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An Assessment of Radiation-Associated Risks of Mortality from Circulatory Disease in the Cohorts of Mayak and Sellafield Nuclear Workers

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Mortality from circulatory disease (CD), ischemic heart disease (IHD) and cerebrovascular disease (CeVD) was investigated in relationship to cumulative doses of external gamma radiation and internal alpha radiation to the liver from deposited plutonium over long follow-up periods in two large cohorts of nuclear workers: the Russian Mayak Worker Cohort (MWC) and the UK Sellafield Worker Cohort (SWC). The MWC comprised 22,374 workers (74.6% males) with 5,123 CD deaths registered during 842,538 person-years of follow-up, while the SWC comprised 23,443 workers (87.8% males) with 2,322 CD deaths registered during 602,311 person-years of follow-up. Dose estimates for external gamma radiation and internal alpha radiation to the liver were calculated via a common methodology, in accordance with an agreed protocol. The mean cumulative external $H_p(10)$ dose was 0.52 Sv for the MWC and 0.07 Sv for the SWC, while the mean cumulative internal dose was 0.19 Gy for the MWC and 0.01 Gy for the SWC. Categorical relative risks (RR) and excess relative risks (ERR) per unit dose were estimated for each cohort and for the pooled cohort when appropriate. The dose responses for CD, IHD and CeVD in relationship to internal alpha-particle dose did not differ significantly from the null for either the MWC, the SWC or the pooled plutonium worker cohort. The ERR/Sv estimates in relationship to external exposure were significantly raised for both cohorts (marginally so for the MWC) for CD and IHD (but not for CeVD), but differed significantly between the two cohorts, the estimate for the SWC being approximately ten times greater than that for the MWC. Examination of the ERR/Sv estimates for two periods of first employment at the two facilities revealed that the significant heterogeneity was confined to the earlier sub-cohorts, and that the estimates for the later sub-cohorts were compatible. The two sub-cohorts for the later first-employment periods were pooled, producing risk estimates that were raised, but not significantly so: ERR/Sv for CD, IHD and CeVD of 0.22 (95% CI: –0.01, 0.49), 0.22 (95% CI: –0.06, 0.57) and 0.24 (95% CI: –0.17, 0.80), respectively. The reasons for the complex pattern of results found in this study are unclear. Among potential explanations are the influence of differences in background CD mortality rates, an effect of other occupational factors, substantial uncertainties in doses, particularly during earlier periods of operations, as well as confounding and/or modifying factors that were not taken into account in the current analysis.

INTRODUCTION

Evidence has long existed for an increased risk of circulatory disease (CD) after high levels of exposure to external sources of penetrating ionizing radiation, such as that experienced by the Japanese A-bomb survivors (*1–4*) or by patients treated with radiotherapy (*5*). In recent years, there has been growing evidence of increased risk of CD from lower levels of exposure (*6–24*). Since CD accounts for a substantial proportion of morbidity and mortality in human populations, it is important to thoroughly investigate the potential radiation-associated excess risks of CD after low-level exposure.

Much of the evidence supporting an association between CD and low-level radiation is derived from epidemiological studies of occupational exposure. If a worker is employed in radiation work over a number of years, occupational exposure at low dose rates can accumulate to produce moderate, and even high, doses over a working lifetime, especially when exposure occurred in earlier periods of radiation work. There is substantial epidemiological evidence showing that protracted exposure to radiation in the workplace may increase the risk of CD comes from the

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studies of workers at the Mayak Production Association (PA) (*6–8, 17, 18, 23, 24*) in the Russian Federation, and those conducted at nuclear facilities in the United Kingdom (UK) operated by the former British Nuclear Fuels Limited (BNFL) (*10*), which included the large group of workers at the Sellafield nuclear complex in northwest England. Although these studies found associations between CD risks and exposure to external sources of penetrating (mainly) gamma radiation, exposure of workers at Mayak and Sellafield also included internal exposure to alpha particles from intakes (largely through inhalation) of plutonium (*7, 17, 18, 23–27*).

Studies of the Mayak workers provided some evidence for an association between plutonium exposure and the risk of CD (*7, 17, 18, 23, 24*), but the estimation of the tissue-specific doses received from plutonium intake is complex, as is the identification of the relevant target tissue(s) for any radiation-related risk of CD, which complicates the interpretation of findings. Consequently, further investigation of the potentially increased risk of CD from exposure to both external gamma rays and alpha particles emitted by internally deposited plutonium was warranted, and the joint study of plutonium workers at Mayak and Sellafield was the objective of Sub-project 3 of the large SOLO project funded by the European Union (http://www.solo-fp7.eu).

Although both CD incidence and mortality data are available for the Mayak worker cohort, only mortality data for CD are available for the Sellafield worker cohort, and to date only the results of an analysis of CD mortality in relationship to external gamma-ray exposure (and not internal alpha particles) for the entire BNFL workforce (rather than just for Sellafield workers) have been reported (*10*). Furthermore, while the exposures to external gamma rays and internal plutonium alpha particles experienced by workers at Mayak in the early years of operations (which commenced in 1948) were the highest that have been reported in an occupational cohort, those at Sellafield (which commenced operations in 1950) were among the highest recorded from Western Europe and North America, so a study combining the investigation of both workforces would be desirable.

Here we report the risks of CD mortality in the cohorts of Mayak and Sellafield nuclear workers in relationship to exposure to gamma rays from external sources and alpha particles from internally deposited plutonium. When appropriate, i.e., in the absence of statistically significant heterogeneity between equivalent risk estimates for the two cohorts, CD mortality risks are derived from a pooled analysis of the two datasets.

MATERIALS AND METHODS

The datasets for the Mayak and Sellafield worker cohorts were made available to researchers under an agreed-upon protocol within the SOLO project with the permission of the respective data custodians. Data for individual workers were not provided; instead, data was provided for categories that had been previously agreed upon, after discussions with, and presentations to, those responsible for supplying the data. Classification of data into categories used in the current analysis is presented in Supplementary Table S1 (http://dx.doi.org/10.1667/RR14468.1.S1).

Study Cohorts and Follow-up

The Mayak PA, located in the Southern Urals, is the first and largest Russian nuclear enterprise, and includes main facilities needed for weapons-grade plutonium production (namely, reactors, a radiochemical plant and a plutonium production plant), as well as auxiliary facilities (including a water treatment plant, machinery and repair plant and power network plants, etc.). Initially, the Mayak worker cohort (MWC) comprised 22,377 nuclear workers, who were first employed at one of the main facilities of Mayak between 1948 and 1982 regardless of sex, age, nationality or duration of employment. Some contradictions between occupational history and vital status data were found for three workers, and for that reason they were excluded from the MWC. Therefore, the MWC comprised 22,374 workers (of whom 43 individuals were accidentally acutely exposed to high external gamma radiation). Of these workers, 7,499 (33.5%) provided a urine sample for analysis for internal exposure to plutonium.

For each MWC member (74.6% males), follow-up started from the date of first employment and ended at the earliest of the following events: date of death, December 31, 2008 for all workers known to be alive and residing in Ozyorsk (the closed city neighboring Mayak), December 31, 2005 for all workers known to be alive but who had migrated from Ozyorsk by that date, or date of emigration for migrants with unknown vital status. Information on dates and causes of death for Ozyorsk residents and emigrants were collected from different sources. For residents, the sources of primary information were medical records, case histories, autopsy protocols, medical death certificates and death certificates issued by civil registry offices in Ozyorsk. The same information for emigrants was provided by the Medical and Dosimetry Registry for Mayak Workers and collected from death certificates issued by civil registry offices in places of migration. Methods and sources used to collect vital status data have been reported in detail elsewhere (*18*, *28–30*).

The Sellafield worker cohort (SWC) was comprised of employees of BNFL, the United Kingdom Atomic Energy Authority (UKAEA) or the Ministry of Supply (MoS), who were first employed at the Sellafield site between 1947 and 2002 (*10*). Workers were classified as ''radiation workers'' or ''non-radiation workers'' according to whether or not they were monitored with personal dosimeters (generally film badges) for external gamma-ray exposure, which was done if there was a possibility of non-trivial exposure from external sources of radiation; the current cohort is restricted to consider the 23,443 Sellafield radiation workers only. A subset of 12,192 radiation workers (52%) was potentially exposed to plutonium; those radiation workers assessed to be potentially exposed to non-trivial quantities of plutonium provided a urine sample for analysis for the purpose of estimating internal alpha-radiation exposures (*25–27*).

For each worker of the SWC (87.8% males), follow-up started from the date of first employment and ended at the earliest of the following events: date of death, December 31, 2005 for those individuals who were known to be alive, date of migration for those individuals who were known to have emigrated from the UK, or date of employment termination for those workers whose vital status was unknown at the end of the follow-up. Methods and sources used to collect vital status data have been reported in detail elsewhere (*10*).

Causes of death were coded consistently in both cohorts in accordance with the International Classification of Diseases, 9th revision (ICD-9) (*31*). Mortality risk was investigated for all CD (ICD-9: 390–459 codes), as well as for ischemic heart disease (IHD) (ICD-9: 410–414 codes) and cerebrovascular disease (CeVD) (ICD-9: 430–438 codes) separately.

TABLE 1
Main Characteristics of the Mayak and Sellafield Worker Cohorts, the Combined Radiation Worker Cohort and Plutonium Worker Cohort

Main characteristics	MWC	SWC	RWC	PuWC
Number of cohort members	22,374	23,443	45,817	19,691
(Person-years)	(842,538)	(602,311)	(1,444,849)	(628,006)
Cohort members monitored for plutonium exposure				
Total number	7,499	12,192	19,691	19,691
Person years, total	307,358	320,648	628,006	628,006
Person years after the date of first urinalysis sample	123,795	281,840	405,635	405,635
Females (%)	25.4	12.2	18.6	16.7
Mean duration of follow-up, years	37.9 (SD 14.1)	25.7 (SD 13.7)	32.0 (SD 14.0)	29.9 (SD 13.9)
Known vital status (%)	95	98	96.5	99
Deceased (%)	53.8	21.2	36.9	34.1
Alive (%)	46.2	78.8	63.1	65.9
Migrants (%)[a]	41.3	2	21.1	2.5
Lost to follow-up (%)[b]	5	2	3.5	1
Mean age at first employment, years				
Males	25.3 (SD 8.6)	32.3 (SD 11.0)	27.6 (SD 10.0)	29.1 (SD 9.4)
Females	26.5 (SD 10.2)	28.3 (SD 10.6)	26.7 (SD 10.3)	28.0 (SD 9.5)
Mean duration of employment, years				
Males	18.3 (SD 14.8)	13.3 (SD 11.3)	15.5 (SD 13.2)	19.5 (SD 11.7)
Females	17.4 (SD 12.8)	10.6 (SD 8.7)	15.1 (SD 12.0)	15.9 (SD 9.5)
Mean age at death of workers known to have died by the end of the follow-up, years				
Males	60.2 (SD 13.6)	67.2 (SD 12.9)	62.8 (SD 13.8)	65.6 (SD 12.5)
Females	68.5 (SD 12.4)	65.9 (SD 16.2)	68.4 (SD 12.6)	67.6 (SD 14.3)
Mean age of workers known to be alive at the end of the follow-up, years				
Males	63.5 (SD 10.1)	52.0 (SD 14.9)	56.7 (SD 14.3)	56.0 (SD 13.1)
Females	71.8 (SD 9.3)	47.2 (SD 13.8)	62.3 (SD 16.4)	60.0 (SD 12.1)

Notes. MWC = Mayak Worker Cohort; SWC = Sellafield Worker Cohort; RWC = Radiation Worker Cohort (all the workers from both the MWC and SWC); PuWC = Plutonium Worker Cohort (a subset of the RWC including all workers monitored for exposure to plutonium).

[a] For the MWC, those who had emigrated from Ozyorsk by 31 December of 2005; for the SWC, those who had emigrated from the UK by the end of the follow-up.

[b] For the MWC, workers with unknown vital status; for the SWC, workers with unknown vital status and those who had emigrated from the UK.

Table 1 summarizes the main characteristics of each of the MWC and the SWC, and the pooled cohorts: the Radiation Worker Cohort (RWC, all the workers from both the MWC and the SWC) and the Plutonium Worker Cohort (PuWC, a subset of the RWC including all workers monitored for exposure to plutonium). The SWC includes workers employed during 1947–2002, whereas the MWC includes workers employed during 1948–1982, which accounts for the younger average age of the Sellafield workers at the end of follow-up; average age at death, however, is somewhat higher for male (but not female) Sellafield workers. The current study did not take into account information on smoking, alcohol consumption, body mass index and blood pressure (or other established non-radiation risk factors for CD mortality) since, although such information was available for the MWC (for 85% of the workers) and for some SWC members, compatible information between the two cohorts was incomplete. Analyses of the Mayak workforce that have taken account the available data on non-radiation risk factors (smoking, alcohol consumption, body mass index and hypertension) have shown that these factors only modestly affect the associations between CD mortality and radiation exposure (*18*) (see Discussion for more details).

The pooled worker cohort (RWC) thus includes 45,817 workers (81.4% males) with 1,444,849 person-years of follow-up; vital status is available for 96.5% of RWC members, and of these, 36.9% are known to have died (Table 1). The PuWC includes 19,628 workers (85.3% males) with 405,635 person-years of follow-up (after first urine sampling); vital status is available for 99% of PuWC members, and of these, 34.1% are known to have died (Table 1).

Dosimetry Data

In the MWC, doses from external gamma rays were calculated using the Mayak Worker Dosimetry System-2008 (MWDS-2008) (*32, 33*); doses from internally deposited plutonium were also estimated based on MWDS-2008 data, but using an updated dosimetry protocol (*34–36*). In the SWC the dosimetry with respect to external gamma rays has been described in previously published studies (*10*, *26*). Internal alpha-radiation doses from plutonium for the SWC were estimated on the basis of the same methodology as that used for the MWC (*33–36*). Annual doses from external gamma rays were available for each member of the study cohorts. In the current study, we used $H_p(10)$ personal dose equivalent for exposure to external gamma rays (i.e., the dose delivered at 10-mm depth of tissue), measured in Sievert (Sv).

Absorbed doses from alpha radiation to organs/tissues from internally deposited plutonium were estimated from measurements of plutonium in urine using biokinetic models of the behavior of plutonium in the body and dosimetry models (*33–36*). Plutonium is distributed heterogeneously within the body, so that once it has entered the bloodstream (usually from the lung) it deposits preferentially in the liver and bone. The current dosimetry systems do not provide dose estimates for blood vessels, heart or brain (the organs/tissues where the diseases under consideration here occur). For this reason, and compatible with previously published studies of the MWC (*6, 7, 17, 18, 23, 24*), the analysis was based on alpha-particle absorbed dose to the liver, measured in gray (Gy). Measurements below the limit of detection were taken into account when internal alpha-particle radiation doses were calculated (*34–36*). Only 41% of the Mayak workers judged to have been exposed to potentially

substantial quantities of plutonium provided a urine sample for the assessment of exposure; approximately one-third of these samples were obtained after the worker had left employment at Mayak. At Sellafield, all employees doing work in which they were potentially exposed to non-trivial quantities of plutonium had their exposures assessed through urinalysis (although that level of exposure considered to be trivial diminished over time), with only very few providing urine samples after retiring from Sellafield (*26, 27*).

The biokinetic model used as the basis for estimating internal alpha-particle doses consists of three main parts: a systemic model, a gastrointestinal tract (GIT) model and a respiratory tract (RT) model. The systemic model describes plutonium metabolism within the liver and other organs/tissues, excluding RT and GIT. All the dose estimates to organs/tissues based on the systemic biokinetic model are highly correlated (Spearman rank correlation coefficient = 0.99) (*33–36*). To model plutonium activity in different organs and tissues, the modified ICRP-66 model was used (*37*); the GIT model is described in ICRP-30 (*38*).

The issue of the value to be adopted for the slow absorption coefficient for plutonium nitrate in the lung remained unresolved when doses from internal alpha radiation were calculated for the current study. For this reason, two datasets were created, corresponding to two different values of this coefficient: one was based on Mayak worker post-mortem examinations ($SS1 = 2.5 \cdot 10^{-4}$ d^{-1}) and the other on investigations based on excretion data from Public Health England (PHE) volunteers ($SS2 = 2.2 \cdot 10^{-3}$ d^{-1}). The ratios between mean cumulative absorbed doses to the liver due to incorporated plutonium estimated, using the two coefficients (SS1/SS2), were 0.8 (SD = 6.6) for the MWC and 1.2 (SD = 13.3) for the SWC.

Statistical Methods

Analyses of non-radiation factors were first performed to determine which factors influenced CD mortality rates. The radiation risk analysis consisted of a categorical analysis in which relative risks (RR) for CD, IHD and CeVD were calculated for 11 categories of external gamma-ray doses (<0.05, 0.05–0.10, 0.10–0.15, 0.15–0.20, 0.20–0.30, 0.30–0.50, 0.50–0.75, 0.75–1.00, 1.00–2.00, 2.00–3.00, 3.00+ Sv) and 12 categories of alpha-particle dose to the liver due to incorporated plutonium (<0.002, 0.002–0.005, 0.005–0.01, 0.01–0.02, 0.02–0.05, 0.05–0.10, 0.10–0.15, 0.15–0.20, 0.20–0.30, 0.30–0.50, 0.50–1.0, 1.0+ Gy), which included adjustments for other variables. Workers exposed to the lowest doses (<0.05 Sv for external gamma radiation and <0.002 Gy for internal alpha radiation) were used as the reference categories. The analysis of risk associated with dose from internal alpha particles was restricted to workers monitored for internal exposure and included only person-years after the initial date of plutonium monitoring. As noted above, only 41% of the Mayak workers assessed to have been potentially exposed to substantial quantities of plutonium provided a urine sample for analysis, while essentially 100% of those Sellafield workers potentially exposed to non-trivial quantities of plutonium provided a urine sample. The RR were calculated by maximum likelihood using the AMFIT module of EPICURE software (Risk Sciences International Inc., Ottawa, Canada) (*39*); 95% confidence intervals (CI) for RR and *P* values were obtained based on maximum likelihood methods.

Poisson regression (AMFIT module) was used to analyze CD mortality in relationship to doses from external and internal exposures. These analyses provided excess relative risk (ERR) estimates per unit dose, 95% CI and *P* values. Dose-response models for exposure to external gamma- and internal alpha-radiation were considered separately. Data were fitted based on the model, $B = B_0(1 + \beta D)$, where B represents CD mortality rates, B_0 is the background CD mortality rate calculated using the stratified model and β is the increase of CD mortality rates per unit dose, D.

In both RR and ERR analyses adjustment was made by stratification for the following nonradiation factors: sex (male/female), attained age (five-year intervals from 15–84 years and 85+ years), calendar period (five-year intervals from 1947–2005 and 2006–2008) and migration status (Ozyorsk resident/emigrant for MWC; not applicable for SWC), and also dose to the liver from internal alpha radiation when analyzing exposure to external gamma-radiation and *vice versa*. Unmonitored for internal exposure person-years were included in a separate category when stratifying for internal alpha-particle dose. Analyses were also performed for gamma-radiation doses unadjusted for alpha-radiation doses and *vice versa*, to assess the effect of this adjustment on results. Initially, analyses were also performed modeling the ERR, with external and internal doses both included simultaneously, but the results did not differ notably from those reported here. Birth cohort is derivable from attained age and calendar period, so was not included as a factor in the radiation analyses.

Each cohort (MWC and SWC) was analyzed separately, and where appropriate (i.e., in the absence of significant heterogeneity between cohorts), the pooled radiation worker cohort (RWC) or the pooled plutonium worker cohort (PuWC) was also analyzed. To determine whether there were statistically different radiation effects on CD mortality risks between the two cohorts (MWC and SWC), a model with an interaction term (cohort * exposure) was fitted to the pooled dataset and a *P* value obtained from the likelihood ratio test comparing models with and without the interaction term; an adjustment (via stratification) for cohort (MWC/SWC) was additionally included.

In all analyses, to account for disease latency, cumulative doses lagged by 10 years were used. Workers were considered unmonitored for exposure to plutonium until the date of the first urinalysis assessment; for the MWC, urinalysis for plutonium started only in the 1970s, while for the SWC, monitoring commenced at the beginning of plutonium separation operations at the facility. We used the plutonium exposure assessment method based on the Mayak slow absorption coefficient, SS1 (see Dosimetry section above).

Sensitivity Analyses

Deviations from a linear dose-response model were assessed by fitting alternative models: quadratic (Q, $1 + \beta D^2$), linear-quadratic (LQ, $1 + \beta_1 D + \beta_2 D^2$) and linear-exponential [LE, $1 + \beta_1 D \exp(-\beta_2 D)$] dose-response models. We used differences in maximum likelihood to compare nested models or the Akaike information criterion (AIC) (*40*) for non-nested models.

In addition to nonlinearity tests, analyses for dose-restricted cohorts (i.e., including only those workers exposed to external gamma radiation at a cumulative dose <2.0 Sv, <1.0 Sv, <0.5 Sv and <0.3 Sv, or to alpha radiation at a cumulative liver dose <1.0 Gy, <0.5 Gy, <0.3 Gy and <0.1 Gy) were also performed.

Of the MWC and SWC members, 25.4% and 12.2%, respectively, were female. Accordingly, in addition to the combined male-plus-female cohorts, all radiation risk analyses (as described above) were repeated for male workers only.

Additional sensitivity analyses were performed: 1. Analyses using a five-year dose lag (instead of a 10-year lag); 2. Analyses including workers considered unmonitored until the date of the first urinalysis assessment plus two years, to address the possibility that workers of the MWC might have been selected to provide a urine sample because of their poor health; 3. Analyses using a dataset based on investigations of plutonium lung solubility in PHE volunteers (SS2).

Given that working conditions in the earlier years of operation of the facilities are likely to have differed substantially from those in later years, sub-cohorts of workers first employed in ''earlier'' or ''later'' periods were considered; these periods were selected *a priori*. For the MWC, the two first-employment periods were taken to be 1948–1958 and 1959–1982, because worker protection measures changed markedly in 1958–1959. For the SWC, the two sub-periods were 1947–1957 and 1958–1982, because the 1957 Windscale accident caused additional safety measures to be introduced at Sellafield. For the later sub-cohorts, it was decided that the same end-date for first employment would be used, so that Sellafield was aligned with Mayak

(i.e., a date of joining before January 1, 1983). To decide whether there were statistically different radiation effects on CD mortality risks between the first-employment periods for each cohort, a model with an interaction term (first-employment period * exposure) was fitted to the pooled dataset and a *P* value was obtained from the likelihood ratio test comparing models with and without the interaction term; adjustment (via stratification) for first-employment periods (earlier or later) was included.

Ethics Approval

This study was based on records, and did not require personal contact among researchers and cohort members. The project was reviewed and approved by the Southern Urals Biophysics Institute (SUBI) Advisory Board in the Russian Federation, and in the UK by the Nuclear Decommissioning Authority (NDA) - Public Health England (PHE) Epidemiology Governance Group and by The Proportionate Review Sub-committee of the National Research Ethics Service Committee London - Hampstead (REC reference 13/LO/0321).

RESULTS

Dosimetry of Exposure to External Gamma and Internal Alpha Radiation

The distribution of workers by cumulative external gamma-ray dose is shown in Fig. 1A. Cumulative doses from external radiation in the MWC ranged widely, with 17% of workers exposed at (unlagged) doses >1.0 Sv (and 6.0% >2.0 Sv) and 35% receiving doses <0.1 Sv. In contrast, the SWC included only 0.2% of workers who were exposed at cumulative doses >1.0 Sv (and none >2.0 Sv), while 80% received external gamma-ray doses <0.1 Sv. In the MWC, the mean cumulative external gamma-ray dose was 0.55 Sv (SD = 0.76, range = 0–8.4 Sv) for males and 0.44 Sv (SD = 0.65, range = 0–6.8 Sv) for females, with mean annual external doses of 0.04 Sv (SD = 0.11, range = 0–5.1 Sv) and 0.03 Sv (SD = 0.10, range = 0–3.2 Sv), respectively. In the SWC, the mean cumulative external gamma-ray dose was 0.08 Sv (SD = 0.15, range = 0–1.88 Sv) for males and 0.01 Sv (SD = 0.02, range = 0–0.35 Sv) for females, with mean annual external doses of 0.01 Sv (SD = 0.01, range = 0–0.73 Sv) and 0.002 Sv (SD = 0.003, range = 0–0.06 Sv), respectively. The mean cumulative external $H_p(10)$ dose was 0.38 (SD = 0.63, range = 0–8.4) Sv for the RWC and 0.40 (SD = 0.65, range = 0–5.7) Sv for the PuWC.

Supplementary Fig. S1A (http://dx.doi.org/10.1667/RR14468.1.S1) shows that the mean annual individual doses from external gamma rays were highest in the earlier years of operations in both cohorts, but that at Mayak these were an order of magnitude greater than at Sellafield. For example, in 1952 the mean annual external dose in the MWC was 0.30 Sv, and in the SWC, 0.02 Sv; but doses decreased sharply in the MWC over the following years to 0.05 Sv by 1960, while in the SWC doses reduced modestly to 0.01 Sv. Subsequently, annual external doses continued their general decline until the end of follow-up. Supplementary Fig. S1A shows the marked difference in the external doses received by Mayak workers during the 1940s and 1950s compared to those received in later years.

The distribution of workers with plutonium-in-urine measurements (of those workers assessed to be exposed to plutonium, 41% were monitored in the MWC and effectively 100% in the SWC) by cumulative plutonium alpha-particle absorbed dose to the liver is shown in Fig. 1B. The cumulative liver dose was >0.1 Gy for more than 20% of the monitored MWC members. In contrast, few SWC members accumulated liver doses from plutonium that were this high, and the proportion of individuals exposed at doses <0.005 Gy was 80%. In the MWC, the mean cumulative alpha-particle dose to the liver was 0.16 Gy (SD = 0.47, range = 0.007–10.5 Gy) in males and 0.26 Gy (SD = 0.81, range = 0–14.9 Gy) in females, with mean annual alpha-particle doses of 0.004 Gy (SD = 0.012, range = 0–0.3 Gy) and 0.006 Gy (SD = 0.021, range = 0–0.6 Gy), respectively. In the SWC, the mean cumulative liver dose was 0.01 Gy (SD = 0.06, range = 0–5.58 Gy) in males and 0.004 Gy (SD = 0.02, range = 0–0.30 Gy) in females, with mean annual alpha-particle doses of 0.0004 Gy (SD = 0.003, range = 0–0.28 Gy) and 0.0002 Gy (SD = 0.0006, range = 0–0.007 Gy), respectively. In the PuWC, the mean cumulative internal dose was 0.06 (SD = 0.30, range = 0–14.9) Gy. The mean annual individual plutonium alpha-particle doses to the liver in the two cohorts are shown in Supplementary Fig. S1B (http://dx.doi.org/10.1667/RR14468.1.S1); the first substantial quantities of plutonium were present at Mayak in 1949 and at Sellafield in 1952. The substantial differences between the internal liver doses received from plutonium intakes during the earlier and later years of operation at the two installations are shown in Supplementary Fig. S1B, and the difference is particularly noteworthy for Mayak.

The distributions of cumulative doses tend to be lognormal (Fig. 1). The correlation between individual cumulative doses from external gamma rays and internal plutonium alpha particles was relatively strong in both the MWC and SWC at 0.52 and 0.68, respectively.

Mortality Risks in Relationship to Nonradiation Factors

Supplementary Tables S2–S4 (http://dx.doi.org/10.1667/RR14468.1.S1) summarize the analysis results for relative risks (RR) of mortality from CD, IHD and CeVD associated with potential nonradiation confounding factors in the MWC and SWC. As anticipated, the analyses showed that mortality from CD, IHD and CeVD was significantly lower in females compared to males and increased with increasing attained age of workers in both cohorts. Additionally, mortality from CD, IHD and CeVD varied with calendar period in both the MWC and SWC. In the MWC mortality from CD, IHD and CeVD was significantly decreased among female emigrants (but not among male emigrants). Subsequent analyses were adjusted for these potential confounding factors.

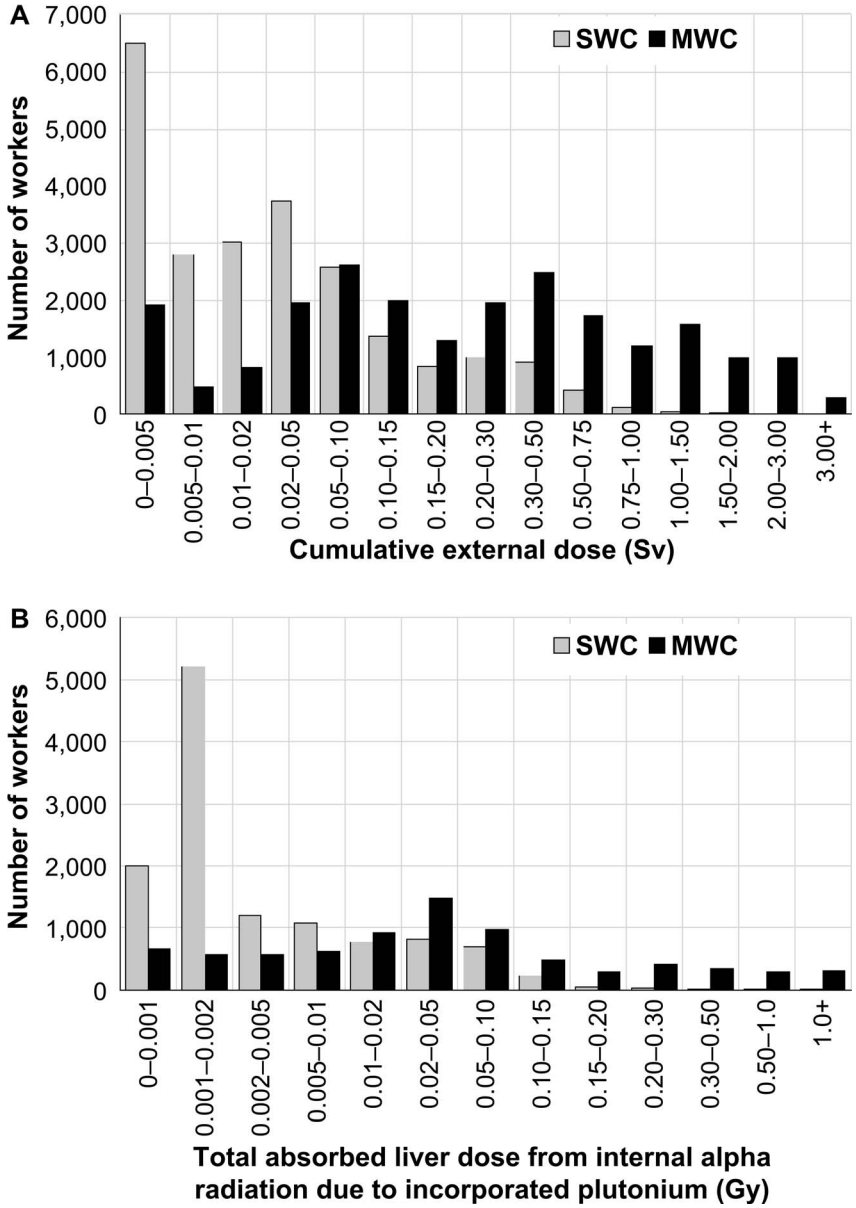

FIG. 1. Distribution of workers in the Sellafield Workers Cohort (SWC) and in the Mayak Workers Cohort (MWC) by (panel A) cumulative recorded external gamma-radiation dose and by (panel B) cumulative absorbed alpha-particle dose to the liver due to incorporated plutonium.

Mortality Risks in Relationship to External Gamma-Radiation Exposure

In the MWC, by the end of the 842,538 person-years of follow-up, 5,123 deaths (44.8% of total deaths) were registered with CD as the underlying cause of death. Of these, 2,905 (57%) were from IHD and 1,610 (31%) from CeVD. In the SWC, 2,322 deaths from CD (47.6% of total deaths) were registered during the 602,311 person-years of follow-up. Of these, 1,560 (67%) IHD and 438 (19%) CeVD deaths were registered. Deaths from other circulatory diseases accounted for the remaining deaths in the MWC (12%) and the SWC (14%). In the RWC, 7,445 deaths from CD were registered during 1,444,849 person-years of follow-up.

Results of the categorical analysis of RR of CD, IHD and CeVD mortality in relationship to cumulative external gamma-ray dose with a 10-year lag are shown in Table 2. These categorical analyses did not show significantly raised risks of CD, IHD or CeVD mortality in the MWC. In contrast, for the SWC significantly increased RR of CD mortality were found for the four groups with cumulative external radiation doses >0.20 Sv and <1.0 Sv (but not in the 1.0–2.0 Sv dose group), largely due to IHD mortality; no significantly increased CeVD mortality risks were observed.

Linear dose-response estimates (ERR/Sv) for mortality from CD, IHD and CeVD associated with the cumulative external gamma-ray dose with a 10-year lag are summarized

TABLE 2
Circulatory Disease, Ischemic Heart Disease and Cerebrovascular Disease Mortality Relative Risks for the Mayak, Sellafield and (where appropriate) Pooled Radiation Workers Cohorts, in Relationship to Categories of Cumulative External Gamma-Ray Dose

				Circulatory disease		Ischemic heart disease		Cerebrovascular disease	
Dose, Sv	Cohort	Mean dose	Person-years	RR (95% CI)	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	No. of cases
0–0.05	MWC	0.011	374,622	1	1029	1	569	1	334
	SWC	0.013	466,698	1	1133	1	746	1	223
	RWC	0.011	841,320	-[a]	2162	-[a]	1315	1	557
0.05–0.10	MWC	0.074	71,822	0.91 (0.82, 1.03)	432	0.93 (0.80, 1.09)	247	0.83 (0.68, 1.03)	130
	SWC	0.074	51,522	1.06 (0.93, 1.21)	323	**1.17 (1.00, 1.36)**	228	0.78 (0.57, 1.08)	51
	RWC	0.074	123,344	-[a]	755	-[a]	475	0.82 (0.69, 0.98)	181
0.10–0.15	MWC	0.124	47,531	0.99 (0.87, 1.12)	351	1.03 (0.87, 1.21)	201	0.94 (0.76, 1.17)	114
	SWC	0.123	25,986	1.13 (0.96, 1.33)	191	1.21 (0.99, 1.46)	132	1.03 (0.71, 1.49)	36
	RWC	0.124	73,517	-[a]	542	-[a]	333	0.96 (0.80, 1.16)	150
0.15–0.20	MWC	0.174	34,626	0.85 (0.74, 1.00)	249	0.88 (0.73, 1.06)	141	0.77 (0.60, 1.00)	78
	SWC	0.174	15,893	1.09 (0.90, 1.32)	126	1.10 (0.86, 1.39)	82	1.11 (0.73, 1.69)	27
	RWC	0.174	50,519	-[a]	375	-[a]	223	0.84 (0.68, 1.05)	105
0.20–0.30	MWC	0.247	53,378	0.93 (0.82, 1.04)	431	0.92 (0.78, 1.07)	238	0.91 (0.74, 1.11)	141
	SWC	0.245	18,300	**1.26 (1.07, 1.49)**	190	**1.36 (1.11, 1.66)**	131	0.88 (0.58, 1.34)	30
	RWC	0.246	71,678	-[a]	621	-[a]	369	0.91 (0.76, 1.09)	171
0.30–0.50	MWC	0.392	69,398	0.91 (0.82, 1.01)	591	0.91 (0.79, 1.05)	332	0.84 (0.69, 1.01)	178
	SWC	0.388	15,600	**1.26 (1.07, 1.49)**	206	**1.41 (1.15, 1.71)**	145	0.96 (0.65, 1.43)	37
	RWC	0.391	84,998	-[a]	797	-[a]	477	0.86 (0.73, 1.02)	215
0.50–0.75	MWC	0.618	49,938	1.01 (0.90, 1.13)	481	0.98 (0.84, 1.15)	264	0.99 (0.81, 1.21)	156
	SWC	0.6	6,108	**1.29 (1.03, 1.61)**	101	**1.32 (1.00, 1.74)**	63	1.39 (0.88, 2.20)	27
	RWC	0.615	56,045	-[a]	582	-[a]	327	1.04 (0.87, 1.25)	183
0.75–1.00	MWC	0.869	35,386	0.97 (0.85, 1.11)	332	0.98 (0.82, 1.17)	187	0.98 (0.78, 1.22)	112
	SWC	0.846	1,622	**1.60 (1.15, 2.21)**	42	**1.64 (1.10, 2.47)**	27	0.77 (0.31, 1.95)	5
	RWC	0.868	37,008	-[a]	374	-[a]	214	0.98 (0.79, 1.22)	117
1.00–2.00	MWC	1.442	72,370	0.97 (0.87, 1.07)	773	1.05 (0.91, 1.20)	456	**0.82 (0.68, 0.99)**	232
	SWC	1.221	582	0.91 (0.48, 1.73)	10	0.84 (0.37, 1.92)	6	0.96 (0.23, 4.05)	2
	RWC	1.438	72,952	-[a]	783	-[a]	462	0.84 (0.70, 1.00)	234
2.00–3.00	MWC	2.395	25,777	1.09 (0.95, 1.25)	350	**1.20 (1.00, 1.43)**	216	0.87 (0.68, 1.12)	98
	SWC	-	-	-	-	-	-	-	-
	RWC	2.395	25,777	-[a]	350	-[a]	216	0.89 (0.69, 1.14)	98
3.00+	MWC	3.771	7,690	1.11 (0.89, 1.38)	104	1.01 (0.75, 1.36)	54	1.24 (0.85, 1.80)	37
	SWC	-	-	-	-	-	-	-	-
	RWC	3.771	7,691	-[a]	104	-[a]	54	1.27 (0.88, 1.83)	37

Notes. Analyses using 10-year dose lag. Adjustments for sex, attained age, calendar period, migration status and dose from internal alpha radiation were included. Mayak lung solubility assumption was used and the workers were considered unmonitored until the date of the first urinalysis assessment. Statistically significant ($P < 0.05$) estimates are shown in bold type. MWC = Mayak Worker Cohort; SWC = Sellafield Worker Cohort; RWC = Radiation Worker Cohort (all workers from both the MWC and SWC).

[a] Significant heterogeneity between the ERR/Sv estimates for the MWC and SWC (see Table 3), so pooled RR estimates for the RWC are not given.

in Table 3. For the full dose range, increased ERR/Sv estimates for mortality from CD and IHD were found in both cohorts, which were statistically significant, marginally so for the MWC. The ERR/Sv estimates for CeVD mortality did not differ significantly from zero. The ERR/Sv estimates for CD and IHD mortality in the SWC were approximately one order of magnitude higher than those for the MWC (Table 3). For example, the IHD mortality ERR/Sv was 0.06 (95% CI: 0.01, 0.13) for the MWC, but 0.53 (95% CI: 0.14, 1.00) for the SWC. The linear dose responses for CD mortality in relationship to the cumulative external radiation dose for the MWC and the SWC are shown in Fig. 2.

Analyses of sub-cohorts of the MWC restricted to dose ranges <2.0, <1.0, <0.5 and <0.3 Sv showed that the ERR/Sv for CD and IHD mortality steadily decreased and became negative with the narrowing of the dose range. In contrast, in sub-cohorts of the SWC analyzed using the same dose restrictions, the ERR/Sv increased and remained statistically significant, even for the narrowest dose range of <0.3 Sv (Table 3). Such patterns could be indicative of nonlinearity in the dose responses for CD and IHD, and this was further assessed.

For the MWC, when the dose responses for CD, IHD and CeVD mortality with cumulative external gamma-radiation dose were analyzed for evidence of nonlinearity, tests based on comparisons between linear and linear-quadratic models as well as linear and linear-exponential models were statistically non-significant ($P > 0.5$) (Supplementary Table S5; http://dx.doi.org/10.1667/RR14468.1.S1). The linear dose-response model also provided a slightly (nonsignificantly) better fit to the data than the quadratic model (e.g., the difference in AIC was 1.274, for IHD mortality).

TABLE 3
Circulatory Disease, Ischemic Heart Disease and Cerebrovascular Disease Mortality for the Cohorts: Linear Dose Responses for the Mayak, Sellafield and (where Appropriate) pooled Radiation Workers Cohorts in Relationship to Cumulative External Gamma-Ray Dose, for Various Cumulative Dose Ranges

		Circulatory disease		Ischemic heart disease		Cerebrovascular disease	
Dataset	Cohort	ERR/Sv	*P* value[a]	ERR/Sv	*P* value[a]	ERR/Sv	*P* value[a]
Full dataset	MWC	0.04 (–0.00, 0.09)	**0.013**	**0.06 (0.01, 0.13)**	**0.018**	+0.00 (–0.06, 0.08)	>0.50
	SWC	**0.42 (0.12, 0.78)**		**0.53 (0.14, 1.00)**		0.05 (–0.46, 0.79)	
	RWC	-[b]		-[b]		+0.00 (–0.06, 0.08)	
<2 Sv	MWC	–0.00 (–0.06, 0.06)	**0.006**	0.04 (–0.04, 0.14)	**0.015**	–0.07 (–0.16, 0.04)	>0.50
	SWC	**0.42 (0.12, 0.78)**		0.52 (0.14, 1.00)		0.05 (–0.46, 0.79)	
	RWC	-[b]		-[b]		–0.07 (–0.16, 0.04)	
<1 Sv	MWC	–0.02 (–0.14, 0.12)	**0.001**	–0.03 (–0.19, 0.14)	**<0.001**	–0.01 (–0.21, 0.24)	>0.50
	SWC	**0.57 (0.23, 0.97)**		**0.73 (0.29, 1.27)**		0.10 (–0.47, 0.91)	
	RWC	-[b]		-[b]		+0.00 (–0.19, 0.24)	
<0.5 Sv	MWC	–0.24 (–0.47, 0.01)	**<0.001**	–0.26 (–0.56, 0.09)	**<0.001**	–0.33 (–0.71, 0.12)	>0.50
	SWC	**0.73 (0.24, 1.31)**		**1.07 (0.43, 1.85)**		–0.06 (–0.87, 1.09)	
	RWC	-[b]		-[b]		–0.28 (–0.63, 0.14)	
<0.3 Sv	MWC	–0.45 (–0.86, 0.00)	**0.004**	–0.42 (–0.97, 0.20)	**0.006**	–0.57 (–1.23, 0.23)	>0.50
	SWC	**0.81 (0.06, 1.69)**		1.15 (0.20, 2.31)		–0.48 (–1.70, 1.26)	
	RWC	-[b]		-[b]		–0.55 (–1.15, 0.16)	

Notes. Analyses using 10-year dose lag. Adjustments for sex, attained age, calendar period, migration status and dose from internal alpha radiation were included. Mayak lung solubility assumption was used and the workers were considered unmonitored until the date of the first urinalysis assessment. Statistically significant ($P < 0.05$) estimates are shown in bold type.

[a] *P* value for test of heterogeneity between the ERR/Sv estimates for the MWC and the SWC.

[b] Significant heterogeneity between the ERR/Sv estimates for the MWC and the SWC, so a pooled ERR/Sv estimate for the RWC is not appropriate.

In contrast, for the SWC, when analyzing CD mortality associated with the cumulative external gamma radiation dose, tests for nonlinearity in the dose response via comparison between linear and linear-quadratic models as well as linear and linear-exponential dose models were statistically significant, with the nonlinear models providing better fits to the data ($P = 0.015$ and $P = 0.032$, respectively) (Supplementary Table S5; http://dx.doi.org/10.1667/RR14468.1.S1), but the linear dose response fitted the data better than a quadratic one ($\Delta AIC = 6.140$). This pattern of

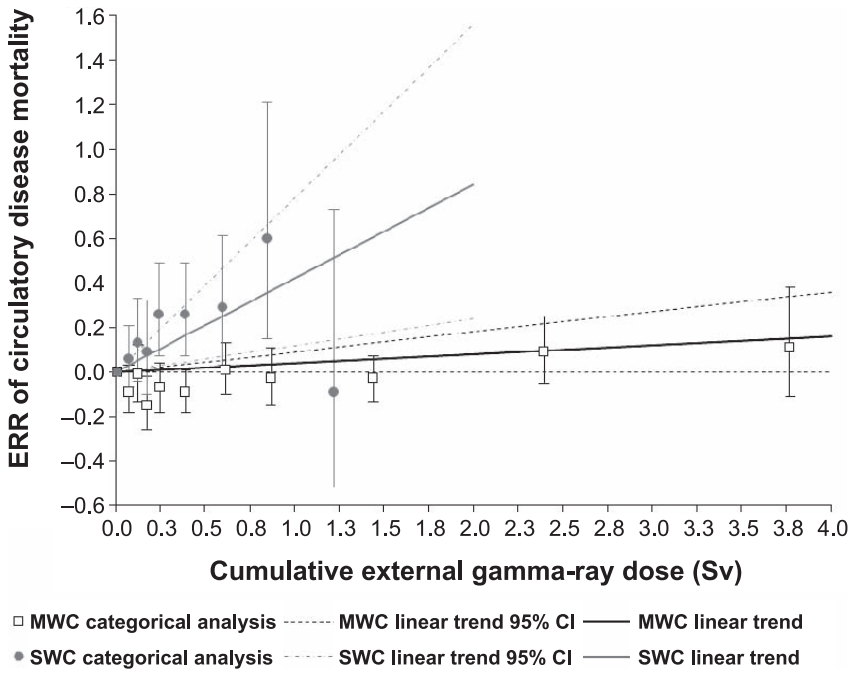

FIG. 2. Variation of the excess relative risk (ERR) of circulatory disease (CD) mortality with the cumulative gamma-radiation dose from external sources for the MWC and the SWC (whole cohorts). Points are estimates for dose groups and lines are fitted linear dose responses. Error bars and bands are 95% confidence intervals.

findings for the dose response for CD mortality was due to IHD mortality, with the results for CeVD mortality being unremarkable (Supplementary Table S5). The nonlinearity of the dose response for CD mortality in the SWC is shown in Fig. 2, where the influence of the negative ERR for the uppermost 1.0–2.0 Sv dose category is apparent, although based on just 10 CD deaths, of which six deaths were from IHD (see Tables 2 and 3); the dose responses were no longer significantly nonlinear when the cumulative dose was restricted to <1 Sv (Supplementary Table S5).

Heterogeneity analysis revealed that the estimated effects of external gamma radiation exposure on CD and IHD (but not CeVD) mortality were statistically different (i.e., $P < 0.05$) between the two cohorts regardless of the dose range, and that the contrast between the dose responses for CD and IHD mortality becomes more apparent as the external dose range becomes more restricted (Table 2 and Fig. 2).

Analysis results for CD, IHD and CeVD mortality associated with cumulative external gamma-radiation dose for male workers only were similar to those for the cohorts as a whole, and are summarized in Supplementary Tables S6–S8 (http://dx.doi.org/10.1667/RR14468.1.S1).

Sensitivity analyses using a five-year lag, the SS2 rather than the SS1 lung solubility parameter, disregarding two years of follow-up after the date of the first urinalysis, and not adjusting analyses for alpha-radiation dose, did not reveal any significant differences from the main findings (unpublished results).

Mortality Risks in Relationship to Internal Alpha-Radiation Exposure

In the MWC, among members with measured plutonium in urine, from the date of the first urine sampling to the end of 123,795 person-years of follow-up, 1,627 deaths (42.8% of all deaths) were registered with CD as the underlying cause of death. Of these, 963 (59%) and 533 (33%) were from IHD and CeVD, respectively. In the SWC, among workers monitored for exposure to plutonium, from the date of providing the first urine sample to the end of 281,840 years of follow-up, 1,160 deaths from CD (47.7% of all deaths) were registered. Of these, 781 (67%) IHD and 215 (19%) CeVD deaths were registered. In the PuWC, 2,787 deaths from CD (37.4% of the number of CD deaths in the RWC) were registered during 405,635 person-years of follow-up.

The results of the categorical analysis for RR of CD, IHD and CeVD mortality in relationship to accumulated liver dose from internal plutonium alpha-particle radiation considering a 10-year lag are shown in Table 4. The number of person-years of observation for these analyses was greatly reduced (see Table 1) compared to the external gamma-radiation analyses, especially in the MWC, and therefore, statistical power was reduced considerably.

The categorical analysis for the MWC did not reveal any significant RR for mortality from CD, IHD or CeVD, except for a raised risk of CeVD mortality in workers exposed to internal alpha radiation at cumulative liver doses of 0.100–0.200 Gy. An equivalent analysis for the SWC demonstrated significant RRs for mortality from CD for cumulative doses from alpha radiation of 0.010–0.020 and 0.050–0.100 Gy, as well as a significant RR for mortality from CeVD after internal doses of 0.150–0.200 Gy (Table 4).

Linear dose-response estimates (ERR/Gy) for mortality from CD, IHD and CeVD associated with the cumulative liver dose from internal alpha radiation considering a 10-year lag are summarized in Table 5 for various dose ranges in the cohorts. Dose-response analysis did not reveal any significant associations of CD, IHD or CeVD mortality with plutonium dose in the MWC or the SWC for either the full or dose-restricted datasets, except for the ERR/Gy of CeVD mortality in the SWC when the cumulative doses were restricted to <0.5 and <0.3 Gy.

When analyzing CD, IHD and CeVD mortality associated with absorbed liver dose from plutonium alpha particles in the MWC and the SWC, tests for nonlinearity based on comparisons between linear and linear-quadratic as well as linear and linear-exponential dose responses were statistically nonsignificant ($P > 0.05$) (Supplementary Table S5; http://dx.doi.org/10.1667/RR14468.1.S1). The differences between AIC for linear and quadratic models did not exceed 5.99, with the linear model providing a slightly better fit for all outcomes except for IHD mortality in the SWC and for CeVD mortality in the MWC, when the quadratic model provided a slightly (nonsignificantly) better fit.

Heterogeneity analysis (Table 5) did not reveal any statistically significant differences in the effects of internal alpha radiation on CD, IHD or CeVD mortality between the two cohorts, which may be due, in part, to low statistical power. No significant associations were found for CD, IHD or CeVD mortality with internal alpha-radiation dose in the pooled PuWC, except for the ERR/Gy for CeVD mortality with a <0.3 Gy cumulative dose restriction.

Analysis results for CD, IHD and CeVD mortality associated with cumulative liver dose from internal alpha radiation for male workers only were similar to those for the cohorts as a whole and are summarized in Supplementary Tables S8–S10 (http://dx.doi.org/10.1667/RR14468.1.S1).

Sensitivity analyses using a five-year lag, the SS2 rather than the SS1 lung solubility parameter, disregarding two years of follow-up after the date of the first urinalysis, and not adjusting analyses for gamma-radiation dose, did not result in any significant differences from the main findings (unpublished results).

Mortality Risks in Relationship to Period of First Employment

Of the total of 22,374 Mayak workers, 12,295 (497,488 person-years) and 10,079 (345,050 person-years) were first employed in the earlier (1948–1958) and later (1959–1982) periods of operation, respectively. Of the total of 13,627

TABLE 4
Circulatory Disease, Ischemic Heart Disease and Cerebrovascular Disease Mortality for the Mayak, Sellafield and Pooled Plutonium Workers Cohorts, in Relationship to Categories of Cumulative Internal Alpha-Radiation Dose to the Liver from Plutonium

Dose, Gy	Cohort	Mean dose	Person-years	Circulatory disease		Ischemic heart disease		Cerebrovascular disease	
				RR (95% CI)	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	No. of cases
<0.002	MWC	0.001	25313	1	113	1	79	1	20
	SWC	0.001	226366	1	529	1	363	1	95
	PuWC	0.001	251678	1	642	1	442	1	115
0.002–0.005	MWC	0.003	10436	0.68 (0.49, 0.95)	55	0.54 (0.35, 0.82)	31	1.35 (0.71, 2.57)	19
	SWC	0.003	19283	1.04 (0.85, 1.27)	134	1.15 (0.91, 1.46)	98	0.76 (0.45, 1.27)	19
	PuWC	0.003	29719	0.92 (0.77, 1.09)	189	0.93 (0.76, 1.15)	129	0.94 (0.64, 1.39)	38
0.005–0.010	MWC	0.007	11822	1.09 (0.83, 1.42)	141	0.99 (0.71, 1.38)	85	1.59 (0.91, 2.76)	48
	SWC	0.007	13942	0.96 (0.78, 1.19)	128	1.04 (0.81, 1.34)	92	0.76 (0.45, 1.27)	20
	PuWC	0.007	25764	1.05 (0.90, 1.23)	269	1.07 (0.88, 1.30)	177	1.12 (0.80, 1.57)	68
0.010–0.020	MWC	0.014	15228	0.97 (0.75, 1.25)	209	0.90 (0.65, 1.24)	126	1.16 (0.68, 1.99)	66
	SWC	0.014	10832	**1.22 (1.00, 1.49)**	165	1.19 (0.93, 1.52)	105	1.15 (0.73, 1.79)	31
	PuWC	0.014	26060	1.11 (0.96, 1.29)	374	1.09 (0.91, 1.32)	231	1.06 (0.77, 1.47)	97
0.020–0.050	MWC	0.033	20769	1.05 (0.82, 1.35)	338	1.00 (0.74, 1.37)	211	1.15 (0.68, 1.94)	100
	SWC	0.032	7803	1.01 (0.81, 1.25)	120	1.04 (0.79, 1.35)	78	0.96 (0.59, 1.56)	25
	PuWC	0.033	28572	1.10 (0.94, 1.27)	458	1.12 (0.93, 1.34)	289	1.01 (0.73, 1.38)	125
0.050–0.100	MWC	0.072	13800	1.06 (0.81, 1.39)	228	0.89 (0.63, 1.24)	128	1.42 (0.82, 2.45)	79
	SWC	0.069	2478	**1.51 (1.14, 2.01)**	58	1.38 (0.96, 2.00)	34	1.79 (0.98, 3.27)	14
	PuWC	0.072	16278	**1.21 (1.02, 1.44)**	286	1.08 (0.86, 1.35)	162	1.32 (0.94, 1.87)	93
0.100–0.150	MWC	0.123	6977	1.10 (0.82, 1.48)	131	0.87 (0.59, 1.27)	70	1.62 (0.91, 2.89)	50
	SWC	0.121	674	1.09 (0.63, 1.89)	14	0.90 (0.42, 1.94)	7	1.80 (0.73, 4.43)	6
	PuWC	0.123	7650	1.19 (0.96, 1.47)	145	0.99 (0.74, 1.32)	77	1.48 (0.99, 2.19)	56
0.150–0.200	MWC	0.172	4447	1.13 (0.82, 1.56)	90	0.89 (0.58, 1.35)	47	**1.90 (1.04, 3.46)**	39
	SWC	0.17	227	1.41 (0.65, 3.04)	7	0.36 (0.05, 2.60)	1	**3.43 (1.28, 9.21)**	5
	PuWC	0.172	4674	1.24 (0.97, 1.60)	97	0.98 (0.70, 1.39)	48	**1.80 (1.18, 2.76)**	44
0.200–0.300	MWC	0.243	4717	1.22 (0.89, 1.67)	103	1.07 (0.72, 1.59)	61	1.58 (0.85, 2.92)	35
	SWC	0.237	133	1.24 (0.39, 3.96)	3	1.27 (0.31, 5.25)	2	–	0
	PuWC	0.243	4850	**1.33 (1.04, 1.70)**	106	1.24 (0.91, 1.70)	63	1.38 (0.86, 2.19)	35
0.300–0.500	MWC	0.387	4088	0.97 (0.70, 1.35)	88	0.72 (0.46, 1.11)	46	1.34 (0.72, 2.51)	31
	SWC	0.367	63	0.85 (0.11, 6.42)	1	–	–	–	–
	PuWC	0.387	4150	1.06 (0.81, 1.38)	89	0.82 (0.57, 1.18)	46	1.18 (0.73, 1.91)	31
0.500–1.000	MWC	0.704	3276	1.09 (0.77, 1.53)	71	0.96 (0.62, 1.49)	41	1.50 (0.79, 2.86)	26
	SWC	0.573	17	–	–	–	–	–	–
	PuWC	0.703	3293	1.18 (0.88, 1.57)	71	1.10 (0.76, 1.60)	41	1.34 (0.81, 2.22)	26
1.000+	MWC	1.974	2922	1.06 (0.73, 1.53)	60	1.00 (0.63, 1.60)	38	1.42 (0.72, 2.83)	20
	SWC	1.325	22	2.11 (0.28, 15.61)	1	4.11 (0.54, 31.03)	1	–	–
	PuWC	1.969	2944	1.16 (0.85, 1.59)	61	1.19 (0.80, 1.76)	39	1.27 (0.73, 2.20)	20

Notes. Analyses using 10-year dose lag. Adjustments for sex, attained age, calendar period, migration status and dose from external gamma rays were included. Mayak lung solubility assumption was used and the workers were considered unmonitored until the date of the first urinalysis assessment. Statistically significant ($P < 0.05$) estimates are shown in bold type.

radiation workers at Sellafield first employed before 1983, 3,757 (147,840 person-years) and 9,870 (317,331 person-years) were first employed in the earlier (1947–1957) and later (1958–1982) periods, respectively. Table 6 summarizes the main characteristics of these earlier and later sub-cohorts of the MWC and the SWC (see also Supplementary Fig. S2; http://dx.doi.org/10.1667/RR14468.1.S1).

The ERR/Sv estimates for CD, IHD and CeVD mortality in relationship to cumulative external dose for the earlier and later first-employment sub-cohorts of the MWC and the SWC, lagged by 10 years, are shown in Table 7 and illustrated in Fig. 3. The risk of mortality from CD (but not from IHD or CeVD separately) was significantly increased in both earlier sub-cohorts, but the CD mortality risk in the SWC was significantly higher than that in the MWC–ERR/Sv estimates of 0.60 (95% CI: 0.17. 1.13) and 0.05 (95% CI: +0.00, 0.10), respectively ($P = 0.01$), as it also was for IHD mortality (Table 7). For the later sub-cohorts, the ERR/Sv estimates for the MWC and the SWC were similar for both CD and IHD mortality (and although the difference for CeVD mortality was notable, it was not significant). In contrast to the earlier sub-cohorts, there was no significant heterogeneity among the estimates: for CD mortality, the ERR/Sv was 0.25 (95% CI: –0.01, 0.58) for the MWC and 0.15 (95% CI: –0.25, 0.66) for the SWC ($P > 0.5$); for IHD mortality the ERR/Sv was 0.24 (95% CI: –0.08, 0.66) for the MWC and 0.19 (95% CI: –0.33, 0.88) for the SWC ($P > 0.5$). The dose responses for CD and IHD mortality in the SWC for the later sub-cohorts were significantly nonlinear (and were therefore influential in the significant downward curvature of the dose responses for the full period), but this was largely due to five deaths from CD and two deaths from

TABLE 5
Circulatory Disease, Ischemic Heart Disease and Cerebrovascular Disease Mortality for the Cohorts: Linear Dose Responses for the Mayak, Sellafield and Pooled Plutonium Workers Cohorts, in Relationship to Cumulative Internal Alpha-Radiation Dose to the Liver from Plutonium, for Various Ranges of Cumulative Dose

		Circulatory disease		Ischemic heart disease		Cerebrovascular disease	
Dataset	Cohort	ERR/Gy	*P* value[a]	ERR/Gy	*P* value[a]	ERR/Gy	*P* value[a]
Full dataset	MWC	0.03 (–0.07, 0.17)	0.181	+0.00 (na, 0.20)	0.356	0.07 (na, 0.37)	0.217
	SWC	1.06 (na, 3.49)		0.61 (na, 3.12)		3.75 (na, 12.44)	
	PuWC	0.04 (–0.06, 0.18)		0.02 (na, 0.22)		0.08 (na, 0.39)	
<1 Gy	MWC	–0.03 (–0.35, 0.35)	0.452	–0.12 (–0.49, 0.35)	0.410	0.17 (–0.41, 0.96)	0.085
	SWC	0.89 (na, 3.80)		–1.04 (–0.37, 1.84)		5.60 (–0.39, 15.05)	
	PuWC	–0.01 (–0.33, 0.38)		–0.15 (–0.50, 0.31)		0.24 (–0.35, 1.08)	
<0.5 Gy	MWC	–0.05 (–0.59, 0.60)	0.255	–0.57 (–1.13, 0.16)	>0.50	0.53 (–0.51, 1.97)	0.087
	SWC	1.44 (–0.92, 4.54)		–1.04 (na, 2.43)		**6.32 (0.01, 16.18)**	
	PuWC	0.03 (–0.51, 0.69)		–0.59 (–1.14, 0.11)		0.77 (–0.32, 2.31)	
<0.3 Gy	MWC	0.55 (–0.39, 1.72)	0.398	–0.13 (–1.18, 1.19)	>0.50	1.74 (–0.11, 4.39)	0.123
	SWC	1.88 (–0.77, 5.19)		–0.46 (–3.04, 3.27)		**7.77 (0.88, 18.13)**	
	PuWC	0.73 (–0.20, 1.83)		–0.17 (–1.16, 1.05)		**2.42 (0.44, 5.12)**	
<0.1 Gy	MWC	0.06 (–2.59, 3.26)	0.191	–1.18 (–4.14, 2.66)	0.353	–0.55 (–4.55, 5.28)	0.144
	SWC	3.54 (–0.64, 8.67)		1.70 (–3.08, 7.88)		7.82 (–1.57, 22.12)	
	PuWC	1.21 (–1.13, 3.99)		–0.23 (–2.92, 3.03)		1.42 (–2.67, 7.12)	

Notes. Analyses using 10-year dose lag. Adjustments for sex, attained age, calendar period, migration status and dose from external gamma rays were included. Mayak lung solubility assumption was used and the workers were considered unmonitored until the date of the first urinalysis assessment. Statistically significant ($P < 0.05$) estimates are shown in bold type.

[a] *P* value for test of heterogeneity between the ERR/Gy estimates for the MWC and the SWC.

TABLE 6
Main Characteristics of Subcohorts of the Mayak and Sellafield Workers Cohorts by Period of the First Year of Employment

	Mayak Workers Cohort		Sellafield Workers Cohort	
Main characteristics	1948–1958	1959–1982	1947–1957	1958–1982
Number of sub-cohort members	12,295	10,079	3,757	9,870
(Person-years)	(497,488)	(345,050)	(147,840)	(317,331)
Females (%)	29	21	5	9
Number of deaths from:				
Circulatory disease	3,601	1,522	1,239	1,027
Ischemic heart disease	2,016	889	834	683
Cerebrovascular disease	1,140	470	244	187
Mean cumulative external gamma-ray dose (mSv)	810.1 (SD 872.2)	155.0 (SD 213.0)	165.1 (SD 215.4)	91.9 (SD 151.0)
Males	874.8 (SD 912.2)	175.6 (SD 231.2)	172.6 (SD 218.5)	99.0 (SD 156.1)
Females	652.6 (SD 743.1)	77.2 (SD 84.0)	26.4 (SD 31.6)	19.8 (SD 32.3)
Mean annual external gamma-ray dose (mSv)	60.2 (SD 152.6)	9.3 (SD 21.9)	12.1 (SD 14.4)	7.3 (SD 10.9)
Males	61.8 (SD 157.6)	10.5 (SD 24.1)	12.3 (SD 14.5)	7.6 (SD 11.1)
Females	55.6 (SD 136.8)	4.7 (SD 7.1)	4.7 (SD 6.1)	2.7 (SD 4.0)
No. of sub-cohort members monitored for plutonium exposure	3,748	3,751	1,886	4,621
(Person-years, total/after date of first urinalysis sample)	(170,998/63,012)	(136,360/60,781)	(79,317/73,516)	(155,810/137,481)
No. of deaths registered among workers with measured plutonium in urine from:				
Circulatory disease	1,208	590	632	494
Ischemic heart disease	721	360	427	327
Cerebrovascular disease	389	172	125	87
Mean cumulative absorbed internal alpha-radiation dose (mGy)	354.5 (SD 870.7)	34.6 (SD 96.3)	34.5 (SD 66.7)	9.3 (SD 83.4)
	95% percentile 1,572.6	95% percentile 137.1	95% percentile 138.1	95% percentile 29.7
Males	294.4 (SD 658.7)	41.2 (SD 110.9)	34.6 (SD 66.9)	9.3 (SD 85.9)
	95% percentile 1,401.3	95% percentile 171.4	95% percentile 137.9	95% percentile 29.7
Females	476.2 (SD 1180.2)	17.4 (SD 31.1)	30.8 (SD 61.2)	8.4 (SD 19.5)
	95% percentile 2,219.5	95% percentile 70.2	95% percentile 181.4	95% percentile 30.2
Mean annual absorbed internal alpha-radiation dose (mGy)	7.5 (SD 20.4)	0.9 (SD 2.5)	1.2 (SD 1.9)	0.3 (SD 3.1)
Males	6.6 (SD 15.9)	1.0 (SD 2.8)	1.2 (SD 1.9)	1.2 (SD 1.5)
Females	8.9 (SD 26.3)	0.4 (SD 0.8)	0.3 (SD 3.2)	0.3 (SD 0.5)

TABLE 7
Linear Dose Responses for Circulatory Disease, Ischemic Heart Disease and Cerebrovascular Disease Mortality in the Mayak and Sellafield Worker Cohorts and Pooled Cohorts (the Combined Radiation or the Plutonium Worker Cohorts) in Relationship to Cumulative External Gamma- and Internal Alpha-Radiation Doses for the Two Sub-Periods of First-Employment in each Cohort

			Circulatory disease			Ischemic heart disease			Cerebrovascular disease		
Dose	Cohort	First-employment period	ERR/Sv or ERR/Gy	*P* value[a]	*P* value[b]	ERR/Sv or ERR/Gy	*P* value[a]	*P* value[b]	ERR/Sv or ERR/Gy	*P* value[a]	*P* value[b]
Gamma (Sv)	MWC	1948–1958	**0.05 (+0.00, 0.10)**	0.15	**0.01**	0.06 (–0.00, 0.13)	0.31	**0.01**	0.04 (–0.04, 0.13)	0.18	>0.50
		1959–1982	0.25 (–0.01, 0.58)			0.24 (–0.08, 0.66)			0.40 (–0.09, 1.12)		
	SWC	1947–1957	**0.60 (0.17, 1.13)**	0.18	>0.50	**0.75 (0.20, 1.47)**	0.20	>0.50	0.31 (–0.40, 1.48)	0.27	0.17
		1958–1982	0.15 (–0.25, 0.66)			0.19 (–0.33, 0.88)			–0.37 (na, 0.72)		
	RWC	Earlier	--[c]	0.18		--[c]	0.32		0.04 (–0.04, 0.13)	0.39	
		Later	0.22 (–0.01, 0.49)			0.22 (–0.06, 0.57)			0.24 (–0.17, 0.80)		
Alpha (Gy)	MWC	1948–1958	0.04 (–0.06, 0.19)	>0.50	0.39	0.02 (na, 0.23)	0.43	0.47	0.07 (na, 0.38)	0.32	0.07
		1959–1982	–0.02 (na, 1.71)			–0.59 (na, 1.56)			1.43 (na, 6.84)		
	SWC	1947–1957	1.27 (na, 4.93)	>0.50	0.36	–0.97 (na, 2.58)	0.20	0.14	6.43 (na, 20.12)	>0.50	>0.50
		1958–1982	1.26 (na, 7.43)			2.02 (na, 11.89)			–0.26 (na, 38.61)		
	PuWC	Earlier	0.04 (–0.06, 0.19)	0.49		0.02 (na, 0.23)	>0.50		0.08 (na, 0.40)	0.33	
		Later	0.36 (na, 1.92)			0.37 (na, 2.41)			1.39 (na, 6.61)		

Notes. Analysis using 10-year dose lag. Adjustments for sex, attained age, calendar time, migration status and dose from external gamma rays or internal alpha particles were included. Mayak lung solubility assumption was used and the workers were considered unmonitored until the date of the first urinalysis assessment. Statistically significant ($P < 0.05$) estimates are shown in bold type. na = not available due to non-convergence

[a] *P* value for the heterogeneity of the CD, IHD and CeVD mortality risk estimates between the first year of employment periods within each cohort (MWC, SWC and RWC/PuWC).

[b] *P* value for the heterogeneity of the CD, IHD and CeVD mortality risk estimates between the MWC and the SWC in each period of the first year of employment (before 1959/1958 and after 1958/1957, respectively).

[c] Significant heterogeneity between the ERR/Sv estimates for the MWC and the SWC, so a pooled ERR/Sv estimate for the RWC is not appropriate.

IHD with doses >1 Sv, and the dose responses were no longer significantly nonlinear when the dose range was restricted to <1 Sv.

The ERR/Gy dose-responses for internal alpha radiation, for CD, IHD and CeVD mortality, were notably different between the MWC and the SWC, both in earlier and later first-employment sub-cohorts, but the differences were not statistically significant, potentially due to low statistical power (Table 7).

Tests for heterogeneity of risk estimates between earlier and later first-employment sub-cohorts within either the MWC or the SWC did not show any significant differences for any of the disease types analyzed for exposure to either external or internal radiation.

Pooled analyses were not performed for external radiation dose and CD or IHD mortality in the earlier sub-cohorts because of significant heterogeneity between the ERR/Sv estimates for the MWC and the SWC; the pooled analysis for CeVD mortality in the earlier RWC sub-cohort produced an ERR/Sv estimate that did not differ significantly from zero (Table 7). The pooled analysis for CD, IHD and CeVD mortality associated with the internal alpha-particle dose in the earlier PuWC sub-cohort showed increased ERR/Gy estimates, although none was statistically significant (Table 7). The pooled analyses considering data for later sub-cohorts of Mayak and Sellafield workers showed positive dose responses for mortality from CD, IHD and CeVD, in relationship to both external gamma rays and internal alpha particles, although no slope was statistically significant. For the later periods, for CD mortality the pooled analyses for the RWC gave an ERR/Sv for external radiation dose of 0.22 (95% CI: –0.01, 0.49) (see Table 7 and Supplementary Fig. S3; http://dx.doi.org/10.1667/RR14468.1.S1), while for the PuWC the ERR/Gy for internal radiation dose was 0.36 (95% CI: <0, 1.92); risk estimates for IHD and CeVD did not differ significantly from the equivalent estimates for CD mortality (Table 7).

The above results remained largely unaffected when only the male workers of each sub-cohort were analyzed (Supplementary Table S11; http://dx.doi.org/10.1667/RR14468.1.S1), as was also the case when a five-year rather than 10-year lag, the SS2 rather than SS1 lung solubility parameter, or disregarding of two years of follow-up after the date of the first urine sample, were used (unpublished data).

DISCUSSION

In the current study, we investigated potential relationships between mortality from CD (as a whole and for the two major subtypes, IHD and CeVD) and cumulative recorded doses from external gamma radiation and internal alpha particles to the liver from plutonium in cohorts of nuclear workers from the Mayak and Sellafield installations. The MWC and the SWC are large cohorts of radiation workers with long follow-up periods and wide ranges of external and internal doses. CD, IHD and CeVD mortality risks were estimated for each cohort using the same statistical models and a consistent approach to the calculation of individual doses from external gamma and internal alpha radiation. Where appropriate (i.e., when the equivalent estimates for each cohort did not differ significantly), the data from the cohorts were combined in pooled analyses. The MWC included a larger proportion of women than the SWC, but analyses including men only were similar to those for the cohorts as a whole.

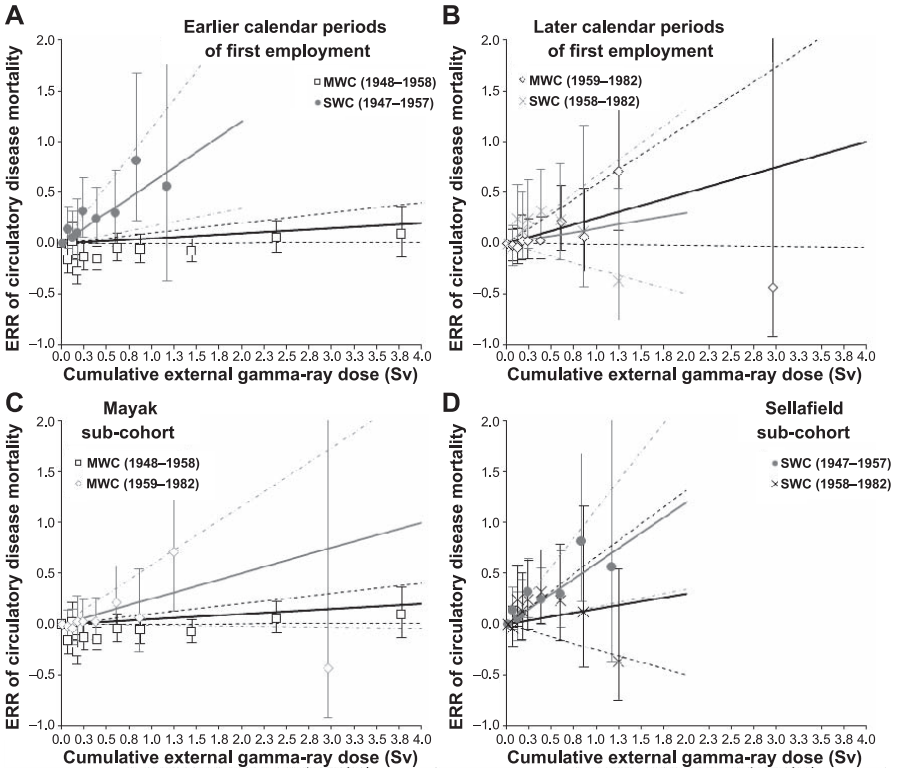

FIG. 3. Variation of the ERR of CD mortality for the whole cohort with the cumulative gamma-radiation dose (Sv) in the Mayak and Sellafield nuclear workforces by four sub-cohorts of workers: those first employed in the earlier or later period of operations, at either the Mayak or Sellafield installation. Ten-year dose lag was used for the analyses. Adjustments for sex, attained age, calendar period, migration status and dose from external gamma rays were included. Mayak lung solubility assumption was used and the workers were considered unmonitored until the date of the first urinalysis assessment.

External Dose

The results demonstrated significant associations between CD and IHD, but not CeVD, mortality and the cumulative external gamma-radiation dose in both cohorts. However, the ERR/Sv estimates for CD and IHD mortality differed significantly between the two worker cohorts by approximately one order of magnitude, the associations for the MWC being of marginal statistical significance and notably weaker when compared to those for the SWC: for the MWC, the ERR/Sv estimates for mortality from CD, IHD and CeVD were 0.04 (95% CI: –0.00, 0.09), 0.06 (95% CI: 0.01, 0.13) and +0.00 (95% CI: –0.06, 0.08), respectively, while for the SWC the corresponding estimates were 0.42 (95% CI: 0.12, 0.78), 0.53 (95% CI: 0.14, 1.00) and 0.05 (95% CI: –0.46, 0.79), respectively. The marked difference in the dose responses for CD mortality is shown in Fig. 2. Since significant heterogeneity between equivalent risk estimates for the two cohorts was found, pooled analyses were not conducted as the underlying radiation-associated risks being estimated could differ between the workforces for reasons that have not been established.

Risk patterns of CD, IHD and CeVD mortality in the MWC and SWC, with respect to cumulative external dose, exhibit notable features (see Fig. 2 for CD mortality). For the MWC, the tendency is for categorical RRs to be <1.0 for the eight dose groups in the range 0.05–2.0 Sv when compared with the <0.05 Sv reference dose group (Table 2), although this did not result in an ERR/Sv dose response that differed significantly from linearity when a number of alternative models were investigated. This pattern of generally decreased RRs for low-to-moderate cumulative external doses in the MWC could have a number of possible explanations. These include, *inter alia*, the competing risks of other diseases (especially cancers of the lung, liver and bone resulting from large, potentially unmonitored, intakes of plutonium) or a substantial underestimation or non-recording of certain doses (e.g., neutron doses). For the SWC, the ERR/Sv dose responses for both CD and IHD show significant nonlinearity, curving downward towards higher doses (Fig. 2 and Supplementary Table S5; http://dx.doi.org/10.1667/RR14468.1.S1) so that the dose responses for restricted ranges of external doses have steeper slopes than those for the full dose range (Table 3). However, the numbers of CD and IHD deaths in the SWC with external doses >1 Sv are small (10 and 6, respectively) and the dose responses no longer depart significantly from linearity if cumulative doses are restricted to <1 Sv (Supplementary Table S5).

The analysis of CD mortality risk in two sub-cohorts at each installation, defined, *a priori*, by year of first

employment (see Table 7 and Fig. 3), demonstrated that significant heterogeneity in risk estimates for external radiation exposure was found only for CD and IHD mortality for the earlier first-employment sub-cohorts of the MWC and the SWC (1948–1958 and 1947–1957, respectively). No significant differences were found among the later sub-cohorts (1959–1982 and 1958–1982 for the MWC and SWC, respectively). For these later sub-cohorts a linear dose-response model for the pooled RWC produced ERR/Sv estimates of 0.22 (95% CI: –0.01, 0.49) for CD mortality (see Supplementary Fig. S3; http://dx.doi.org/10.1667/RR14468.1.S1), 0.22 (95% CI: –0.06, 0.57) for IHD mortality and 0.24 (95% CI: –0.17, 0.80) for CeVD mortality.

A challenge to interpreting the results for the later sub-cohorts is that the significant nonlinearity in the Sellafield dose responses for CD and IHD mortality found for the full cohort (as discussed above) is largely due to significant downward curvature in the later first-employment sub-cohort (see Fig. 3), leading to steeper slopes for the SWC dose responses for this later period if cumulative doses are restricted to <0.5 Sv (see Fig. 3). Why this significant nonlinearity is present in the SWC for the later, but not the earlier, first-employment sub-cohort is unclear since, for example, it would be expected that external doses would be more accurately recorded in the later years of operations at the site so that dose misclassification was less likely during the later period. Even so, the numbers of CD and IHD deaths in the SWC during the later period with doses >1 Sv are small, at 5 and 2 deaths, respectively, and the downward curvature becomes nonsignificant if the dose range is restricted to <1 Sv. Of interest is the comparability of the slopes of the CD mortality external dose responses for the SWC between the earlier and later first-employment periods for doses <0.75 Sv (see Fig. 3).

In contrast, it is in the earlier first-employment period for the MWC that RRs less than 1.0 for the low-to-moderate external dose groups are present; this pattern is also apparent for the full period (as discussed above), but not for the later period (Fig. 3). This is consistent with an explanation related to employment during the early years of operations at Mayak when working conditions were particularly harsh, radiation doses were high and their measurement and recording less reliable than in later years, and there were also exposures to various chemical agents (mainly acids and organic solvents). However, the patterns of risks with cumulative external dose displayed by the two workforces in the first-employment periods is complex and not readily interpreted.

Internal Dose from Plutonium Exposure

The analysis of mortality from CD, IHD and CeVD in relationship to the liver dose accumulated from internal alpha radiation emitted by plutonium did not reveal a significant dose-response in either of the cohorts or in the pooled cohort. The ERR/Gy estimates from the pooled analysis were largely a reflection of the Mayak findings because of the dominance of the MWC data due to the magnitude of the plutonium exposures experienced by the monitored workers. For some of the categorical RRs, the pooled analysis showed effect estimates that did not seem consistent with the estimates from separate cohort analyses (see, for example, the CD mortality RRs for the 0.2–0.3 Gy dose group shown in Table 4). As noted in Materials and Methods, the models for these analyses allowed the effects of sex, attained age and calendar period to differ between cohorts, since this was expected. Thus, in theory, the pooled analysis should allow for these factors in a way that is consistent with the separate analyses. Nevertheless, the results from the pooled analysis may not be reliable because the distribution of sex, attained age and calendar period differs in important ways between the two cohorts; for example, there were only a few women in the higher exposure categories at Sellafield, but much larger numbers at Mayak. However, the same apparent anomalies were seen when the analysis was confined to male workers, but were evident only when relatively small numbers of deaths in the SWC were involved.

For liver doses of alpha particles from deposited plutonium, the analyses are more complex than those for doses of external penetrating gamma rays, because internal doses have to be derived indirectly from measurements of plutonium excreted in urine and are associated with large uncertainties. Also, the doses of alpha radiation to the liver are (presumably) only surrogates for the doses to organs/tissues that might be relevant to the risk of CD mortality, although doses from plutonium to these other systemic organs/tissues will be highly correlated with the liver dose. Doses from plutonium to organs/tissues such as the brain, heart or vessel walls will be considerably less than the dose to the liver (the main organ of plutonium deposition), so the ERR/Gy when using these doses will be greater than the risk estimate when using the liver dose, although the absence of a significant dose response for the liver dose from plutonium suggests that the issue of which organ/tissue dose to use does not appear to be a crucial one for risk estimation. The solubility of plutonium nitrate in the lung, and therefore the dose to the lung, remains an unresolved issue, but this has a limited impact on the internal doses of potential relevance to CD mortality risk because, as mentioned above, these doses refer to a systemic biokinetics model rather than to a respiratory one. The problems associated with the monitoring for exposure to plutonium at both installations should also be considered: measurements of plutonium in urine at Sellafield before 1971 were potentially affected by cross-contamination of samples (*26*), and although no personal protective equipment to prevent inhalation of radioactive materials was used at Mayak before 1959, leading to large intakes of plutonium, urinalysis for plutonium at Mayak only started in 1970 and has included just 41% of the workers considered to be

potentially exposed to substantial quantities of plutonium (*33*).

Comparison with Previous Studies

The findings of this study may be compared with the results of earlier studies of cohorts of Mayak and Sellafield workers. When making this comparison for the MWC, the following differences should be borne in mind: 1. Dose estimates for internal alpha radiation have been modified; 2. The analyses in this study did not take into account major nonradiation risk factors for CD (smoking, alcohol consumption, body mass index and hypertension); 3. The current analysis included workers acutely exposed to high doses of external radiation (although affecting only 43 individuals) as well as 67 workers with single intakes of large amounts of plutonium (via inhalation or skin damage) who were not included in previous studies of the MWC; 4. Person-years of follow-up in the two years after the first urine sampling were not excluded from the principal analysis. Nonetheless, for the MWC, Azizova, *et al*. (*18*) reported a CD mortality ERR/Gy of external radiation of 0.10 (95% CI: 0.02, 0.21), which does not differ notably from the corresponding ERR/Sv estimate in the current study of 0.04 (95% CI: –0.00, 0.09). For BNFL workers (strongly influenced by the SWC), McGeoghegan, *et al*. (*10*) reported a CD mortality ERR/Sv of external dose of 0.50 (90% CI: 0.26, 0.79), while the ERR/Sv for the SWC found in the current study was 0.42 (95% CI: 0.12, 0.78). Analyses of CD mortality in relationship to alpha-radiation dose have not previously been reported for the SWC, but the results for CD mortality risk in the MWC are broadly consistent with results of previous studies: Azizova, *et al*. (*18*) reported a CD mortality ERR/Gy of 0.13 (95% CI: <0, 0.35), which compares with that of 0.03 (95% CI: –0.07, 0.17) in this study.

We have pointed to various seemingly anomalous aspects of the findings of the current study, which require explanations before the results can be reliably interpreted. Among these are the ERR/Sv estimates for cumulative external dose, for which the values for CD and IHD mortality for the SWC are significantly higher than those for the MWC and exhibit significant non-linearity, which is largely due to downward curvature in the later first-employment period (although based on a limited number of deaths at high cumulative doses). Potentially of relevance to the SWC findings is the pattern of CD mortality in male BNFL workers (a large proportion from Sellafield) found in the study of McGeoghegan, *et al*. (*10*). The overall external dose ERR/Sv for CD mortality was significant at 0.50 (90% CI: 0.26, 0.79). However, when workers were categorized into four subgroups [''industrial workers'' (i.e., ''blue collar workers''); ''nonindustrial workers'' (i.e., ''white collar workers''); those workers who had been monitored for exposure to external radiation only; and those workers who had been monitored for exposure to both external and internal radiation], the resulting ERR/Sv estimates (with respect to gamma-ray dose only) displayed significant heterogeneity. The largest external dose ERR/Sv estimate for CD mortality was found for those workers monitored for exposure to external radiation only, who tended to have received lower cumulative gamma-ray doses. These puzzling findings may reflect the varying presence of background risk factors in different groups of BNFL workers, and the significantly lower CD SMR (70; 95% CI: 67, 73) for nonindustrial employees compared to that (89; 95% CI: 87, 91) for industrial employees lends support to this suggestion (and the overall pronounced ''healthy worker effect'' for CD mortality in the BNFL workforce should be noted).

The influence of major established CD mortality risk factors was not taken into account in the current study, since there was a lack of information on nonradiation risk factors in the SWC. Consequently, the possibility of confounding factors affecting the findings of the current study must be considered. However, analyses of the MWC, for which explicit data on a number of potentially important confounders (smoking, alcohol consumption, body mass index and hypertension) are available for most workers, have shown that adjustment of the estimates of ERR per unit dose to account for the presence of these factors has little impact on either the external or internal radiation risk estimates for CD mortality (*18*). Nonetheless, the markedly differing background risks of CD mortality experienced by the two cohorts (Supplementary Fig. S4; http://dx.doi.org/10.1667/RR14468.1.S1) could provide at least part of the explanation for the patterns of risks found in this study; while the sex- and age-standardized CD mortality rates in the UK steadily declined with time, those in the Russian Federation fluctuated around an approximately constant rate and the rate was 3.5-fold higher than the corresponding rate in the UK by the end of the study follow-up period (Supplementary Fig. S5). We are planning to conduct analyses of the excess absolute risk (EAR) of CD mortality in terms of dose as one way of investigating the influence of background risk on radiation-associated effects.

Adjustment for duration of employment (or of radiation monitoring) has been done in some worker studies to account for the so-called ''healthy worker survivor effect''; workers who remain employed tend to be healthier than those who leave employment (*41*). We were not able to adjust for duration of employment because the necessary data had not been provided in the datasets. Previous separate analyses of the MWC and the SWC have not shown that adjustment for duration of employment had a substantial impact on CD mortality associations. Azizova, *et al*. (*18*) found that CD mortality ERR/Gy estimates for external and internal doses were minimally affected by adjustment for employment duration at Mayak: external gamma-ray dose ERR/Gy estimates were 0.06 (95% CI: 0.01, 0.12) and 0.05 (95% CI: >0, 0.11) with and without adjustment, respectively. Similarly, McGeoghegan, *et al*.

(*10*) found that adjustment for duration of employment in their analysis of CD mortality and external radiation dose in the BNFL workforce (which will have been strongly influenced by the Sellafield workforce) had ''no material effect'' on their findings: ERR/Sv values using a 15-year lag were 0.54 (90%CI: 0.21, 0.92) and 0.65 (90% CI: 0.36, 0.97) with and without adjustment, respectively.

The current study adds to the evidence relating to the risk of CD and low-level exposure to radiation, recently reviewed by Azizova, *et al*. (*17, 23*) and Little (*16*). The pattern of results from studies of CD after low or moderate acute doses and protracted exposures at low dose rates does not point to an obvious explanation, causal or otherwise, for the reported associations (*42–47*). Studies of CD in the Japanese atomic bomb survivors have produced results that do not invite a straightforward interpretation because of, *inter alia*, substantial variation of risks between disease subtypes (*42–44*). Studies of Russian ''liquidators'' of the Chernobyl accident have reported raised risks of CD incidence with respect to external dose, but based on a surprisingly high proportion of cases among the liquidators (*45, 46*). The authors of the recent INWORKS analysis of CD mortality among nuclear workers (including those from Sellafield), which showed significantly increased ERR/Sv external dose, warned that heterogeneity of risks did not permit firm conclusions to be drawn (*47*). The findings of the current study reinforce the need for a careful interpretation of a complex set of results, and for future studies to address outstanding issues, such as the influence of major non-radiation risk factors for CD on reported radiation-associated risk estimates. Of substantial bearing on the uncertainty surrounding the interpretation of these epidemiological associations is the lack of understanding of biological mechanisms that could be responsible for low-level radiation exposure increasing the risk of CD, and Little (*16*) has observed that there is an urgent need for further research in this area.

CONCLUSION

The analysis of mortality from CD, IHD and CeVD in cohorts of Mayak and Sellafield nuclear workers did not reveal any significant dose responses for the cumulative internal alpha-particle dose to the liver from deposited plutonium for the MWC, SWC or pooled PuWC. The ERR/Sv estimates with respect to cumulative external gamma-ray dose were significantly raised in both cohorts (marginally so for the MWC) for CD and IHD (but not CeVD) mortality, but the estimates for the SWC were approximately tenfold and significantly larger than those for the MWC. This significant heterogeneity between the study cohorts precluded the derivation of an ERR/Sv estimate for the pooled RWC. This pattern of findings for external exposure was repeated for CD and IHD mortality in the MWC and SWC for workers first employed in the earlier periods of operation at the two installations. However, the ERR/Sv external dose estimates for the two worker cohorts for the later first-employment periods are statistically compatible and suggestive of radiation-associated risks of CD, IHD and CeVD mortality: for the pooled RWC, the ERR/Sv estimates are non-significantly positive at 0.22 (95% CI: –0.01, 0.49), 0.22 (95% CI: –0.06, 0.57) and 0.24 (95% CI: –0.17, 0.80), respectively.

The patterns of risk found in this study are complex. Of particular note are the marked and significant differences between the ERR/Sv external dose estimates for CD and IHD mortality for the MWC and SWC for the earlier first-employment periods. The conspicuous difference in the background absolute risk of CD mortality in the two worker cohorts may have had a role in generating the results reported here. Further investigations are required to provide a proper understanding of these findings.

SUPPLEMENTARY INFORMATION

Table S1. Data categorization for the Mayak and Sellafield worker cohorts.

Table S2. CD mortality: analyses of nonradiation factors.

Table S3. IHD mortality: analyses of nonradiation factors.

Table S4. CeVD mortality: analyses of nonradiation factors.

Table S5. CD, IHD and CeVD mortality in the MWC and the SWC: nonlinear dose-responses in relationship to external gamma and internal alpha radiation doses.

Table S6. CD, IHD and CeVD mortality relative risks (RRs) for male workers only, for the MWC, the SWC and (where appropriate) the pooled RWC, in relationship to categories of cumulative external gamma-ray doses.

Table S7. CD, IHD and CeVD mortality for male workers only: linear dose responses for the MWC, the SWC and (where appropriate) the pooled RWC, in relationship to cumulative external gamma-ray doses, for various ranges of cumulative dose.

Table S8. CD, IHD and CeVD mortality for male workers only in the MWC and the SWC: nonlinear dose responses in relationship to external gamma and internal alpha-radiation doses.

Table S9. CD, IHD and CeVD mortality relative risks (RRs) for male workers only, for the MWC, the SWC and the pooled PuWC, in relationship to categories of cumulative internal alpha-radiation dose to the liver from plutonium.

Table S10. CD, IHD and CeVD mortality for male workers only: linear dose responses for the MWC, the SWC and the pooled PuWC, in relationship to cumulative internal alpha-radiation dose to the liver from plutonium, for various ranges of cumulative dose.

Table S11. Linear dose responses for CD, IHD and CeVD mortality for male workers only in the MWC, the SWC and the pooled cohorts (RWC or PuWC) in relationship to cumulative external gamma- and internal alpha-radiation doses for the two subperiods of first employment in each cohort.

Fig. S1. Mean annual individual dose by calendar year for the Sellafield Workers Cohort (SWC) and the Mayak Workers Cohort (MWC) from (panel A) external gamma rays and (panel B) alpha particles to the liver from internally deposited plutonium.

Fig. S2. Mean annual individual dose by calendar year for earlier and later first-employed workers in the MWC and the SWC from (panel A) external gamma rays and (panel B) alpha particles to the liver from internally deposited plutonium.

Fig. S3. Variation of the ERR of CD mortality with the cumulative gamma radiation dose from external sources for the pooled RWC in the later first-employment periods. Points are estimates for dose groups and lines are fitted linear dose responses. Error bars and bands are 95% confidence intervals.

Fig. S4. Overall mortality rates (MR) from (panels A–C) all CDs, IHD and CeVD, respectively, in the MWC and SWC by sex and attained age (year).

Fig. S5. Sex- and attained age-standardized (SDR) CD mortality rates in the Russian Federation and in the UK by calendar year, as reported by the WHO Regional Office for Europe (European Mortality Database: http://data.euro.who.int/hfamdb).

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