, chronic lymphocytic leukaemia; COPD, chronic obstructive pulmonary disease; ERR, excess relative risk; EST, estimate; MN, malignant neoplasm; NE, not estimable; NHL, non-Hodgkin's lymphoma; WLM, working-level months.

among Caucasian males, including differences by pay code, are generally consistent with those observed previously by Cragle *et al*.[3] As in that study, all-cause mortality results suggest a healthy worker effect only in salaried employees and elevated all-cancer SMR only in hourly employees. The previously observed stomach cancer excess in salaried males has lessened somewhat and is no longer statistically significant, while the statistically significant lung cancer excess in hourly employees persists. A new finding is excess mortality from malignancies of the peritoneum and other and unspecified digestive tract sites. No worker dying from these causes held a job judged to have potential for asbestos exposure, and only single deaths from asbestosis and mesothelioma were reported.

Previous studies of FMPC employees were restricted to Caucasian males. Notable among females in this study was a statistically significant excess of urinary tract malignancies in salaried workers, but deaths were too sparse to permit further analysis. Results of regression analyses differ from those of previous examinations of Caucasian male FMPC workers. The positive, statistically significant relations between lung cancer and external and internal radiation dose seen in some previous studies were not observed here. Although the updated SMR for lung cancer was significantly elevated among hourly Caucasian males, no significant relations were seen between this outcome and any radiation metric. Cragle *et al*[3] suggested that the relation between lung cancer and external dose category observed in the previous study was driven by excesses in the highest-dose categories. In the current study, no trend was observed, and although the highest category had a positive parameter estimate, the effect was far from statistically significant.

Previous studies also tended to group mortality outcomes because of case scarcity, some grouping NMRD very broadly[2 3] and others grouping most lymphohaematopoietic malignancies together for exposure-response analyses.[4 5] The current study used smaller outcome groupings for greater aetiologic homogeneity, but continued to be hampered by case scarcity in relation to the number of exposures considered. Chronic NMRD was previously associated with internal dose; in the current study, COPD, the largest subgroup of NMRD deaths, was not significantly associated with any type of radiation exposure.

A new finding of interest was the relation between intestinal cancer and organ dose. Although no non-radiologic exposure was retained in the models of intestinal cancer and organ dose, incomplete control for confounding by dust or some other chemical cannot be ruled out.

The negative, significant relation between leukaemia and organ dose, not observed in previous studies of this workforce, reflects clustering of cases in the very low-dose region and the preponderance of controls in the right tail. Dose uncertainty resulting in exposure misclassification may explain the observed risk attenuation. Another potential explanation is induction of leukaemia at lower doses among susceptible individuals.[33–35]

A number of factors likely contributed to between-study discrepancies. The additional follow-up ascertained new cases for many outcomes, including 155 additional lung cancer deaths in Caucasian males; differences in dose distribution among these new cases compared with those ascertained earlier could alter exposure-response results. Furthermore, exposures were evaluated differently in this study, with incorporation of external dose accrued at other facilities and assessment of absorbed organ dose. One previous study considered trichotomised estimated exposures to uranium dust.[2] Another used estimated lung burdens from in vivo (whole-body counting) data and

Table 4 Summary of multivariable Cox proportional hazards categorical regression modelling for Caucasian male Fernald workers (mortality through 2004) for outcomes of a priori interest with at least 25 cases

Outcome	Model	Organ dose (μGy)*	EST	PL 95% CI‡	External dose (mGy)	EST	PL 95% CI‡	Radon decay products (WLM)	EST	PL 95% CI‡
MN lung	M1	Unexposed	Ref		Unexposed	Ref		0.0–0.51	Ref	
		>0.0–14	0.17	(−0.25 to 0.79)	>0.0–2.0	−0.049	(−0.36 to 0.34)	>0.51–5.4	−0.22	(−0.55 to 0.13)
		>14–170	0.0056	(−0.38 to 0.56)	>2.0–9.0	−0.018	(−0.31 to 0.30)	>5.4–20	−0.30	(−0.70 to 0.089)
		>170–1500	−0.21	(−0.54 to 0.25)	>9.0–40	−0.084	(−0.41 to 0.24)	>20–42	−0.16	(−0.58 to 0.29)
		>1500	0.027	(−0.37 to 0.60)	>40	0.17	(−0.19 to 0.64)	>42	−0.16	(−0.60 to 0.31)
	M2	ERR (per 100 μGy)	0.0022	(−0.00093 to 0.0070)	ERR (per 100 mGy)	0.13	(−0.26 to 0.68)	ERR (per 10 WLM)	−0.0070	(−0.013 to 0.0068)
	M3	ERR (per 100 μGy), 1%§	0.00064	(−0.0044 to 0.0073)	ERR (per 100 mGy), 1%	0.093	(−0.40 to 0.75)	ERR (per 10 WLM), 1%	0.0011	(−0.012 to 0.023)
	M4	HR (at 100 μGy)	1.002	(0.999 to 1.005)	HR (at 100 mGy)	1.2	(0.76 to 1.7)	HR (at 10 WLM)	0.999	(0.97 to 1.004)
COPD	M1	0.0–24	Ref		Unexposed	Ref		0.0–4.3	Ref	
		>24–150	0.71	(−0.36 to 2.6)	>0.0–2.0	0.21	(−0.69 to 2.2)	>4.3–14	0.57	(−0.47 to 2.4)
		>150–650	0.50	(−0.40 to 2.3)	>2.0–16	−0.50	(−0.96 to 0.51)	>14–30	0.46	(−0.44 to 2.2)
		>650–2100	0.70	(−0.37 to 2.8)	>16–49	−0.31	(−1.5 to 1.2)	>30–45	1.3	(−0.05 to 4.1)
		>2100	0.36	(−0.87 to 2.3)	>49	0.58	(−0.89 to 3.2)	>45	0.36	(−0.64 to 2.1)
	M2	ERR (per 100 μGy)	−0.0062	(−0.0065 to 0.000062)	ERR (per 100 mGy)	0.54	(−0.00025 to 1.4)	ERR (per 10 WLM)	−0.018	(−0.018 to 0.0027)
	M3	ERR (per 100 μGy), 1%	0.000048	(−0.0059 to 0.013)	ERR (per 100 mGy), 1%	0.45	(−0.38 to 1.8)	ERR (per 10 WLM), 1%	−0.017	(−0.017 to 0.025)
	M4	HR (per 100 μGy)	0.996	(0.99 to 1.002)	HR (per 100 mGy)	1.7	(0.93 to 2.8)	HR (at 10 WLM)	0.99	(0.96 to 1.01)
MN intestine	M1	0.0–0.01	Ref		Unexposed	Ref				
		>0.01–0.98	−0.39	(−0.78 to 0.49)	>0.0–3.0	−0.20	(−0.70 to 0.74)			
		>0.98–4.4	0.24	(−0.51 to 1.9)	>3.0–9.1	0.38	(−0.38 to 1.8)			
		>4.4–36	−0.24	(−0.78 to 0.91)	>9.1–28	−0.18	(−1.2 to 1.0)			
		>36	1.7	(0.17 to 5.7)	>28	−0.23	(−1.0 to 0.73)			
	M2	ERR (per 100 μGy)	NS		ERR (per 100 mGy)	NS				
	M3	ERR (per 100 μGy), 1%	NS		ERR (per 100 mGy), 1%	NS				
	M4	HR (at 100 μGy)	2	(1.05 to 3.2)	HR (at 100 mGy)	0.57	(0.18 to 1.4)			
MN pancreas	M1	0.0–0.13	Ref		0.0–<2.0	Ref				
		>0.13–1.5	0.44	(−0.36 to 2.2)	2.0–<7.0	0.36	(−0.54 to 2.3)			
		>1.5	0.46	(−0.38 to 2.1)	≥7.0	−0.52	(−0.96 to 0.52)			
	M2	ERR (per 100 μGy)	NS		ERR (per 100 mGy)	NS				
	M3	ERR (per 100 μGy), 1%	NS		ERR (per 100 mGy), 1%	NS				
	M4	HR (at 100 μGy)	0.61	(0.015 to 3.5)	HR (at 100 mGy)	0.59	(0.11 to 1.9)			
NHL	M1	0.0–0.26	Ref		Unexposed	Ref				
		>0.26–7.2	0.19	(−0.65 to 4.1)	>0.0–9.9	0.21	(−0.59 to 3.9)			
		>7.2	0.090	(−0.79 to 4.3)	>9.9	0.42	(−1.3 to 4.9)			
	M2	ERR (per 100 μGy)	NS		ERR (per 100 mGy)	NS				
	M3	ERR (per 100 μGy), 1%	NS		ERR (per 100 mGy), 1%	NS				
	M4	HR (at 100 μGy)	1.2	(0.89 to 1.5)	HR (at 100 mGy)	0.77	(0.14 to 2.5)			

Continued

Table 4 Continued

Outcome	Model	Organ dose (μGy)*	EST	PL 95% CI‡	External dose (mGy)	EST	PL 95% CI‡	Radon decay products (WLM)	EST	PL 95% CI‡
Leukaemia	M1	0.0–0.22	Ref		Unexposed	Ref				
(excluding CLL)		>0.22–2.8	0.095	(−0.55 to 1.4)	>0.0–7.0	−0.47	(−0.89 to 0.25)			
		>2.8	−0.20	(−0.70 to 0.61)	>7.0	−0.36	(−0.89 to 0.57)			
	M2	ERR (per 100 μGy)	NS		ERR (per 100 mGy)	NS				
	M3	ERR (per 100 μGy), 1%	NS		ERR (per 100 mGy), 1%	NS				
	M4	HR (at 100 μGy)	0.18	(0.012 to 0.80)	HR (at 100 mGy)	2.8	(0.87 to 6.0)			
MN stomach	M1	0.0–0.05	Ref		0.0–1.0	Ref				
		>0.05–6.2	−0.51	(−0.93 to 0.86)	>1.0–3.0	1.1	(−0.20 to 4.9)			
		>6.2	0.62	(−0.66 to 4.8)	>3.0	0.15	(−0.76 to 2.0)			
	M2	ERR (per 100 μGy)	0.041	(−0.20 to 5.6)	ERR (per 100 mGy)	1.0	(−0.31 to 6.1)			
	M3	ERR (per 100 μGy), 1%	NS		ERR (per 100 mGy), 1%	NS				
	M4	HR (at 100 μGy)	1.002	(0.16 to 2.5)	HR (at 100 mGy)	1.8	(0.42 to 4.9)			

*Target organ varied by outcome (see online supplementary table S5); estimates of cumulative exposure incorporate a 10-year lag period for non-leukaemia outcomes (2-year lag period for leukaemia excluding CLL).
†All multivariable models are adjusted for pay code (hourly/salaried) and birth year (spline terms) and consider all radiologic exposures simultaneously. Model M_1 is linear ERR with a categorical treatment of exposure; model M_2 is linear ERR with continuous treatment of exposure; model M_3 is like model M_2, but incorporates a 1% trim; and model M_4 is log-linear with a continuous treatment of exposure. Models of lung cancer and COPD are additionally adjusted for occupational exposure to acids; models of NHL are additionally adjusted for occupational exposure to trichloroethylene.
‡Profile likelihood 95% CIs.
§1% denotes a 1% trimmed model which excluded risk sets for which the case exceeded the 99th percentile and all controls that exceed the 99th percentile.
CLL, chronic lymphocytic leukaemia; COPD, chronic obstructive pulmonary disease; ERR, excess relative risk; EST, estimate; MN, malignant neoplasm; NE, not estimable; NS, no solution found; NHL, non-Hodgkin's lymphoma; RDP, Radon decay products; WLM, working-level months.

urinalysis data to represent internal dose for all-health outcomes studied, and analysed the effects of internal and external doses separately.[3] By contrast, the software used in the current investigation facilitated calculation of absorbed doses for organs appropriate to the outcomes of interest, and radiation terms were considered both jointly and separately. Uranium urine concentrations were used to estimate radiation dose; however, excreta values may be a marker for other agents integral to the uranium compounds absorbed by exposed individuals. The concomitant effects are indistinguishable; hence, any observed association cannot be solely attributed to the effects of ionising radiation. There is sparse information on the relative biological effectiveness of uranium alpha particles for induction of some malignancies (eg, haematopoietic and digestive cancers); therefore, cautious interpretation of risks from uranium assimilation is warranted.

None of the previous studies analysed the effects of RDP. The suggestion by Hornung *et al*[16] that RDP may be the predominant radiologic exposure associated with lung cancer among FMPC workers was not borne out in this study. RDP exposure showed a non-significant negative relation with lung cancer; the direction of the response changed when either workers employed for less than a year were excluded (data not shown) or when outliers were trimmed. The RDP estimates, based on location rather than individual dose data, have substantial uncertainty, and involve assumptions about workers' locations, seasonal and diurnal variations in wind and temperature, the difference in RDP levels outside and within buildings and more. These assumptions hinder definitive evaluation of the relations between RDP and lung cancer at the facility. The current study was the first to evaluate all three radiation terms (external dose, organ dose and RDP) simultaneously.

Although both radiologic and non-radiologic exposures were considered, incomplete control for potential confounders remains an issue. The scarcity of exposed cases for some outcomes, and the prioritisation of radiation exposures resulted in limited statistical power to evaluate the role of non-radiologic exposures in the models. Furthermore, the non-radiologic exposures were evaluated using only a summary metric for duration of dichotomised exposure potential, with no metrics for intensity or temporality included.

Interpretation is also hindered by incomplete control for smoking and other lifestyle factors. Electronic smoking data were limited, and the collection of hard-copy smoking data, which were also sporadic, was deemed impractical. While inclusion of pay code in all models likely effects partial control for smoking, and mortality findings for lifestyle-related outcomes not evaluated a priori do not suggest an extremely strong role for lifestyle-related factors, individual smoking data would permit a more thorough assessment of the role of smoking in the elevated lung cancer SMR among hourly workers.

In summary, with 15 additional years of follow-up, mortality patterns have not changed greatly among Caucasian male FMPC workers. Further assessment of increased risks of bladder and renal cancers among Caucasian females might be enhanced by additional mortality follow-up or use of a cancer incidence design. While follow-up is now substantial for this cohort, average radiation doses are low and the cohort is relatively small, resulting in limited statistical power for sparse outcomes like leukaemia. Re-examination after another 10 years of follow-up have accrued may be warranted.

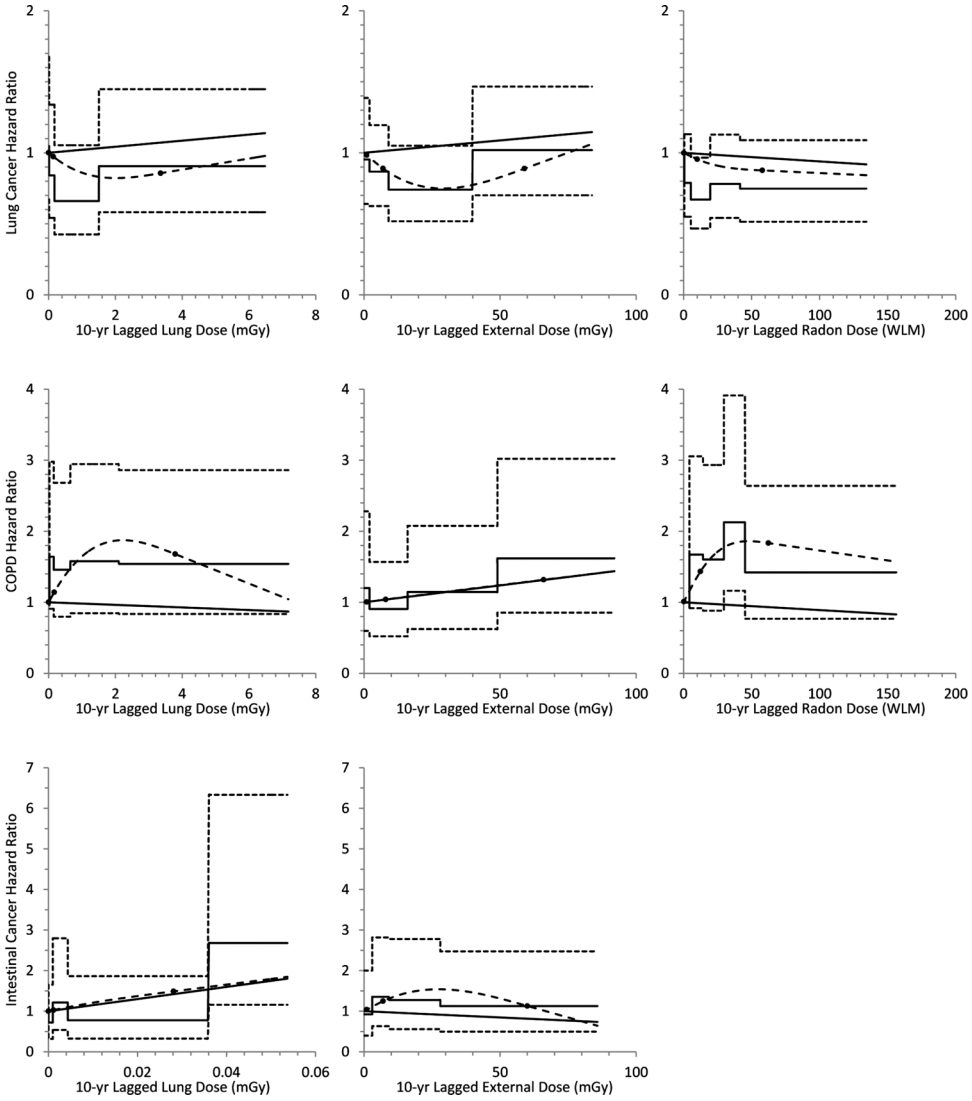

Figure 1 Categorical, linear and natural (restricted cubic) regression spline models evaluating exposure-response relations for lung cancer, COPD and intestinal cancer (outcomes of a priori interest with at least 50 cases) for Caucasian male Fernald workers (1951–2004).

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