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Title page

Manuscript title

Risk of lung cancer mortality in nuclear workers from internal exposure to alpha particle-emitting radionuclides

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Running title

Lung cancer in nuclear workers and alpha-emitters

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Competing financial interests

All authors declare that they have no competing financial interests. WA, DB, KB, RB, RC, AF, and AER are employed currently or were employed in the nuclear industry.

Abstract

Background

Carcinogenic risks of internal exposures to alpha-emitters (except radon) are relatively poorly-understood. Since exposure may occur in environmental, malicious, accidental and occupational settings, understanding consequent risks is a priority for radiation protection. An occupational study in nuclear workers addresses this need as detailed historical dosimetry data are available.

Objectives

To quantify dose-response relationships between lung dose from alpha-emitters and lung cancer in nuclear workers.

Methods

A case-control study was conducted, nested within cohorts of fuel cycle workers in Belgium, France and UK. Cases were workers who died from lung cancer; 1-3 controls were matched by age, sex and facility. Lung doses from alpha-emitters were estimated using retrospective dosimetry. Excess odds ratios (EOR) of lung cancer per gray (Gy) of lung dose were estimated.

Results

The study comprised 553 cases and 1333 controls. Median positive total alpha lung dose was 2.42mGy (mean: 8.13mGy; maximum: 316mGy); for plutonium and uranium it was 1.27mGy and 2.17mGy, respectively. EOR/Gy (90% confidence interval)—adjusted for external radiation, socioeconomic status and smoking—was 11.00 (2.62, 23.72) for total alpha dose, 50.20 (16.98, 106.20) for plutonium, and 5.33 (-1.93, 17.96) for uranium.

Conclusions

Risk estimates for lung cancer due to internal alpha doses from uranium and plutonium were similar to those estimated previously in plutonium workers, and in uranium miners exposed to radon and its

progeny. Although EOR/Gy is greater for plutonium than uranium, confidence intervals overlap. Expressed as risk/equivalent dose (relative biological effectiveness: 20) our estimates are compatible with those in atomic bomb survivors.

Introduction

Background

Knowledge of long-term health effects of ionising radiation is chiefly derived from studies of populations exposed to photons (X-rays and gamma rays), particularly the Japanese atomic bomb survivors (Preston et al. 2007) and populations receiving external radiation doses through occupational, medical and environmental exposures (UNSCEAR 2006). Considerably less is known about long-term impacts of internal exposure to emitters of alpha particles. Since internal exposures to alpha-emitters may occur in environmental, malicious, accidental and occupational settings, understanding attendant long-term risks is a priority in radiation protection.

The nuclear industry encompasses the generation of nuclear energy, production of nuclear weapons, enrichment and reprocessing of nuclear fuel, and reactor research. Monitoring of photon radiation exposures is straightforward; complete records are available from the industry's inception. Epidemiological studies of nuclear workers have chiefly examined associations between cancers and photon radiation exposure (Cardis et al. 1995, 2005; Leuraud et al. 2015; Richardson et al. 2015). However, at some facilities—particularly those involved in the fuel cycle and weapons production—workers may receive internal doses from incorporation of radionuclides, in particular uranium and plutonium, by inhalation, ingestion or contamination of wounds. Following inhalation/incorporation, the dose to an organ or tissue depends on the radionuclide/element, its physicochemical form and intake route (Zhivin et al. 2014). Alpha particles produce more ionisation per cell than an equivalent photon dose i.e. they have increased relative biological effectiveness (RBE). In radiation protection the RBE for alpha particles is taken to be 20 (ICRP 1991). While sufficient epidemiological evidence exists to declare some radionuclides as human carcinogens (e.g. plutonium and radon progeny), risks remain poorly-quantified (e.g. plutonium), and evidence of carcinogenicity is limited for others (e.g. uranium) (IARC 2009).

Relatively large lung doses can result from inhalation of uranium/plutonium, depending on solubilities of the materials inhaled. Lung cancer risk from internal exposure to these radionuclides is therefore of

particular interest. It is well-established that prolonged exposure to radon progeny increases lung cancer risk (ICRP 2010; Kreuzer et al. 2010). Studies of cancer risks associated with plutonium have been conducted in highly-exposed individuals in the Mayak worker cohort (MWC) (Gilbert et al. 2013) and less highly-exposed workers at Sellafield (Omar et al. 1999), with uranium and plutonium in nuclear workers in the US (Boice et al. 2011; Brown et al. 2004; Richardson and Wing 2006; Wing et al. 2004), and with thorium and radium in medical patients (Harrison and Muirhead 2003). Few studies, however, have carried out individual reconstruction of lung doses from incorporated alpha-emitters and dosimetry has largely been based on limited bioassay data, resulting in uncertain doses, particularly at low doses.

An increased risk of solid cancer in relation to external photon radiation dose was found in the International Collaborative Study (ICS), a 15-country cohort study of nuclear workers (Cardis et al. 2005, 2007) and in the International Nuclear Workers Study (INWORKS), a continuation of the ICS restricted to the USA, UK and France (Richardson et al. 2015). The ICS excluded workers with potential for internal exposure to alpha-emitters as reconstruction of doses from these was impracticable at the cohort level. Smoking information was not available in the ICS or INWORKS.

Objectives

The aim of this study was to quantify any dose-response relationship between cumulated lung dose from alpha-emitters and lung cancer mortality among nuclear workers monitored for uranium and/or plutonium exposure in five European cohorts.

Methods

Study design

Within the large EU-funded Alpha-Risk project, a case-control study of lung cancer mortality was conducted, nested in a set of five cohorts identified in the much larger ICS (Muirhead et al. 2009), comprising workers from Belgium, France and the UK (Table 1). This was the most efficient design as it reduced data collection (internal monitoring and smoking) and individual dose reconstruction compared with a cohort study. The activities covered by these facilities include: nuclear research and development, waste treatment, fuel production and reprocessing, construction and operation of experimental reactors, development of fast breeder reactors, and nuclear weapons research and production.

Study population

The study population included all workers employed for ≥1 year at a facility in a study cohort monitored for internal exposure to plutonium and/or uranium through urinalysis on or after a date, t_1, defined as the earliest date at which reliable bioassay data were available (Table 1). For uranium, t_1 corresponded to the start of operation of a facility; early plutonium bioassays may have been unreliable, hence t_1 was defined as the year after which these data could be used to produce accurate and unbiased dose assessments.

Workers employed for <1 year were excluded, as they may not be comparable to longer-term workers in terms of cancer risk. Contract workers were excluded as participating facilities as their work histories and exposures could not be comprehensively reconstructed nor their mortality followed up.

Occupational and dosimetric histories were reconstructed for workers employed at more than one facility or employed several times at the same facility; final dose assessments for these subjects were conducted at the facility of last employment. Cases were defined as all deaths within the study populations and mortality follow-up periods (Table 1) for which lung cancer was either the underlying cause of death or an associated cause where no other cancer was listed as an underlying cause.

Controls were alive and at risk in the year of death of the case ("reference date"); one to three controls were matched to each case by age at reference date (within 5 years), sex and facility (for cohorts comprising more than one geographically distinct facility, this facility was used as the matching variable). Controls born closest to the date of birth of the case were preferentially selected. Controls were eligible for reselection as a control for another case and for subsequent selection as a case.

Dosimetry

Individual annual external doses, compiled for each worker for the purposes of other epidemiological studies (Cardis et al. 2007), were obtained. Individual lung doses from internally-incorporated alpha-emitters—chiefly plutonium and uranium, and some others (radium, actinium, thorium, curium, polonium, radium-protactinium and americium)—were estimated for each subject annually from start of potential exposure up to and including the reference date of the relevant case. Doses were reconstructed from bioassay data (primarily urinalysis but also faecal analysis) and other monitoring results, where available, using a common dosimetry methodology developed and tested by the study dosimetry sub-committee as detailed in the accompanying paper (Bérard et al. In press). Doses depended on assumptions regarding radioactive materials to which a worker was exposed, lung absorption characteristics, and intake regimes (acute or chronic). We generated four indices of internal dose: total alpha dose (all radionuclides); alpha dose from plutonium; alpha dose from uranium; and total dose from other alpha-emitters.

Doses were estimated using the Human Respiratory Tract Model (HRTM) (ICRP 1994), in which the lung is partitioned into three regions: bronchial (BB), bronchiolar (bb) and alveolar interstitial (AI). For the main analysis, doses were estimated to each region, and to the lung as a whole, because doses to these regions from radionuclide-bearing aerosols vary considerably and the radiosensitivities of cells in these regions are assumed to differ. Dose estimates were provided for four types of cell: basal (BB_{bas}) and secretory (BB_{sec}) cells in the BB region, Clara cells in the bb region and endothelial cells in the AI region. Dose to the three regions were summed using weights of 1/3 for AI and bb regions and 1/6 for BB_{sec} and BB_{bas} sub-regions, as recommended by the ICRP (ICRP 1994). This weighted

lung dose has been used in epidemiological studies of radon and its progeny (Rage et al. 2012) and is extensively used in radiation protection (ICRP 2010). Studies of MWC have used a different approach, wherein dose is calculated as total energy deposited in the lungs divided by lung tissue mass so—as a sensitivity analysis—we also generated mass-averaged lung doses (weights: BB=0.0006; bb=0.0017; AI=0.9977).

Potential confounding

Information was available on the matching variables—age, sex and facility—as well as socioeconomic status (SES). Facility is important in terms of controlling for other potential workplace exposures and for geographically-determined factors (e.g. natural background radiation). SES serves as a surrogate for lifestyle factors associated with cancer including smoking and diet. Some nuclear industry jobs may be more common among certain SES strata; confounding would result if exposure potential were related to particular jobs. SES was assigned to each subject based on job title—corresponding to either job at time of hiring (France), last job (UKAEA, AWE), or job of longest duration (other cohorts). For AWE, Belgium, France, and UKAEA, SES was assigned according to a regrouping of the British Registrar General's classification, from 1 (unskilled) to 4 (intermediate and professional) (OPCS 1980); for BNFL, detailed classification was not possible so workers were assigned categories 5 and 6, indicating "industrial" (paid weekly) and "non-industrial" (paid monthly) work, respectively (Table S1); "non-industrial" included managerial, scientific and clerical staff; "industrial" comprised the remainder. This definition of SES was used in the ICS. As a sensitivity analysis, SES was re-coded such that categories 1, 2 and 5 were combined (lower SES), and categories 3, 4 and 6 were combined (higher SES).

Smoking is the main risk factor for lung cancer and an important potential confounder in this study. The record-based nature of this study precluded collection of comprehensive information on lifetime smoking status. Smoking information was extracted from occupational medical records from routine medical examinations. For Belgium and AWE, smoking information appeared well-documented at the entry medical examination but not in subsequent examinations. For UKAEA and BNFL, information

was available for approximately 40% of workers but completeness of records was heterogeneous. In France, smoking information was not recorded in early time periods. From the mid-1970s onwards, recording of information on smoking was more systematic in all facilities. Given the heterogeneous data available for each worker's employment history, and no definitive retrospectively-collected data regarding lifetime smoking habits, "never smoker" was assigned if any data after the age of 40 indicated the worker never having smoked. "Ever smoker" was assigned when any record of smoking appeared in medical records. Where neither of condition was met, or where no information was available, "unknown" status was assigned.

Statistical analysis

The aim of the study was to derive estimates of the excess relative risk (in terms of the EOR) of lung cancer per gray (Gy) of absorbed dose to the lung from alpha-emitters as a group and for plutonium and uranium separately. All information was truncated at the reference date. Conditional logistic regression models based on matched sets were fitted using the PECAN module of EPICURE software (Preston et al. 2008). The EOR was estimated using a mixture model comprising a linear function of dose and a log-linear function of other covariates, as is typical in radiation epidemiology, defined:

$$EOR = \alpha_{s(i)} e^{\beta_x x}(1 + \beta_z z)$$

where x is a vector of covariates, β_x are estimated covariate parameters, z is a vector of cumulated doses minus a lag, β_z is the dose-response slope i.e. the EOR/Gy, and $\alpha_{s(i)}$ is a set of stratum parameters indicating numbers of cases and controls in each matched set. In common with most modern radiation epidemiology studies, we aimed to investigate the magnitude of increased cancer risk associated with radiation exposure, and therefore followed the convention of reporting 90% confidence intervals (CIs) and one-sided p-values. Profile likelihood-based CIs were estimated.

All main analyses were adjusted systematically for external dose, SES and smoking, through inclusion in the log-linear subterm of the model, and for age, sex and facility through matching. Attained age, age at start of employment, and duration of employment were investigated as potential confounders of

associations between alpha doses and lung cancer mortality, by including them in the model and evaluating whether estimates of radiation-induced risk changed by ≥10%. We investigated effect modification of the association of lung cancer mortality with alpha dose by attained age, age at start of employment and duration of exposure, as well as by sex, cohort, smoking and SES. For each model an interaction term was introduced as an exponent of alpha dose. Heterogeneity of risk was evaluated based on a likelihood ratio test between models including and excluding the interaction. Departures from linear dose-response were tested including quadratic and logarithmic transformations in the linear term (logarithm of dose+1 to prevent exclusion of zero-dose subjects).

Cumulated doses were lagged by 10 years as is typical in studies of nuclear workers and lung cancer (Cardis et al. 2005). Sensitivity analyses were conducted for lags of 5 and 15 years. Other sensitivity analyses included: estimating risk without adjusting for SES or smoking, restricting analyses to men, and exploring heterogeneity among cohorts by running models that omitted cohorts one-by-one. The highly-skewed dose data (a large proportion of workers had zero or near-zero doses) precluded extensive categorical analysis: four categories were defined based on visual inspection of histograms of dose (Table 2).

Results

In total, 553 cases of lung cancer and 1333 controls were included (Table 3); 9 controls subsequently became cases. 67% of subjects were ≥65 years old at the reference date. Most began employment before 1965, ~35% before 1955. Mean date of death was 1989 (median: 1988, standard deviation: 10.5). BNFL contributed the largest number of subjects (339 cases; 1010 controls).

Distributions of internal alpha doses and photon doses were highly positively skewed (Table S2). Median positive alpha dose to the lung from all radionuclides was 2.43 mGy (mean: 8.13 mGy; maximum: 316 mGy; interquartile range (IQR): 7.76 mGy). Median positive alpha doses to the lung from plutonium and uranium were 1.27 mGy (mean: 5.09 mGy; maximum: 110 mGy; IQR: 4.27 mGy) and 2.17 mGy (mean: 6.45 mGy; maximum: 302 mGy; IQR: 5.93 mGy), respectively. The numbers of subjects with positive doses for plutonium, uranium and other alpha-emitters were 711, 1409 and 56, respectively.

Median total alpha doses were highest to the bronchial secretory (BB_{sec}) cells, and lowest for bronchial basal (BB_{bas}) cells (Figure S1). Ranges and medians of average lung doses generated using the alternative weighting scheme were broadly similar (Figure S2).

We found a dose-response relationship for total alpha dose: the EOR/Gy, adjusted for external dose, smoking and SES was 11.00 (90% CI: 2.62; 23.72) (Table 4). This effect was independent of external dose. The EOR/Gy for plutonium and uranium adjusted for external dose, smoking and SES were 50.20 (90% CI: 16.98; 106.20) and 5.33 (90% CI: -1.93; 17.96), respectively.

Most subjects smoked during their lifetime (84% of cases; 62% of controls). There were very few never smokers (1% of cases; 4% of controls). Smoking status was unknown for 17% of cases and 38% of controls. Analyses of the risk of lung cancer due to smoking gave ORs of 9.21 (90% CI: 4.03, 21.04) and 2.53 (90% CI: 1.10, 5.84) for ever smokers and those of unknown smoking status, respectively (Table S3).

Removing SES or smoking from the model (Table S4) led to ≥10% change in the risk estimates for total alpha, uranium and plutonium doses (with the exception of SES for plutonium) suggesting that both variables confound the association between lung cancer and alpha dose. Reclassification of SES into two groups resulted in little change to the risk estimates (Table S5).

We found no evidence for modification of the effect of total alpha dose by smoking (p-value: 0.35), attained age (p-value: >0.50), age at start of employment (p-value: >0.50), SES (p-value: 0.08), cohort (maximum likelihood estimate for some parameters could not be calculated), or duration of employment (p-value: >0.50). Similarly, no effect modification by any covariate was identified for models of plutonium and uranium dose individually.

We detected no evidence of a departure from linearity of the associations for total alpha, plutonium or uranium. Likelihood ratio tests indicated that the fits of models of log(dose+1) and dose+dose^2 were no improvement over linear models of dose. Results of categorical analyses are plotted in Figure 1. For plutonium the EOR of the highest category was very high, based on small numbers of subjects (Table 5), with very wide CIs that just include the continuous analysis estimate. A sensitivity analysis was carried out wherein the reference category included only subjects with zero doses. Patterns of risk estimates across categories for all internal dose variables were similar to those observed in the main analyses (Table S6).

Sensitivity analyses of 5- and 15-year lags produced estimates of EOR/Gy similar to those for a 10-year lag (Table S7). Restricting to males (n=1863) gave an EOR/Gy for total alpha dose of 10.92 (90% CI: 2.58; 23.57), essentially the same as the main analysis result. Numbers were too low to restrict to females.

Estimates of EOR/Gy for individual lung regions were heterogeneous, particularly for total alpha dose (Table S8). Generally, however, CIs on the dose-response estimates were wide and overlapping, precluding further interpretation. Although median average lung doses were similar to ICRP weighted lung doses (analyses restricted to UK cohorts as doses to individual lung regions were not available elsewhere), the risk estimates for the two sets of doses differed although CIs were wide and

overlapped (Table S9). There were no great differences between the ratios of the risk estimates for plutonium versus uranium for individual regions of the lung (Table S8). Risks for plutonium were greater than those for uranium by factors of around 7 (for BBbas) to 15 (for bb). Risk estimates for plutonium using average lung dose were ~80% of those estimated using the ICRP weighted dose, compared to about ~200% for uranium. Risks for total alpha dose were higher for average lung dose than ICRP weighted dose. For all dose indices, however, CIs were wide and the results obtained using either weighting system are mutually compatible.

Discussion

This multinational case-control study, combing data from those European nuclear industry cohorts with substantial numbers of workers exposed to uranium and/or plutonium, is the first large-scale study in which organ doses from both plutonium and uranium exposure have been estimated using a common dosimetric model. We found strong evidence that internal exposure to alpha particles in the lung increases lung cancer risk even at the relatively low doses experienced by nuclear industry workers. A linear model proved adequate to describe the shape of the dose-response for total alpha dose, plutonium dose, and uranium dose. External radiation dose did not modify the association. Smoking and SES confounded the association between lung dose and lung cancer risk.

In radionuclide-specific analyses, EOR/Gy appeared higher for plutonium than for uranium. However, CIs were wide and overlapped; given uncertainties in doses absorbed from these radionuclides—particularly plutonium (Puncher et al. 2011)—we cannot draw conclusions regarding possible differences.

Our estimate of EOR/Gy for total alpha dose is higher than, but compatible with, that of previous studies of prolonged exposure to alpha-emitters (Table 6), namely for radon exposure in the French uranium miners cohort (FUMC) (Rage et al. 2012) and for plutonium in the MWC (Gilbert et al. 2013), where doses were higher than in our study. The risk estimates in the present study for plutonium dose are higher than those reported for the MWC (Gilbert et al. 2004, 2013; Kreisheimer et al. 2003), although CIs overlap. The dosimetry used in our study was based on more extensive individual biomonitoring data than MWC which led to more precise (though still uncertain) dose estimates, particularly at low doses (Bérard et al. In press). This precision is reflected in risk estimates at doses <0.2Gy. Our findings are particularly important as other studies of those exposed to internal plutonium at doses lower than those in the MWC (Brown et al. 2004; Omar et al. 1999; Voelz et al. 1997; Wiggs et al. 1994) have not provided clear evidence of an increased risk of lung cancer with increasing plutonium dose (Gilbert et al. 2013). Using a radiation weighting factor (w_R) of 20 to express risk in terms of equivalent dose to the lung in Sv, our estimates are compatible with those of

the atomic bomb survivors (Preston et al. 2007). We were unable to compare our results with many underground miner studies that present risk in terms of working level months. The study of the FUMC, however, reported ERR/Gy for lung cancer mortality and lung alpha doses of 4.48 (95% CI: 1.27; 10.89) (Rage et al. 2012), which is compatible with our results for total alpha dose.

We found no clear evidence of effect modification by attained age, age at start of employment, or duration of employment, though given the generally low doses, we had little statistical power to test for such effects. The similarity of results for different lags reflects much of the exposure having occurred many years before reference dates (mainly before the 1960s).

Although we found no evidence of effect modification by smoking, an EOR/Gy of 7.23 (90% CI: -0.27, 20.67) was estimated for total alpha dose (adjusted for SES) in an analysis restricted to smokers, which indirectly suggests a similar pattern to that observed in the MWC, cohorts of uranium miners, residents exposed to environmental radon and the atomic bomb survivors (Furukawa et al. 2010), where the modifying effect of smoking on radiation is sub-multiplicative.

We found no clear evidence of effect modification by cohort. We could not estimate EOR/Gy for some cohorts individually due to small numbers: models for Belgium, France and UKAEA failed to converge; effect measures for AWE and BNFL individually were imprecise, prohibiting interpretation. However, heterogeneities in risk estimates observed when omitting cohorts one-by-one from the analysis (Table S10) suggest differences in risks among the cohorts. Omitting Belgium, France or UKAEA had a limited impact on the estimates of EOR/Gy for total alpha, plutonium or uranium. Omitting both Belgium and France from the analysis (see ICRP weighted lung dose estimates in Table S9) also hardly changed the EOR/Gy. Omitting AWE decreased the EOR/Gy for total alpha, plutonium and uranium doses. It appears that the subjects in the AWE cohort with relatively higher doses may be influential in the analyses. Omitting BNFL had little impact on EOR/Gy for plutonium dose, but increased the EOR/Gy for uranium dose (and subsequently for total alpha dose). The reasons for this are unclear, but some of the heterogeneity might be due to subtle differences in matching: although controls were matched facility in all cohorts, in BNFL this resulted in a tendency to match on

radionuclide as workers at Sellafield were typically exposed only to plutonium and those at Springfields only to uranium. Also, the physicochemical properties of uranium containing materials modify carcinogenic risk (Zhivin et al. 2014); differences in risk observed when omitting BNFL or AWE from uranium analyses may indicate differences in the physicochemical properties of the uranium compounds in each cohort. Information on non-radiological carcinogenic co-exposures such as organic solvents and cutting fluids (used in milling), metals such as beryllium and lithium (used in nuclear weapons and reactors), and asbestos, was sparse and hence could not be included in risk models.

Differences in EOR/Gy estimated for lung regions reflect heterogeneity of dose across the lung: risk estimates are highest for regions receiving lower doses, and vice versa. It is unclear which region, if any, is the most appropriate for assessing risk as our analysis considered mortality and had no information regarding tumour location, type or histology. Heterogeneity in EOR/Gy for doses to individual lung regions should not be relied upon to provide aetiologically meaningful information on risk.

Since the dosimetry protocol was agreed, modifications to the structure of the HRTM have been recommended (ICRP 2015). Impacts of these modifications were considered in an uncertainty analysis ((Puncher et al. Under preparation)). It would be useful to estimate risk in this population using dosimetry based on the updated model, and to explore the influence on risk estimates of individual-level dosimetric information, such as numbers of bioassays, bioassay data below detection limits, solubility assumptions, and calculated intakes.

A few other cohorts exist in which substantial cohorts have been exposed to uranium, plutonium and other alpha-emitters, in the former USSR and North America. Although studies of uranium and plutonium workers in the USA have been conducted, other than one study of uranium workers (Silver et al. 2013), individual dose reconstruction of the type performed here has not been possible. Applying the present methodology to these cohorts would potentially provide more precise, comprehensive dose estimates on which to base multinational risk analyses. Results could then be compared with risk

estimates derived from the very different exposure situation of the MWC, which provides the most information on risk of internal exposures to plutonium.

Conclusions

The current study is the first in which individual estimates of dose from multiple alpha-emitters have been used to estimate the risk of lung cancer mortality in large European cohorts of nuclear industry. Most subjects in the current study had low lung doses from uranium and/or plutonium. Our study demonstrates an increased risk of lung cancer associated with doses from these alpha-emitters. Although the risk appears greater for plutonium than for uranium, CIs are wide and overlapping. Our estimates of the EOR per Sv for alpha dose are higher than—but compatible with—those reported in the FUMC, the MWC and atomic bomb survivors. Our study presents useful information on a key issue in radiation protection: the results provide further support for the existing accepted risk estimates associated with internal alpha-emitters and the radiation protection systems based on them, although considerable uncertainties remain and our results cannot be considered definitive.

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Tables

Table 1

Study populations, study periods and *t1* date

		Recruitment period		Mortality follow-up period		Internal exposure monitoring period		Last year for which doses estimated
Cohort	**Study population**	**Start**	**End**	**Start**	**End**	**Pu t1**	**U t1**	
Belgium	Employees of SCK·CEN, Belgonucleaire, and Belgoprocess	1969	2002	1969*	2002	1965	1959	2002
France	Employees of CEA and AREVA NC (former COGEMA) that never worked as miners, were employed at facilities grouped as North (La Hague, Brennilis), Paris (Saclay, Fontenay-aux-Roses) and South (Pierrelatte, Marcoule, Grenoble, Cadarache), were monitored for plutonium or uranium through urinalysis, and were monitored for external radiation only from 1967	1950	1994	1968*	2003	1967	1967	2003
UKAEA	All UKAEA workers at Harwell, Winfrith and Dounreay	1946	2002	1946	2002	1970	N/a	2001
AWE	All AWE workers employed at Aldermaston	1950	1982	1950	2002	1963	1963 (enriched)	2002
							1968 (depleted)	2002
BNFL	All BNFL and UKAEA workers at BNFL Sellafield and Springfields monitored for plutonium (post-1970 exposure) and/or uranium exposure through urine analyses	1949	2002	1949	2002	1971 (exposure at Sellafield only)	N/a	2002

* Individual causes of death not available before this date

Table 2

Distribution of subjects by dose category

Dose	Dose levels (mGy)	Cases	Controls
Total alpha dose	[0,10]	439	1081
	(10 25]	61	178
	(25 50]	31	58
	(50 ∞]	22	16
Plutonium alpha dose	[0, 10]	507	1271
	(10,25]	30	53
	(25,50]	10	8
	(50,∞]	6	1
Uranium alpha dose	[0, 10]	491	1161
	(10, 25]	33	126
	(25, 50]	19	39
	(50, ∞]	10	7
Other radionuclides alpha dose	[0, 10]	545	1323
	(10, 25]	4	1
	(25, 50]	1	5
	(50, ∞]	3	4
External dose	[0, 100]	448	1059
	(100, 250]	64	137
	(250, 500]	25	82
	(500, ∞]	16	55

Table 3

Distribution of key characteristics of subjects

	Cases (n=553)	**Controls** (n=1333)
Cohort		
Belgium - SCK-CEN	9	19
France – CEA-COGMEA	17	36
UK-AEA	97	108
UK – AWE	91	160
UK – BNFL	339	1010
Sex		
Men	544	1319
Women	9	14
Age at death of case (reference date)		
<55	54	135
55-64	132	318
65-74	242	570
75+	125	310
Year of first exposure to alpha-emitters (dose > 0mGy)*		
<1955	167	496
1955-64	179	417
1965-74	99	167
1975+	107	250
Year of death of case (reference date)		
<1975	75	202
1975-1985	139	322
1985-1995	191	451
>1995	148	358
Socioeconomic status		
All centres except BNFL		
1	32	82
2	12	33
3	60	78
4	110	130
BNFL		
5	301	805
6	38	205
Smoking		
Never	6	48
Ever	457	802
Unknown	90	483

* n = 1882: 3 controls and 1 case have no dose recorded for study period

Table 4

EOR for lung cancer per Gy – matched on sex, age and cohort, lag of 10 years

	EOR/Gy	90%CI*	
Unadjusted models			
Total alpha dose	13.39	4.33	26.68
Plutonium alpha dose	43.87	14.48	92.46
Uranium alpha dose	8.12	-0.42	21.42
External dose	-0.36	<0	0.09
Models adjusted only for external dose			
Total alpha dose	14.10	4.90	27.49
Plutonium alpha dose	43.49	14.89	90.37
Uranium alpha dose	8.69	-0.01	22.07
Fully adjusted models†			
Total alpha dose	11.00	2.62	23.72
Plutonium alpha dose	50.20	16.98	106.20
Uranium alpha dose	5.33	-1.93	17.96
Plutonium alpha dose	49.36	16.18	105.60
Uranium alpha dose	4.19	-2.52	17.07
Plutonium alpha dose	49.39	16.00	105.80
Uranium alpha dose	4.19	-2.52	17.07
Other radionuclides alpha dose	3.66	-3.03	41.92

All analyses for 553 cases and 1333 controls. * Adjusted for smoking, SES and external dose. <0: lower CI is on boundary of parameter space (1/max dose). † Based on likelihood profile.

Table 5

Categorical analysis results, adjusted for external dose, SES and smoking status, lag of 10 years

	Dose category (mGy)	EOR	90% CI†	
Total alpha dose	[0,10]*	0.00	-	-
	(10,25]	-0.23	-0.43	0.02
	(25,50]	0.38	-0.09	1.08
	(50,∞]	1.34	0.25	3.50
Plutonium alpha dose	[0,10]*	0.00	-	-
	(10,25]	0.07	-0.33	0.73
	(25,50]	3.24	0.56	11.24
	(50,∞]	25.48	3.19	341.80
Uranium alpha dose	[0,10]*	0.00	-	-
	(10,25]	-0.31	-0.52	-0.03
	(25,50]	0.29	-0.21	1.06
	(50,∞]	0.60	-0.34	3.03
Other radionuclides alpha dose	[0, 10]*	0.00	-	-
	(10, 25]	11.24	1.00	142.50
	(25, 50]	-0.49	-0.95	1.61
	(50, ∞]	0.45	-0.64	4.75

* Reference category. † Based on likelihood profile.

Table 6

Comparison of current study results with other studies

	Study	Radionuclide / radiation	Number of cases	Mean dose of subjects	ERR/Gy or Sv [1]	CIs	
Lung absorbed doses	Current study	U + Pu + External	553	7.42 mGy	11	2.62*	23.72*
	Men	U + Pu + External	544	7.47 mGy	10.92	2.58*	23.57*
	Mayak (Gilbert et al. 2013):						
	Men	Pu	446	93 mGy	7.4	5†	11†
	Women	Pu	40	165 mGy	24	11†	56†
	French Uranium miners (Rage et al. 2012)	U + External + Rn	66	78 mGy	4.48	1.27*	10.9*
Lung equivalent doses (RBE=20)	Current study	U + Pu	553	148 mSv	0.55	0.13*	1.19*
	Atomic bomb survivors[2]	External	219	600 mGy	0.3	0.08*	0.56*
	Mayak	Pu	486	1980 mSv	0.35	0.24†	0.50†
	French Uranium miners	U + Rn	66	1560 mSv	0.22	0.06†	0.54†

[1]EOR for current case-control study. [2] Restricted to males of working age (20 to 65) – authors' analysis of RERF LSS Report 14 (Ozasa et al. 2012) data. * 90% CI. † 95% CI.

Figure legends

Figure 1 – EOR (90% CI) for categorical analysis of alpha dose, adjusted for smoking, SES and external dose with trend from continuous analysis of alpha dose (90% CI)

Figures