Canadian Nuclear Safety Commission contract 87055-13-0577

MORTALITY RISKS IN THE POOLED ANALYSIS OF THE CANADIAN AND GERMAN URANIUM PROCESSING WORKERS

FINAL REPORT

July 31, 2015

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ABSTRACT

Nuclear fuel cycle workers are exposed to a variety of hazardous materials. Uranium processing is one of the stages of the nuclear fuel cycle and, together with uranium underground mining, employs the largest number of workers, with much smaller groups of workers involved in uranium enrichment and reprocessing and reactor operation. To date, epidemiological studies of uranium underground miners showed significantly increased risks of lung cancer from exposures to radon decay products (RDP). Uranium enrichment workers also have been shown to have increased risks of lung cancer from exposures to reprocessed uranium compounds. Large pooled studies of nuclear reactor workers showed significantly increased risks of solid cancers and leukemia, and, more recently and controversially, of cardiovascular (CVD) and non-malignant respiratory diseases. Workers engaged in uranium processing are exposed to a wide range of radioactive (e.g., gamma-ray) and non-radioactive (e.g., fine or silica dust) exposures from the ore dust, but less to RDP exposures, typical for uranium underground miners. Data from recent studies of the physicochemical characteristics of uranium isotopic types from the nuclear fuel cycle provide additional evidence for an emerging consensus that exposures of workers in the uranium processing industry are substantially different from those of uranium underground miners or enrichment workers or nuclear reactor workers, and that they should be carefully evaluated in separate studies. The purpose of this study was to develop an understanding of the long-term health risks of occupational exposures in the uranium processing industry. The pooled cohort consisted of 7,431 workers from Port Hope, Canada and Wismut, Germany who were exposed to uranium processing, which includes milling and refining, and had detailed annual exposure information. This is one of the largest cohort analyses comprised of workers exposed to a unique combination of RDP exposures and gamma-ray doses as a result of the refining and processing of uranium. Over 90% of workers were followed-up for at least 20 years, allowing sufficient time for occupationally-induced cancers to develop. RDP exposures were broadly similar in the two cohorts, but gamma-ray doses almost four-fold higher among male Port Hope compared to male Wismut workers. We determined that radiation risks of all cancer and non-cancer outcomes were similar in the two cohorts, indicating that the cohorts were suitable for pooling. We observed small and not statistically significant increases in risks of lung cancer due to RDP exposures and of CVD due to both RDP exposures and gamma-ray doses among males. Higher CVD risks among males were observed among those with duration of employment less than 8 years and among those with the youngest age at first WLM exposure. Radiation risks of solid cancers excluding lung cancer were increased both for RDP exposures and for gamma-ray doses, significantly so among women. All other causes of death among males and females were not associated with occupational RDP exposures and gamma-ray doses. Significant findings should be interpreted with caution and could be due to a large number of statistical tests. Continued follow-up of the cohorts and pooling with other cohorts of workers exposed to uranium processing could provide valuable insights into risks from occupational uranium exposures and gamma-ray doses and into suspected differences in risks with other groups of workers involved in the nuclear fuel cycle.

INTRODUCTION

The mortality and cancer incidence follow-up of uranium processing workers are essential to improve our understanding of radiation risks and to ensure that radiation protection programs appropriately protect workers' health. Epidemiological studies, primarily of underground miners, show increases in lung cancer risk from exposures to radon decay products (RDP).[1,2] Uranium processing workers are exposed to a wide array of uranium compounds from the ore dust and to other radioactive mill products, but less to RDP, typical of the workers in the uranium mines. Only a few studies have examined risks of these exposures and had contradictory results, necessitating further research in this area.

BACKGROUND

Uranium has both chemical and radiological toxicity.[3,4] Extraction of uranium from uranium ore involves crushing and grinding, followed by either physical (via radiometric or gravimetric sorting) or chemical (via alkaline or acid leaching resulting in so-called yellow-cake) processing. "Dry" ore processing, in particular, is associated with exposures to dust and high doses of ionizing radiation.[3] Most uranium compounds present during uranium processing emit alpha-radiation, which has been found to be carcinogenic to humans.[5] Exposures to these types of radiation are measured via measurement of radon emanation rates from various radiation-bearing materials (RDP exposures). Enriched uranium is mostly radiotoxic, while chemical toxicity is the main concern for natural and depleted uranium.[3] Both types of toxicity are influenced by the biological solubility of the respective uranium compounds. Chemically toxic soluble uranium compounds could potentially impair kidney function, as has been shown in high dose laboratory animal studies,[3,6,7] while lower dose studies indicated only transient changes.[8] The inhaled particles of insoluble uranium, such as UO_2, are more likely to be retained by the lungs for a long period of time, and may produce a larger radiation dose to the lungs compared to readily soluble uranium compounds. The chemical and radiation toxicity of uranium compounds depends on the route of exposure (inhaled or ingested) and the solubility of compounds, with the most soluble and therefore readily absorbed uranium compounds being the most potent toxins.[3]

The potential for exposure to external gamma-ray radiation is present at each of the stages in the nuclear fuel cycle (**Figure 1**[9]). Workers involved in uranium milling, refining and processing ("uranium processing workers", ~ 5-10% of ~500,000 workers of the nuclear fuel cycle) have the highest exposures to external gamma-ray radiation with average annual effective radiation doses of 10 millisievert (mSv) compared to <5 mSv for other workers.[10] These workers constitute a very distinct group because their cumulative lifetime occupational gamma-ray exposures are 4-5 times higher than external radiation exposures of nuclear workers (100 mSv[11] vs. to 20 mSv[12]) and their RDP exposures are 4-5 times lower than internal exposures of uranium miners (20 working level months (WLM)[11] vs. 90 WLM[13]). Thus, occupational risks of uranium processing workers should be similar to the risks of nuclear reactor workers exposed primarily to gamma-ray radiation. Below, we present a summary of the current knowledge on the target tissues and organs and radiation risks of occupational exposures for workers involved in various stages of nuclear fuel production.

- Studies of workers involved in nuclear fuel production

A previous review of occupational cancer risks among workers involved in the nuclear fuel cycle identified 18 cohort and 5 nested case-control studies published during 1980-2007.[14] In comparison with the general population, cancers of the respiratory system, lymphatic and hematopoietic tissue (leukemia, non-Hodgkin lymphoma (NHL) and multiple myeloma (MM)), digestive system (esophageal, stomach, colorectal, and pancreatic cancer), urinary system (kidney and bladder cancer) and other sites (bone, brain and central nervous system (CNS), and prostate were non-significantly elevated in several cohorts of nuclear workers with potential internal exposures to uranium.[14] We conducted a search of the PubMed database and identified additional 12 studies of uranium workers published during 2008-2015 (9 cohort,[11,15-23] 2 nested case-control[24,25] and 1 cross-sectional[26] studies). In comparison to the general population, fuel fabrication, milling and conversion workers presented significant excess in mortality from lung cancer,[15,18,20,22] lymphatic and hematopoietic, particularly NHL and MM, cancers,[16,18-20,22] and kidney[15] or bladder[22] cancers, but overall mortality was similar to the general population. Heterogeneous exposure indicators in reviewed studies presented significant difficulties in reaching a conclusion on the radiation risks of employment in the nuclear fuel cycle. The majority of studies reported significant or near significant increases in radiation risks of lung cancer among workers with exposures to reprocessed uranium.[11,18-21] NHL and MM mortality were both significantly associated with internal uranium exposure at the U.S. enrichment facilities where uranium workers were exposed primarily to soluble uranium compounds.[19,24] Relative risks were higher for chronic lymphocytic leukemia (CLL) than for other leukemia among Rocketdyne uranium processing workers.[21] Only 4 studies assessed radiation risks of kidney cancer and all showed a non-significant increased risk either with RDP or uranium or uranium/external exposures.[11,20,21,23]

Previous review of workers occupationally exposed to uranium[14] did not consider mortality from non-cancer diseases such as cardiovascular (CVD) or respiratory diseases. Literature search identified 16 studies published during 1980-2015, which reported data on these outcomes among uranium workers (all cohort studies[11,23,27-39]). The majority of studies reported CVD risks comparable or smaller to the general population, most likely due to the *healthy worker effect*.[40] Risks of non-malignant respiratory[15,31] and renal diseases[30,31] were non-significantly increased. Two studies showed a significant increase in radiation risks of CVD based on proxy indicators of internal uranium exposure,[38,39] while several others reported non-significant increases.[11,23] In general, findings of individual studies were limited by low statistical power due to small cohort size and low doses of radiation.

- Studies of uranium processing workers

The focus of occupational exposure studies among uranium underground miners is mostly on exposures through inhalation.[1,6] In contrast, ore processing workers are exposed to natural uranium both through inhalation and ingestion. Uranium processing workers are exposed to uranium dust that originates from handling uranium compounds (UF_6 gas, UO_2 metal, **Figure 1**). Workers engaged in the uranium milling, refining and processing are also exposed to other radioactive and non-radioactive (e.g., fine or silica dust) mill products, but less to RDP exposures, typical of the workers in the uranium mines. Potential uranium-target organs among uranium processing workers are lung, kidney, bone, upper respiratory and digestive tracts, and lymphatic and hematopoietic tissues.[14,41] Recent studies suggest a possible CVD effect in

uranium processing workers,[39] while experimental data indicate that kidneys are considered a target organ for uranium damage.[3]

Only a few studies have examined risks of exposures to uranium milling, refining and processing[11,15,16,20,30,31,42] and had contradictory results, necessitating further research in this area. Published studies of uranium processing workers reported increased risks of lymphatic,[31] pleural cancers[16] and non-malignant respiratory [15,31] and renal diseases.[30,31] A study of non-miners employed at the Grants uranium mill in the U.S.[15] reported no significant increase in risks of any of the cancers potentially related to milling operations. A recent study of workers employed at the AREVA NC uranium processing plant in France reported carcinogenic effect of slowly soluble reprocessed uranium on lung cancer and hematological cancers, suggesting that mortality of uranium millers and processors might be different from mortality of underground uranium miners characterized by increased radiation risks of only lung cancer.[18]

Our recent study of uranium millers and processors from the Port Hope radium and uranium refinery and processing plant in Canada reported a small but not statistically significant increase in risk of lung cancer due to RDP exposures.[11] Lung cancer risks among Port Hope workers with no mining experience were significantly different from RDP-related risks of Canadian Eldorado underground miners. Our analyses also indicated increased radiation-related risks of CVD mortality (excess relative risk per 100 WLM (ERR/100WLM)=0.10, 95% confidence interval (CI): -0.05, 0.32 and ERR/Sv=0.19, 95% CI: -0.07, 0.55), mostly driven by increased risks of ischemic heart disease (IHD), although not statistically significant (ERR/100 WLM=0.16, 95% CI: -0.05, 0.50 and ERR/Sv=0.31, 95% CI: -0.05, 0.88). In models with two terms for RDP exposures and gamma-ray doses, risks were due to gamma-ray doses only, and the fit of the model did not improve with addition of the RDP exposures term (p=0.70). All other causes of death or cancer incidence were not associated with occupational RDP exposures and gamma-ray doses.

Recently, the mortality from internal and external radiation exposures in 4,054 uranium millers with no mining experience from the German study of workers employed at the Wismut facility was published.[23] Analysis showed increased risks of lung cancer mortality due to cumulative radon exposures (ERR/100 WLM=3.39, 95% CI: -0.01, 6.78), but the finding was not statistically significant. The study reported a statistically significant association between cumulative radon exposure and mortality from all cancers, but none of the individual risk estimates were statistically significant.

- Studies of populations exposed to gamma-ray radiation

Risk estimates of gamma-ray radiation exposures are based primarily on the study of atomic bomb survivors (A-bomb) from Japan, who were exposed to acute whole-body gamma-rays (**Table 1**). Study findings have been widely used to estimate risks from occupational radiation exposures and to set occupational standards.[43] Studies of workers occupationally-exposed to radiation have been used to supplement the data from the A-bomb study, but **Table 1** demonstrates that individual occupational studies are generally underpowered. The strongest evidence to date on the long-term health risks of exposures to low-dose gamma-rays is available for lymphatic and hematopoietic cancers.[44-46] Significant positive associations between gamma-ray doses and increased risks of CVD mortality were reported in relation to low (ERR/Sv=0.10,

95% CI: 0.04, 0.15)[47] and moderate-dose radiation exposures (ERR/Sv=0.14, 95% CI: 0.06, 0.23).[48]

- Studies of workers exposed to silica and fine dust and other byproducts of the nuclear fuel cycle production

Exposure to respirable silica dust causes silicosis and pneumoconiosis.[49,50] Over the last several decades, several studies have been published which suggested that silica dust also causes lung cancer.[51] Recent analysis of Wismut uranium workers reported significant silica risks of lung cancer but only among those exposed to very high silica concentrations.[52]

Silica dust risks of non-malignant respiratory diseases among Wismut uranium workers, adjusting for RDP exposures, were not increased in the mortality analysis,[53] but were significantly increased in the analysis of incident respiratory diseases for Wismut workers with long-term low-dose exposures.[54]

- Effects of possible confounding and modifying factors

Nuclear fuel cycle exposures have been linked with lung cancer, lymphatic and hematopoietic cancers, and CVD. Lack of consistent associations for other site-specific cancers could mean that there is no causal relation or that it is obscured by biases or deficiencies in exposure measurement, case classification, duration of follow-up, or some combination of these factors. While exposure data for uranium processing workers are usually quite robust, information on possible independent risks factors such as smoking, heavy alcohol consumption and other lifestyle and social factors is usually lacking.[12] The complicated, multifactorial nature of CVD and possible independent contributions from these unmeasured confounders raise concerns over whether the observed associations for CVD are causal.[47] Most studies of uranium workers noted concomitant exposures to other types of radiation (thorium, radium) and various types of dust,[16] but did not evaluate these associations. Studies of nuclear reactor workers exposed to gamma-rays demonstrated that both time since exposure and age at the time of exposure are strong modifiers of initial exposure effects.[45] The fall in risk with time since exposure occurred more rapidly in those exposed at a younger age than in those exposed at a later age.[12,45] Investigation of modifying factors in studies of uranium processing workers has not been done, possibly due to their low statistical power. None of the studies examined risks among women and possible differences with men.

STUDY OBJECTIVES

Findings of the recent Port Hope[11] and Wismut[23] studies of uranium processing workers were limited by low statistical power, primarily because of the small cohort sizes and low RDP exposures. Dose-response analyses were based on male workers only because of low statistical power to determine risks in a small group of female processing workers. At the time of the publication, the authors of both studies suggested that continued follow-up of the cohorts and pooling with other cohorts of workers exposed to by-products of uranium milling and processing could provide valuable insight into risks from occupational RDP and gamma-ray exposures and into suspected differences in risk with uranium miners.

To improve our understanding of radiation risks of exposure to a complex combination of RDP

exposures and gamma-rays, we pooled the data from the Port Hope study[11] with the data from the study of German uranium millers from the Wismut cohort.[23] Analysis of the combined cohort of uranium processing workers will provide important evidence about the effects of RDP and gamma-ray exposures on mortality in this unique group of workers. Accordingly, we had the following study objectives:

1. To examine radiation-related risks of mortality from site specific-cancers, with special attention to cancers of the lung and bronchi, leukemia and lymphoma, bone, liver and kidney cancers, as well as non-malignant respiratory, renal and cardiovascular diseases in the pooled analysis of Port Hope and Wismut uranium milling and processing workers (n=7,431), separately and together for RDP internal exposures and gamma-ray external exposures.
2. To determine effects of exposures to radium and silica dust on the radiation-related risks of mortality in the pooled analysis of Port Hope and Wismut uranium milling and processing workers.
3. To investigate radiation-related risks of mortality in the exploratory analysis of a cohort of women involved in uranium milling and processing at Port Hope and Wismut (355 and 270 workers, respectively).

MATERIALS AND METHODS

Port Hope

- Cohort characteristics and follow-up

The Port Hope radium and uranium refinery and processing plant became operational in 1932 and continues to operate today as Cameco Corporation Port Hope Conversion Facility (Port Hope). Port Hope workers were exposed to a wide variety of chemicals and radiation types. Workers were also exposed to radium, which tends to naturally concentrate in the bones, potentially exposing the surrounding tissues, including bone marrow, to ionizing radiation.[7] The Port Hope cohort's materials and methods have been described previously in preparation for the updated analysis of Eldorado uranium workers, which also included Port Radium and Beaverlodge miners.[55] In brief, 3,338 potential study subjects came from the personnel records provided by the radium and uranium refining and processing plant in Port Hope, Ontario, originally owned by Eldorado Nuclear Ltd. For inclusion in the study, workers had to be employed at Port Hope during the ages of 15-75 years sometime between 1932 and 1980, had their last contact after 1940, and had to be alive at start of follow-up in 1950 (mortality analysis) or 1969 (cancer incidence analysis). All workers were included regardless of duration of employment. This cohort of 3,039 eligible workers included 36 workers who were previously included in "other sites" category in the Eldorado cohort analysis[55] but more detailed exposure information available in this analysis allowed us to ascertain that they worked for Port Hope. We used National Dose Registry (NDR) information and Eldorado's personnel records to exclude Port Hope workers with any mining experience (n=39), leaving a cohort for analysis of 3,000 workers.

The nominal roll file was linked to the Canadian Mortality Data Base (CMDB) and to the Canadian Cancer Data Base (CCDB) to ascertain mortality from 1950 to 1999 and cancer

incidence from 1969 to 1999. Data in the CMDB are obtained through the vital statistics system for national reporting of vital statistics data. Since the registration of deaths is a legal requirement through the Vital Statistics Acts (or equivalent legislation) in each Canadian province and territory, reporting is virtually complete. Death records originate with the provincial and territorial registrars of vital statistics and are provided regularly to Statistics Canada. Under-coverage is thought to be minimal (1% or less).[56]

The "alive" follow-up (1984-2000) was completed via deterministic linkage with the Historic Tax Summary file using the social insurance number (SIN). This linkage was carried out for the 60% of individuals in the cohort with a valid SIN. Using this method, 41% of the cohort was confirmed "alive" as of December 31, 2000 and 7% were confirmed alive at some time between 1984 and 1998. In addition, probabilistic linkage of the cohort file with the CMDB and the CCDB resulted in ascertainment of death or cancer diagnosis for additional 43% of cohort subjects (1,295 out of 3,000). The remaining 9%, who could not be linked to the Historic Tax Summary file or the CMDB or the CCDB, were considered lost to follow-up and had their termination date at work as the last date alive.

- Assessment of exposures

There were no early radon or RDP measurements taken at Port Hope at the time of start-up in 1932. In the 1930s to 1950s, the RDP estimates were based on quantities of radium present in the plant in ore and at various stages of refinement, measured radon emanation rates from various radium-bearing materials, building air volumes and estimates of air exchange rates. In the early 1970s RDP measurements were done in the yellowcake warehouses, but occupancy was generally low and no exposure estimates were made. The individual annual exposures in working-level-months (WLM) were calculated from working level (WL)[1] estimates for each type of workplace, the proportion of employees in each occupation, and the proportion of time spent in each type of workplace by employees in each occupation.

Gamma radiation was the primary type of radiation exposure at Port Hope. There were no measurements at the time of startup. Film badges were used on some individuals in the late 1940s, and were worn by most radium workers and a sampling of others from mid-1947 to early 1953. Full individual external dosimetry (100% coverage) was in place by about 1970 and individual records were kept. In this analysis, personal gamma-ray doses were calculated from the average dose-rates and time on the job and expressed in mSv for each individual who had not been wearing a badge. All gamma-ray doses were whole-body effective doses.

Measured individual doses were recorded in Eldorado's radiation exposure files; thus, company records were used if available rather than doses from the NDR of Health Canada. The NDR collects and records radiation exposure and dose data for all exposed workers in Canada from 1951 (with some records going back to 1944).[57] Recent work by Cameco indicates that when differences existed between company records and the NDR, they were relatively small (personal communication, John Takala 2012). For all other non-Eldorado radiation exposures from 1951 to 1999, the nominal roll was linked to the NDR records.

[1] The concentration of RDP per liter of air that would result in the ultimate release of 1.3×10^5 MeV of potential alpha-particle energy. 1 WLM is equivalent to one working month (170 hours) in a concentration of 1 WL.

Urinalysis for uranium has been done since the early 1960s and fluorides were added after the UF_6 plant started up. Alpha counting of urine samples from workers exposed to enriched uranium was also done, but on a limited basis. Direct measurement of uranium in the thorax by whole-body counting was added to the monitoring program in the early 1980s but no regular internal dose calculations were done.

Recent analysis of the Port Hope workers,[11] using information not available to Lane *et al*.,[55] has presented the results separately for those uranium processing workers exposed primarily to radium (n=528) and those primarily exposed to uranium (n=2,472). Workers who had worked in radium operations at any time were classified as radium workers, while all other workers who had never worked in radium operations were classified as uranium workers. No other individual exposures have been estimated for this cohort.

Wismut millers

- Cohort characteristics and follow-up

The German Wismut uranium miners cohort study has been described previously.[58] It is a stratified random sample of 58,982 former employees of the uranium mining company Wismut in East Germany, who had worked for at least 6 months during the operation period from 1946 to 1990. The data pertain to a third mortality follow-up from January 1, 1946, through December 31, 2008, with information on the vital status from local registries. Information on the underlying cause of death is based on death certificates from the Public Health offices and their archives and the autopsy files from the Wismut pathology archive. The cohort includes workers from different types of work places (underground, open pit, surface and milling). All workers based on milling facilities, but never underground or in open pit mines, were initially selected (i.e., 4,161 workers). After exclusion of 107 workers with missing information on silica dust exposure, the final uranium millers cohort was comprised of 4,054 individuals.[23]

- Assessment of exposures

Information on date of start of employment, date of end of employment and for each year type of work place, facility and job type was collected from the pay rolls for each cohort member. Exposure to radon progeny, long-lived radionuclides and external gamma radiation was determined based on a comprehensive job–exposure matrix that assigns an average annual exposure value to each facility, work place and job type. Systematic measurements in the mine-shafts started in 1960. Silica and fine dust concentrations before that time were retrospectively estimated by expert rating including reconstruction of historical workplaces and simulation of ventilation conditions.

Statistical analyses

Each individual contributed person-years at risk from the later of the date of hire or the start date of follow-up, defined as January 1st, 1950, for Port Hope workers and January 1st, 1946, for Wismut workers, to the exit date of December 31st, 1999, for Port Hope workers, December 31st,

2008, for Wismut workers or the date of death, or the last date known alive defined as date of last employment or contact, whichever occurred earlier.

Main analyses were based upon internal comparisons and used grouped Poisson regression analyses[59,60] to estimate risks from a simple linear relative risk model:

$$\mathbf{Rate_D = Rate_0 * (1 + (\beta * D) \exp (\Sigma_i \gamma_i z_i))} \qquad \textbf{(Equation 1)}$$

where $Rate_D$ is the rate at dose D, R_0 is the background rate (stratified to adjust for potential confounders such as age, calendar year, silica dust or radium exposures, etc.), D represents factors such as cumulative lagged continuous RDP exposure or gamma-ray whole-body dose, z_i are potential modifying factors such as age at first gamma-ray dose and β and γ_i are coefficients estimated using maximum likelihood techniques.[61] The β coefficient is referred to as the excess relative risk (ERR) per unit of exposure; by adding 1.0 to the ERR one obtains the relative risk at 100 WLM for RDP exposure and per one Sv for gamma-ray dose. In exploratory analyses, we also entered both gamma-ray and RDP exposure terms into the model simultaneously.

To examine the shape of the dose-response, we conducted a series of categorical analyses in which RDP exposures and gamma-ray doses were categorized into 6 to 12 categories chosen to distribute cases evenly between the categories. All relative risks (RR) were calculated relative to a referent category with unexposed subjects (0 WLM for RDP exposures and <1 mSv for gamma-ray exposures).

Confounders were retained in the model if they produced a sizable (≥10%) change in the point estimate of the ERR. Potential confounders of the background rate included age at risk, calendar year, duration of employment, and predominant exposures to radium/uranium (Port Hope) and cumulative exposures to long-lived radionuclides, silica or fine dust and arsenic (Wismut cohort). The summary person-year experience was cross-classified by age at risk (15-19, 20-24… 85-100 years old), calendar year at risk (in 5-year categories), total duration of employment (<6 months and 6 months+),[2] and cumulative exposure, separately for RDP exposures and gamma-ray doses. The person-year weighted mean cumulative exposure in each cross-classified cell was used in the regression analysis. RDP exposures and gamma-ray doses were lagged by 5 years to account for latency period between exposure and cancer incidence and mortality. In exploratory analyses, 10-, 15- and 20-year lags were used for CVD outcomes for comparability with previous studies.[47,63]

Based on literature review,[3,5] we paid special attention to several outcomes that have been shown to be associated with exposures to radium and uranium processing, including cancers of the lung and bronchi, leukemia and lymphoma, bone, liver and kidney cancers, as well as non-malignant respiratory, renal and liver diseases. We also investigated possible associations with cardiovascular outcomes based on recent reports of increased risks from low-dose RDP[64] and gamma-ray exposures[47] in uranium miners and nuclear workers. In the original Port Hope cohort, the underlying causes of death were recoded from the original International Classification of Disease (ICD) code in use at the time of death or diagnosis to ICD-9.[65] Deaths in the Wismut cohort have been recoded to ICD-10. ICD codes for main outcomes of interest are presented in **Supplementary Table S1**.

[2] Total duration of employment was split at 6 months, as risk drops after 6 months but then remains constant. Similar phenomena have been previously observed in other studies.[62]

We investigated modifying effects of various factors from the BEIR VI Committee model and used parameterization from its exposure-age-concentration model [1]:

$Rate_D = Rate_0 * (1.0 + \beta * (w_{5\text{-}14} + \theta_{15\text{-}24}w_{15\text{-}24} + \theta_{25+}w_{25+}) \exp(\varphi_{age\ at\ risk} + \gamma_{exposure\ rate})$ (Equation 2)

where 5-year cumulative lagged RDP exposure (w) is partitioned into time windows (WLM 5-14, 15-24, and 25+ years previously), and φ and γ represent estimates of modifications to the dose-response by categories of age at risk and exposure rate, respectively. In addition, based on recently published analyses of radiation-related risks of CVD, we examined age at first exposure and duration of exposure (employment) as potential modifiers of the dose-response.[66]

Regression parameters, confidence intervals around point estimates and p-values were estimated using the method of maximum likelihood in the AMFIT module of the EPICURE software.[59] Deviances of the models estimated by this method were used to assess model fits and models with smaller deviances were considered to have a better fit. Tests of statistical significance were based on the likelihood ratio test comparing the deviances of two nested models with and without exposure variables, which has a large-sample chi-square distribution with degrees of freedom equal to the difference in the number of parameters estimated. All p-values quoted were two-sided. Because of the form of Equation 1, the possible values of β are limited by the requirement that the corresponding relative risk should not be negative. If the likelihood being sought for a point or bound estimate did not converge, the minimum value for β was given by $-1/D_{max}$, where D_{max} was the maximum dose.

RESULTS

Demographic and exposure characteristics

Table 2 presents the basic characteristics of the pooled cohort of uranium processing workers from the Port Hope and Wismut studies. The mean sex-specific values of lifetime RDP exposures and gamma-ray doses are presented for the cohort as a whole (n=7,431), and separately for women (n=625) and men (n=6,806). RDP exposures and gamma-ray doses were not normally distributed in the two cohorts and in the pooled cohort (all Kolmogorov-Smirnov tests <0.05). RDP exposures and gamma-ray doses were strongly correlated in the two cohorts and in the pooled cohort (Spearman's rho 0.93, 0.74, and 0.71, Wismut, Port Hope and pooled cohort, respectively). Male workers had significantly higher RDP and gamma-ray doses compared to female workers involved in uranium refining and processing (both *P* Wilcoxon Rank Sum Test <0.001). The majority of workers were male (91.6% of the cohort). Historically, females tended to work at office jobs or as laboratory technicians. Few worked in the plants until recent years. There were 270,201 person-years of mortality follow-up in the pooled cohort.

Average age at start of employment was 29 years (SD=10) in Wismut workers and 30 years (SD=11) in Port Hope workers. Workers were employed for an average of 16 years (range: 0-43) in the Wismut and 6 years (range: 0-43) in the Port Hope facilities. All Wismut workers were exposed to non-zero doses of RDP exposures and gamma-ray doses, while among Port Hope workers only 56.2% of workers (n=1,687) had any recorded RDP exposures and 94.3% (n=2,830 workers) had non-zero gamma-ray doses.

Males

Dose-response analyses with continuous exposures

The person-year weighted mean cumulative RDP exposure among males in the pooled cohort was 16.6 WLM (SD=49.8), higher among Port Hope workers compared to Wismut workers (21.1 and 10.0 WLM, respectively). The person-year weighted mean cumulative gamma-ray doses were higher among male Port Hope workers compared to Wismut workers (189.4 and 58.6 mSv, respectively).

- Heterogeneity of risks between the cohorts

We conducted a series of formal tests of heterogeneity of radiation risks of various cancer and non-cancer outcomes between the cohorts. Statistically significant differences were found only RDP-associated risks of lung cancer, indicating that radiation risks were significantly different in the two cohorts (p=0.046 and p=0.381, RDP exposures and gamma-ray doses, respectively). When the model was adjusted for cumulative silica dust exposure in the Wismut cohort, the differences in RDP-associated risks of lung cancer between the cohorts were no longer statistically significant (p=0.296). Formal tests of heterogeneity of radiation risks of other solid cancers and non-cancer outcomes by cohort (Wismut vs. Port Hope) were not statistically significant, indicating that radiation risks of these outcomes were similar in the two cohorts (**Table 3**). We also explored the effects of confounding by cumulative exposures to long-lived radionuclides, fine dust and arsenic in the Wismut cohort and by radium and uranium work in the Port Hope cohort. None of these confounders satisfied the criteria for confounding and were not retained in further models.

- Solid cancers

Radiation risks of solid cancers were increased but not statistically significant, both in analyses of RDP exposures and gamma-ray doses (**Table 3**). When death from lung cancer were excluded from the analysis, radiation risks estimates increased for gamma-ray doses and slightly decreased for RDP exposures. In contrast with the models for all other outcomes, the deviance was slightly smaller for the model with gamma-ray doses compared to the model with RDP exposures only, indicating a better fit of the model (1323.910 and 1323.881, RDP exposures and gamma-ray doses, respectively).

- Lung cancer

Analyses of radiation risks of selected causes of death in the pooled cohort are presented in **Table 3**. We used continuous person-time weighted and 5-year lagged doses in the analyses. Lung cancer mortality tended to increase with increasing RDP exposure, but the risk estimate was not statistically significant (p=0.66). Radiation risks of lung cancer due to gamma-ray doses were also increased but not statistically significant (p=0.96). Models with RDP exposures had smaller deviances compared to the models with only gamma-ray doses (1042.621 and 1042.808, respectively). Similar non-significant increases in radiation risks were observed for a combined category of lung and larynx cancer (**Table 3)**.

- Other solid cancers

Analysis of other cancer outcomes which could be associated with uranium processing and milling work did not yield any significant results. There were no bone cancers and the models for

larynx did not converge due to a small number of outcomes, while risk estimates for kidney and bladder cancer were negative.

- Hematological cancers

Risk analyses models did not converge for MM due to a small number of outcomes. The radiation risk estimates for RDP exposures and gamma-ray doses for non-Hodgkin's lymphoma were on the lower bound of the $-1/D_{max,}$ which produced negative estimates. RDP- and gamma-associated risks of leukemia were increased but not statistically significant (p=0.49 and p=0.98, RDP exposures and gamma-ray doses, respectively).

- Non-cancer outcomes

The estimates of radiation risks of mortality due to all CVD causes were similar for RDP exposures and gamma-ray doses (**Table 3**). Both were not statistically significant (p=0.18 and p=0.30, RDP exposures and gamma-ray doses, respectively), but comparable in size to risk estimates for A-bomb survivors.[48] In models with two terms for RDP exposures and gamma-ray doses, risks were due to RDP exposures only, and the fit of the model did not improve with addition of the gamma-ray dose term (p=0.58, not shown).

Table 4 presents deviances from risk models for CVD mortality associated with RDP exposures and gamma-ray doses lagged by various lag times (0. 5, 10, 15 and 20 years). In general, model deviances were comparable for RDP exposures and gamma-ray doses, which is to be expected due to a high correlation between these exposures. The lowest deviances were estimated for models with unlagged and 5-year lagged exposures, although differences between models with 0 and 20-year lags were very small. All further analyses, unless otherwise stated, were conducted with both exposures lagged by 5 years.

Radiation risks for IHD were similar to the risks estimated for all CVD, while estimated risks for hypertensive disease were four-fold higher and were generally close to null for stroke (**Table 3**). Radiation risks of COPD were negative and the models did not converge for silicosis & anthracosilicosis and nephritis & nephrosis mortality due to a small number of outcomes.

Dose-response analyses with categorical exposures

To further examine the positive, although not statistically significant, finding for CVD mortality, we conducted several exploratory categorical analyses for all CVDs and IHD (**Supplementary Tables 2- 4 and Figures 2-5**). We observed a significant heterogeneity between category-specific RRs for CVD mortality in models with RDP exposures (p=0.007, **Supplementary Table S4**), but the test for linear trend was not statistically significant (p=0.491). In general, relative risks for both exposures were increased by 20-45% compared to the reference categories (0 WLM or <1 mSv). **Figure 3** illustrates that risks of CVD closely followed the risks for IHD mortality, the largest contributor to the CVD grouping in terms of the number of deaths, and that there was some fluctuations in risk below 100 mSv, most likely due to low statistical power of analyses. **Figure 5** plots both RDP- and gamma-ray-associated risks using two different horizontal axes and illustrates a pattern of increased risks, irrespective of exposure and categorization methods.

Dose-response analyses with BEIR-VI type models

Table 5 presents the results of analyses of radiation risks of all CVD using various interaction models. We did not observe significant modifications of the dose-response for CVD mortality in BEIR-VI-type models with dose-rate and age at risk terms (Model 1). Estimates of risks for the two *a priori* factors of interest, age at first exposure and duration of employment, are presented in Models 2 and 3. Although splitting total WLM exposure into three time windows since exposure did not significantly improve the fit (p=0.56), we observed a monotonic decrease in risk with increasing time windows since exposure (**Table 5**). We estimated a significant heterogeneity in radiation risks for duration of employment (p=0.01), with those employed 0-7 years having higher risks compared to those employed 8 or more years. The test for heterogeneity in radiation risks by categories of first age at WLM exposure was not statistically significant (p=0.232), but we observed that those first exposed under the age of 25 years had higher risks compared to those first exposed at age 25 and above.

Females

Person-time weighted cumulative RDP exposures were lower among female workers compared to male workers (6.5 and 16.6 WLM, respectively). Gamma-ray doses were almost four-fold lower among females compared to males (40.8 and 136.8 mSv, respectively). While RDP exposures for female workers were similar in Port Hope and Wismut cohorts (6.7 and 6.3 WLM, respectively), gamma-ray doses were two-fold higher for female Port Hope workers (51.4 and 30.9 mSv, respectively). **Table 6** presents the results of analyses for females with continuous exposures. The radiation risks of solid cancer excluding lung cancer were increased both for RDP exposures and for gamma-ray doses, and were statistically significant for the latter one (p=0.02). While an estimate of radiation risks was negative for all CVD mortality, it was increased for IHD, although not statistically significant (p=0.61 and p=0.80, RDP exposures and gamma-ray doses, respectively). Analyses of other CVD outcomes (hypertensive disease, stroke and other CVD) could not be completed because the statistical models did not converge.

DISCUSSION

This report presents the results of analysis of a pooled cohort of 7,431 uranium workers from Port Hope and Wismut facilities first employed sometime in 1932-1989. This is one of the largest cohort analyses comprised of workers exposed to a unique combination of RDP exposures and gamma-ray doses as a result of the refining and processing of uranium. RDP exposures were broadly similar in the two cohorts, but gamma-ray doses almost four-fold higher among male Port Hope workers. Overall, RDP exposures were highly correlated with gamma-ray doses (Spearman's rho=0.71). Models with RDP exposures had slightly better fit than models with gamma-ray doses for all outcomes with the exception of all solid cancers. We determined that radiation risks of all cancer and non-cancer outcomes were similar in the two cohorts, indicating that the cohorts were suitable for pooling. Although there was some heterogeneity in RDP-associated risks of lung cancer, the radiation risks became more similar after adjustment for silica dust exposures in the Wismut cohort.

Previous analyses of the majority of studies of nuclear reactor workers[67] reported significantly increased risks of all solid cancers due to gamma-ray exposures, but a similar finding in relation to RDP exposures in the cohort of Wismut uranium processing workers is unique[23] and has not been replicated in other studies. In our analyses, radiation risks of solid cancers were increased but not statistically significant both for RDP exposures and for gamma-ray doses, with the exception of significantly increased gamma-ray risks among women. The latter finding should be treated with caution as it could be due to chance after multiple statistical tests.

Our analyses also indicated increased radiation-related risks of CVD mortality (ERR/100 WLM=0.11, 95% CI: -0.04, 0.32 and ERR/Sv=0.13, 95% CI: -0.10, 0.42), mostly driven by increased risks of IHD (ERR/100 WLM=0.08, 95% CI: -0.09, 0.34 and ERR/Sv=0.07, 95% CI: <-0.20, 0.43), both not statistically significant. Dose-dependent increases in risk of CVD from of similar size have been reported in the Port Hope[11] and Wismut[23] uranium processing workers. In the Wismut study,[63] and in the Techa River Cohort exposed to internal and external exposures from various uranium fission products,[68] CVD radiation-related risks increased with increasing lag time. In our analysis, risk estimates changed very little with 10-, 15- and 20-year lags.

Radiation risks of CVD in the pooled cohort were comparable for RDP exposures and gamma-ray doses, however the model with RDP exposures had a slightly smaller deviance. Further exploratory analyses showed monotonic increases in risks of CVD with increasing RDP and gamma-ray exposures. BEIR-VI type model for RDP-associated risks of CVD with age at risk and dose-rate terms did not provide a better fit compared to a conventional model, but we observed a monotonic decrease in risk with increasing time windows since exposure. We estimated a significant heterogeneity in radiation risks for duration of employment and a non-significant but sizeable heterogeneity in radiation risks by categories of first age at WLM exposure. Radiation risks of IHD due to RDP exposures were also increased in women, but not statistically significant.

Cancers of the respiratory system (trachea, bronchus and lung; laryngeal, and pleural cancer), lymphatic and hematopoietic tissue (leukemia, NHL, MM), digestive system (esophageal, stomach, colorectal, and pancreatic cancer), urinary system (kidney and bladder cancer) and other sites (bone, brain and central nervous system (CNS), and prostate were non-significantly elevated in several cohorts of nuclear workers with potential internal exposures to uranium.[14] Studies of uranium processing workers reported increased risks of lymphatic,[16,20,31] intestinal,[20] pleural cancers[16] and non-malignant respiratory[15,20,31] and renal diseases.[30,31] In our analysis, none of these cancer sites were found to be significantly related to workers' RDP exposures or gamma-ray doses. A similar absence of any significant increase in risks of cancers potentially related to milling operations were recently reported for 904 non-miners employed at the Grants uranium mill in the U.S.[15]

One of the strongest advantages of this study is its long-term follow-up with essentially complete ascertainment of cancer incidence and mortality. Another advantage is comparatively high rates of follow-up, achieved by a combination of methods. The large size of the cohort with detailed annual exposure information (n=7,431), percentage of workers deceased (39.5%) and the length of follow-up (50 years in the Port Hope and 63 years in the Wismut cohort) were substantially greater compared to other studies.[15,16,30,31,42] Comparison of risks from RDP and gamma-ray

exposures provided a complementary view of the effects of uranium milling and processing occupational exposures on the risk of cancer and non-cancer outcomes.

The most important limitation of this study is its limited statistical power due very low RDP exposures and low gamma-ray exposures. This could be addressed through further follow-up and pooling of the two cohorts with other cohorts from similar uranium processing operations. There was no information on behavioral risk factors. For smoking to confound the RDP-related risk for lung cancer it should be correlated with both RDP exposure and lung cancer. Smoking was banned at the Port Hope facility in the 1940s and 1950s, and was allowed on a very limited basis thereafter; however, people still smoked outside the workplace. There is no evidence it is associated with RDP exposure in Port Hope workers. Mortality and incidence of tobacco-related cancers in the Port Hope cohort were similar to the general population of Canada, suggesting that smoking was not substantially elevated relative to the general population.[11] No smoking information was available for Wismut uranium processing workers as well.[23]

No assessment of RDP or gamma-ray dose measurement errors on the risk estimates was conducted. RDP concentration estimates were based on plant inventories of radium-bearing materials, published or otherwise known values of radon emanation rates from various materials, building volumes and estimated air exchange rates. The material inventories likely varied day-to-day but over the year would have been exact and, therefore, not a significant contributor to error in annual average concentrations. Random errors in radon emanation rates and building volumes would have been small and a small contributor to error. The equilibrium factor relating RDP to radon concentrations is a function of the air exchange rate and could be a significant contributor to errors in RDP exposures.

There was no individual gamma-ray external dosimetry in the early years of operation in both cohorts, so all early exposures were estimated. For some early years there was missing data on inventories in specific steps of the operation, but a statistical analysis of film badge readings in the Port Hope cohort through these years showed that variance was small and this was not a significant contributor to error.[11] Of greater importance was the variation in individual work habits and the question of whether an individual was actually present in the assumed location in the specific time period. But, since the gamma-ray dose estimates were done based on annual averages, the likely errors would be small. Measurement errors in exposure estimation almost certainly decreased with calendar time; thus recent workers had lower mean errors than earlier workers.

We had no data on exposures to long-lived radionuclides, arsenic, fine or silica dust in the Port Hope cohort. However, recent analysis of Wismut workers indicated that any increase in risks was primarily due to RDP exposures and gamma radiation.[23] In exploratory analyses of the pooled cohort, we did not observe that these exposures had any effect on the background rates with the exception of significant effects for silica dust in RDP-associated models for lung cancer.

CONCLUSIONS

In this analysis of a cohort of workers exposed to uranium milling and processing with detailed annual exposure information, over 90% of workers were followed-up for at least 20 years,

allowing sufficient time for occupationally-induced cancers to develop. We observed a small but not statistically significant increase in risks of lung cancer and CVD due to RDP exposures among males. Higher CVD risks were observed among those with duration of employment less than 8 years and among those with the youngest age at first WLM exposure. Radiation risks of solid cancers excluding lung cancer were increased both for RDP exposures and for gamma-ray doses, significantly so among women. All other causes of death were not associated with occupational RDP exposures and gamma-ray doses among males and femlales. Significant findings should be interpreted with caution and could be due to a large number of statistical tests. Continued follow-up of the cohorts and pooling with other cohorts of workers exposed to byproducts of radium and uranium processing could provide valuable insights into risks from occupational uranium exposures and gamma-ray doses and into suspected differences in risk with uranium miners.

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Table 1. Summary of findings on risks associated with different types of gamma-radiation exposures.

	High-dose acute exposures		Low-dose fractionated exposures
Outcome	**A-bomb**	**Radiation cancer treatments**	**Occupational exposures**
All solid cancers	sign increase[69]	increase in most studies[67]	increase in most studies[67]
Individual cancers	sign increase for most sites, including esophagus, stomach, colon, liver, lung[70]	sign increased for lung, esophagus, colon, bladder; no increase for liver, pancreas[71]	conflicted due to low statistical power[12,45]
Leukemia excl CLL	sign increase[72]	sign increase[71]	increase in most studies[67]
CLL	sign increase[72]	no risk[71]	sign increase in Chernobyl workers;[46] no increase in most studies[67]
MM	conflicted[72,73]	no risk	conflicted[67]
NHL	sign increase in men[74]	conflicted[67]	conflicted[45,67]
CVD	sign increase[48]	sign increase[75]	conflicted[45,47,75]

Abbreviations: A-bomb, atomic bomb survivors; CLL, chronic lymphocytic leukemia; CVD, cardiovascular diseases; exp, exposures; excl, excluding; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; sign, significant.

Table 2. Basic characteristics of the Port Hope and Wismut cohorts.

Characteristic		Port Hope	Wismut	Total
Number of subjects		3,000	4,431	7,431
	Males (%)	2,645 (88.2)	4161 (93.9)	6806 (91.6)
	Females (%)	355(11.8)	270 (6.1)	625 (8.4)
Person-years		175,345	94,856	270,201
Lifetime[a] RDP exposure, WLM, mean (median), range, SD				
	Males	13.3 (0.41) 0-627.6, 45.9	8.5 (5.2) 0-126.9, 9.7	10.4 0-627.6, 29.7
	Females	4.9 (0) 0-62.7, 9.6	7.4 (4.5) 0-44.1, 8.1	6.0 0-62.7, 9.1
Lifetime[a] gamma dose, mSv, mean (median), range, SD				
	Males	116.3 (21.1) 0-5,098.8, 312.1	30.8 (12.3) 0-667.4, 64.4	64 0-5098.8, 205.2
	Females	36.2 (2.6) 0-464.7, 69.7	31.1 (10.7) 0-446.3, 52.3	34 0-464.7, 62.8

Abbreviations: mSv=millisieverts; RDP=radon decay products; WLM=working level months.

[a] Individual exposures cumulated up to the end of follow-up.

Table 3. Excess risk estimates and 95% confidence intervals for RDP exposures and gamma-ray doses for selected cancer and non-cancer causes of death, combined Port Hope and Wismut cohorts, men only.

	Port Hope	Wismut	RDP Exposure			Gamma-Ray Dose		
Cause of Death	**1950-1999 N=3,000**	**1952-2008 N=4,431**	**ERR/ 100WLM[a]**	**95% CI**	**p-value[b]**	**ERR/ Sv[c]**	**95% CI**	**p-value[b]**
Solid cancer	225	408	0.07	<-0.17, 0.48	0.63	0.02	<-0.58, 0/95	0.96
Solid cancer excluding lung cancer	126	245	0.05	<-0.20, 0.56	0.76	0.10	<-0.43, 0.87	0.73
Liver and biliary cancer	4	12	nc			nc		
Lung and larynx cancer	104	171	0.05[d]	<-0.42, 0.84	0.84	-0.01	<-0.58, 0.87	0.89
Lung cancer	99	163	0.13[d]	<-0.41, 1.02	0.66	0.02[d]	<-0.58, 0.95	0.96
Larynx cancer	5	8	nc			-0.20	<-0.20, 9.88	0.73
Kidney cancer	7	12	-0.16	<-0.16, 14.2	0.83	nc		
Urinary bladder cancer	10	22	-0.16	<-0.16, 3.07	0.75	nc		
Non-Hodgkin's lymphoma	7	9	-0.16	<-0.16, 14.9	0.87	-0.20	<0.20, 9.93	0.77
Multiple myeloma	2	7	nc			nc		
All leukemia	6	6	4.57	<-0.16, 16.9	0.49	0.03	<-0.20, 33.6	0.98
All CVD	514	749	0.11	-0.04. 0.32	0.18	0.13	-0.10, 0.42	0.30
Hypertensive disease	13	36	0.41	<-0.81, 3.66	0.52	0.81	<-0.69, 4.71	0.33
IHD	346	360	0.08	-0.09, 0.34	0.42	0.07	<-0.20, 0.43	0.62
Stroke	71	181	-0.01	<-0.16, 0.62	0.99	-0.15	<-0.20, 0.68	0.64
COPD	29	59	-0.16	<-0.16, 0.59	0.39	nc		
Silicosis & Anthracosilicosis	0	2	nc			nc		
Nephritis and nephrosis	7	3	nc			nc		

Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular diseases; ERR/Sv=excess relative risk per 1 sievert; ERR/100 WLM=excess relative risk per 100 WLM; IHD=ischemic heart disease; nc=no convergence; RDP=radon decay products.

[a] Model adjusted for calendar time, age at risk and cohort by stratification. Gamma-ray doses were not included in the model.

[b] P values from the likelihood ratio test comparing nested model with and without the exposure term.

[c] Model adjusted for calendar time, age at risk and cohort by stratification. RDP exposures were not included in the model.

[d] Models with significant ($p<0.05$) heterogeneity of risk estimates between Port Hope and Wismut cohorts.

Table 4. Deviances of various risks models and lag times for CVD mortality.

Exposure	Lag time, years	Deviance	ERR estimate
RDP exposures	0	2,833.334	0.11
	5	2,833.414	0.11
	10	2,833.635	0.11
	15	2,833.882	0.10
	20	2,833.686	0.12
Gamma-ray doses	0	2,834.115	0.13
	5	2,834.151	0.13
	10	2,834.350	0.12
	15	2,834.519	0.11
	20	2,834.514	0.12

Abbreviations: CVD, cardiovascular diseases; ERR, excess relative risk; RDP, radon decay products.

Table 5. Interaction models for CVD mortality by cumulative RDP exposure, male Port Hope and Wismut workers.

Parameter	Number of deaths	Parameter Estimate and 95% CI[a]	P-value[b]	Deviance
Model 1				
Total WLM	1,263	0.14 (-0.13, 0.41)	0.56	3,614.143
WLM 5-14 previously		1		
WLM 15-24 previously		0.13		
WLM 25+ previously		0.08		
Dose-rate (continuous)			0.93	
Age at risk (continuous)			n.c.	
Model 2				
Total WLM[c]	1,263	0.41 (-0.69, 1.51)	0.56	3,612.712
WLM 5-14 previously		1		
WLM 15-24 previously		0.73		
WLM 25+ previously		0.12		
First age at RDP exposure, years			0.23	
14-24	321	1		
25-71	942	0.12 (0.02, 0.86)		
Model 3				
Total WLM[d]	1,263	0.11 (-0.03, 0.24)	0.56	3609.21
WLM 5-14 previously		1		
WLM 15-24 previously		0.88		
WLM 25+ previously		0.01		

Duration of employment, years			0.01
0-7	445	1	
8-46	818	0.07 (0.003, 1.70)	

Abbreviations: CI=confidence interval; CVD=cardiovascular diseases; ERR/100 WLM=excess relative risk per 100 WLM; n.c.=no convergence; RDP=radon decay products.

[a] Model adjusted for calendar time, age at risk and cohort by stratification. Gamma-ray doses were not included in the model.

[b] P values from the test of heterogeneity of category-specific relative risks.

[c] ERR/100 WLM for time since exposure window 5-14 years and first age at RDP exposure 14-24 years.

[d] ERR/100 WLM for time since exposure window 5-14 years and duration of employment < 8 years.

Table 6. Excess risk estimates and 95% confidence intervals for RDP exposures and gamma-ray doses for selected cancer and non-cancer causes of death, combined Port Hope and Wismut cohorts, women only.

Cause of Death[d]	Port Hope	Wismut	RDP Exposure			Gamma-Ray Dose		
	1950-1999 N=270	1952-2008 N=354	ERR/ 100 WLM[a]	95% CI	p-value[b]	ERR/ Sv[c]	95% CI	p-value[b]
Solid cancer	24	24	2.26	-1.09, 10.3	0.26	3.30	-1.34, 14.8	0.24
Solid cancer excluding lung cancer	17	19	3.71	-0.68, 15.4	0.13	10.03	0.78, 35.2	0.02
All CVD	36	59	-0.14	<-1.59, 2.56	0.88	-0.63	<-2.24, 3.33	0.68
IHD	22	26	0.84	<-1.94, 6.95	0.61	0.64	<-3.44, 8.96	0.80

Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular diseases; ERR/Sv=excess relative risk per 1 sievert; ERR/100 WLM=excess relative risk per 100 WLM; IHD=ischemic heart disease; n.c.=no convergence; RDP=radon decay products.

[a] Model adjusted for calendar time, age at risk and cohort by stratification. Gamma-ray doses were not included in the model.

[b] P values from the likelihood ratio test comparing nested model with and without the exposure term.

[c] Model adjusted for calendar time, age at risk and cohort by stratification. RDP exposures were not included in the model.

[d] Models did not converge or had negative radiation risk estimates for all other causes of death.

Figure 1. Nuclear fuel cycle at Port Hope.[9]

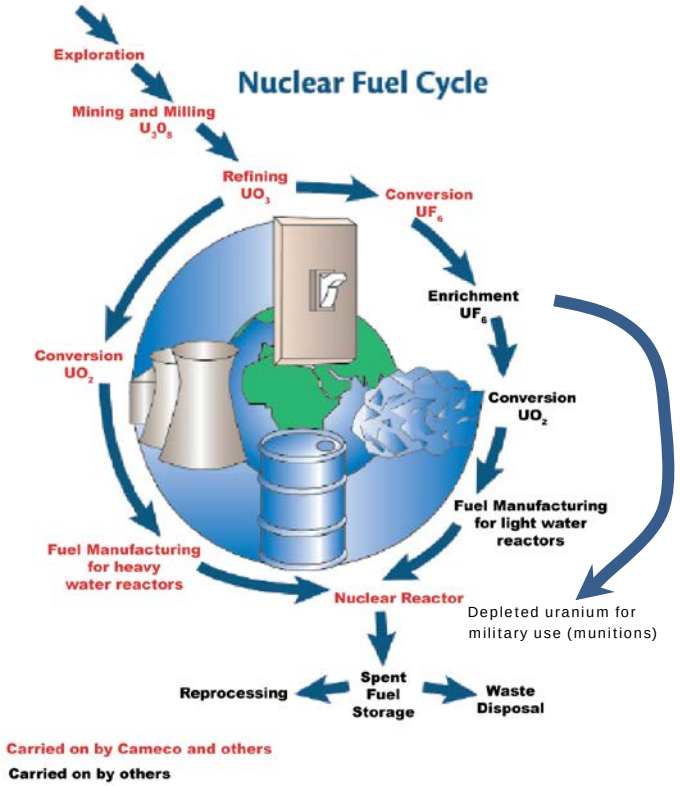


Figure 2. Plot of relative risks of **various CVD mortality outcomes** by mean **gamma dose** for each of twelve dose categories, pooled Port Hope and Wismut cohort. All relative risks were calculated relative to <1 mSv; the referent relative risk is 1.0.

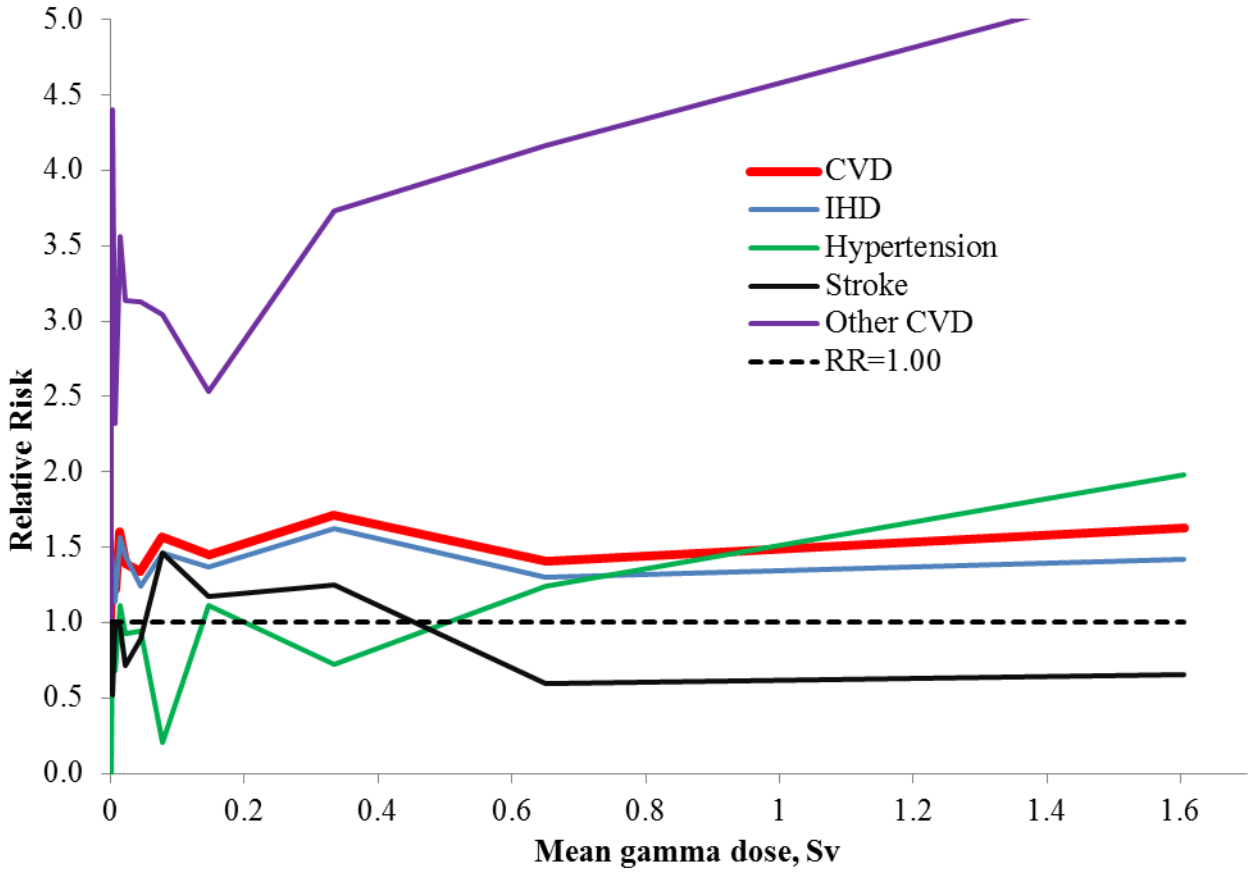


Figure 3. Plot of relative risks of **for CVD and IHD mortality** by mean **gamma dose**, pooled Port Hope and Wismut cohort. All relative risks were calculated relative to <1 mSv; the referent relative risk is 1.0.

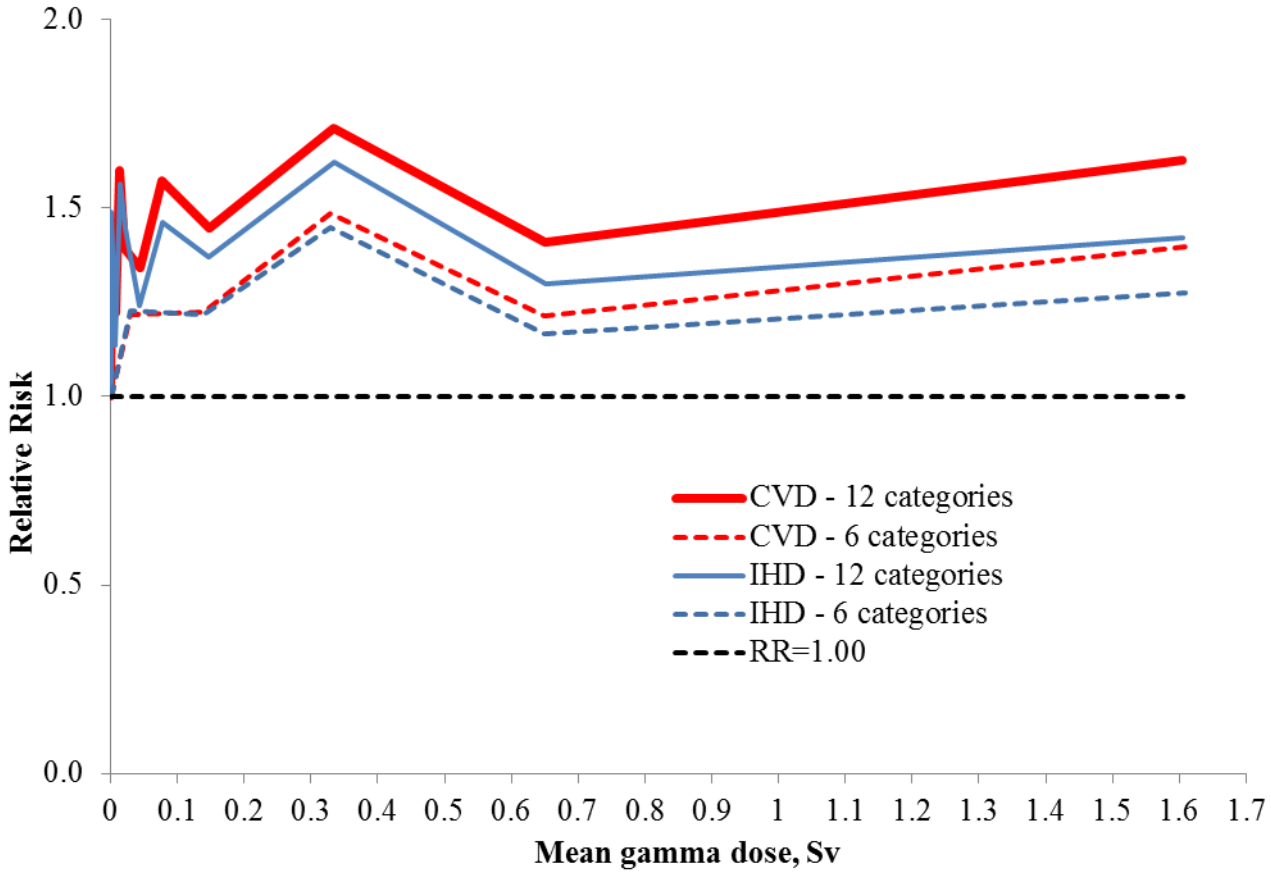


Figure 4. Plot of relative risks of **various CVD mortality outcomes** by mean **RDP exposure** for each of eight dose categories, pooled Port Hope and Wismut cohort. All relative risks were calculated relative to 0 WLM; the referent relative risk is 1.0.

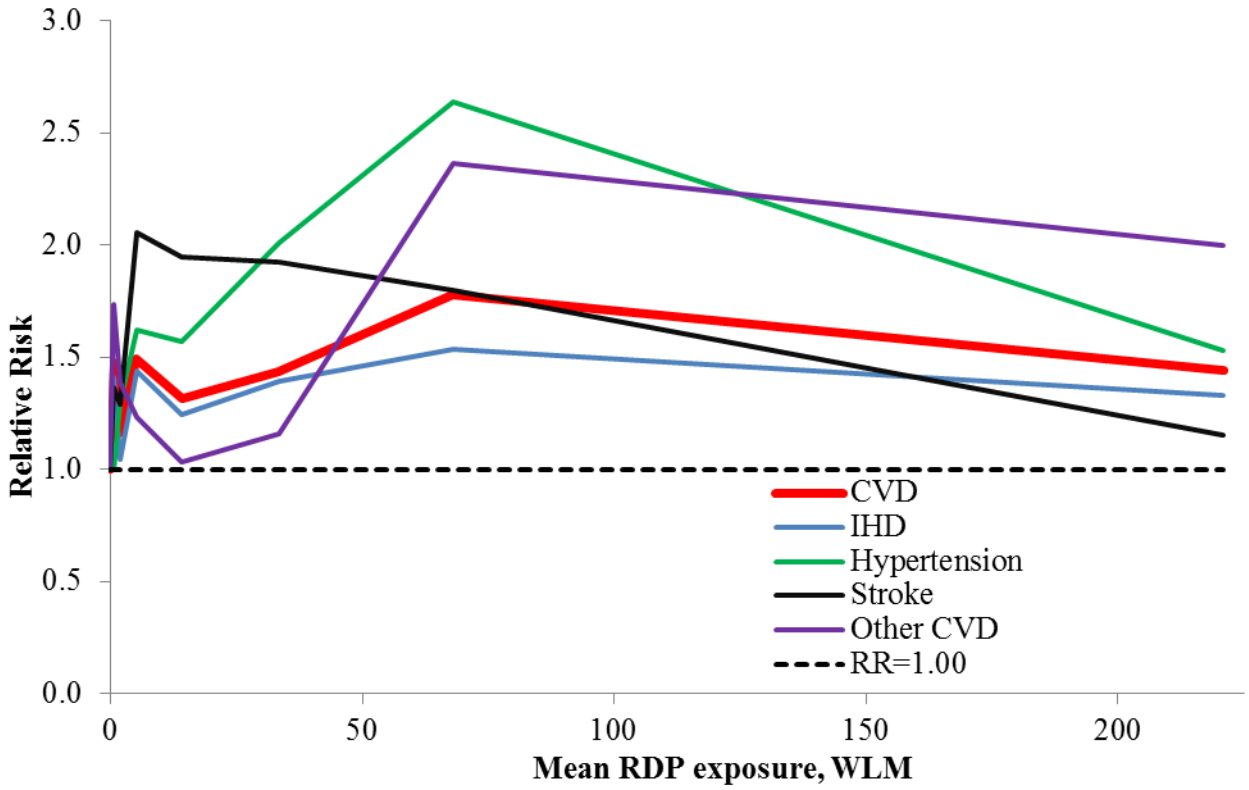
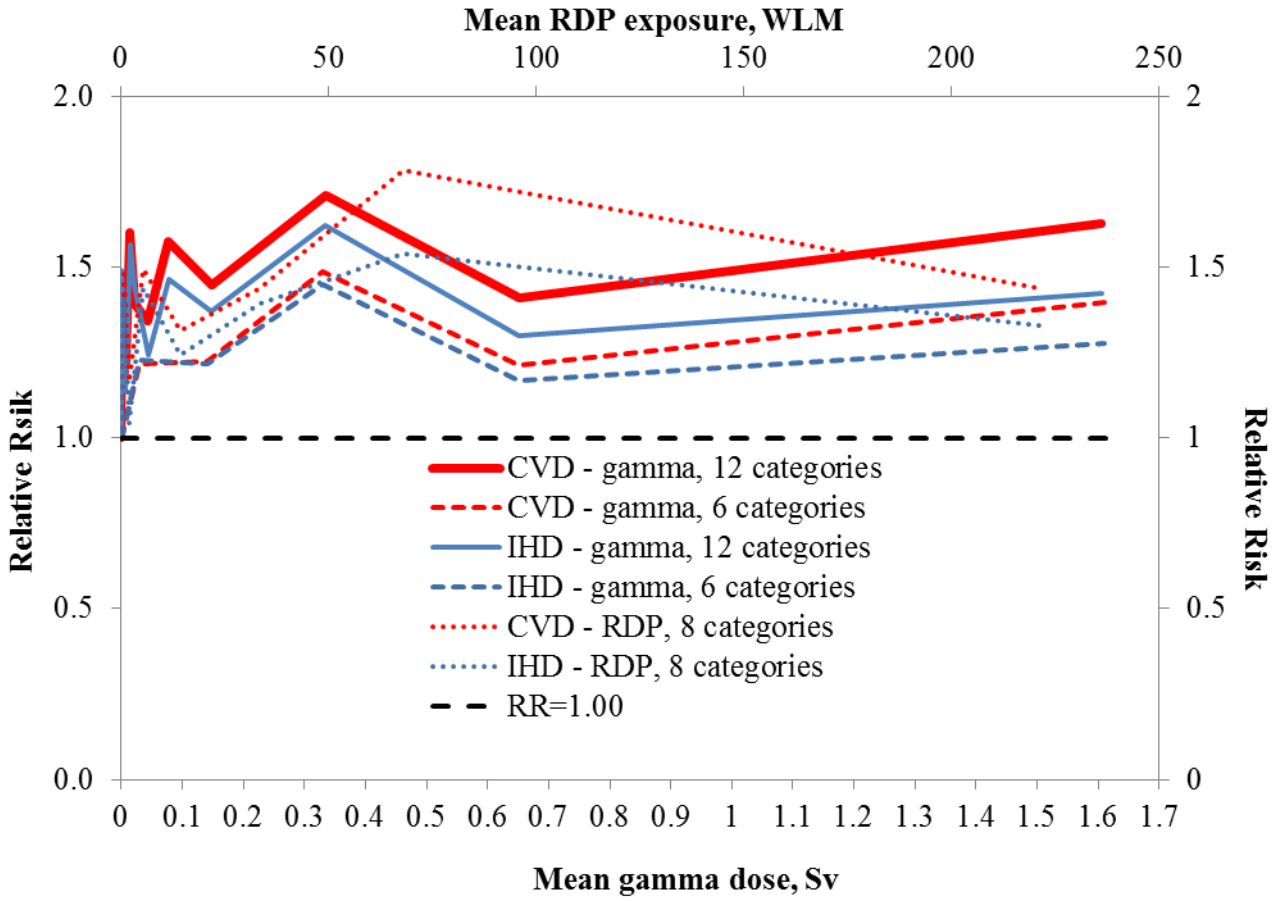


Figure 5. Plot of relative risks of **CVD and IHD mortality** by mean **gamma dose** and **mean RDP exposure**, pooled Port Hope and Wismut cohort. The graph has two different horizontal axes; the referent relative risk is 1.0.



Supplementary Table S1. List of International Classification of Diseases (ICD) codes for causes of death studied in the pooled analysis of Port Hope and Wismut cohorts.

	Port Hope	Wismut
Causes of Death	**ICD-9**	**ICD-10**
Cancer Causes of Death		
Liver	155	C22.0, C22.2-C22.4, C22.7, C22.9
Biliary	155.1-156.9	C22.1, C23-C24
Larynx	161	C32
Lung (including Bronchus)	162.2-162.9	C34
Bones and Joints	170	C40-C41
Urinary Bladder	188	C67
Kidney, Renal Pelvis, Ureter	189	C64-C66
Other Urinary Organs	189.3-189.4, 189.8-189.9	C68
Non-Hodgkin Lymphoma	200, 202.0-202.2, 202.8-202.9	C82-C85, C96.3
Multiple Myeloma	203.0, 238.6	C90.0, C90.2
Chronic Lymphocytic Leukemia	204.1	C91.1
Other Leukemia	204.0, 204.2-204.9, 205, 207-208	C90.1, C91.0, C91.2-C91.9, C92-C95
Non-Cancer Causes of Death		
Cardiovascular diseases[a]		
Hypertensive disease	401-405	I10-I15
Ischemic Heart Disease	410-414, 429.2	I20-I25, I51.6
Stroke	430-438	I60-I69
Other CVD	390-398, 402, 404, 410-448	I00-I09, I11, I13, I20-I51, I70-I78
Pneumonia and Influenza	480-487	J09-J18
Chronic Obstructive Pulmonary Disease and Allied Conditions	466, 490-491, 496	J40-J42, J44
Emphysema	492	J43

Asthma	493	J45-J46
Silicosis & Anthracosilicosis	500, 502	J60, J62
Other Diseases of the Respiratory System	460-465, 467-479, 497-519	J00-J08, J19-J39
Chronic Liver Disease and Cirrhosis Without Mention of Alcohol	571.4-571.9	K73-K74
Nephritis, Nephrotic Syndrome and Nephrosis	580-585, 587	N00-N07, N17-N18

[a] Cumulative grouping, which includes all four CVD outcomes.

Supplementary Table S2. Radiation risk estimates and 95% confidence intervals for **CVD and IHD mortality** by category of **cumulative gamma dose**, male Port Hope and Wismut workers.

Dose Categories, Sv	Mean Dose, Sv	Cases		Person-years		RR[a, b]	95% CI
		CVD					
12 categories		No.	%	No.	%		
0	0	20	2%	42,649	17%	1	
0-0.001	0.001	37	3%	17,549	7%	1.448	0.83-2.52
0.001-0.005	0.003	113	9%	34,293	14%	1.424	0.87-2.32
0.005-0.010	0.007	129	10%	35,729	14%	1.222	0.75-1.98
0.010-0.018	0.014	148	12%	27,812	11%	1.6	0.99-2.59
0.018-0.032	0.022	212	17%	32,155	13%	1.392	0.87-2.24
0.032-0.058	0.044	206	16%	22,188	9%	1.342	0.84-2.16
0.058-0.102	0.077	130	10%	12,946	5%	1.573	0.97-2.55
0.102-0.240	0.147	106	8%	11,081	4%	1.447	0.89-2.37
0.240-0.500	0.334	85	7%	5,849	2%	1.711	1.04-2.82
0.500-1.000	0.651	42	3%	2,692	1%	1.411	0.81-2.45
1.000-5.097	1.605	35	3%	1,643	1%	1.628	0.92-2.88
Total	0.137	1,263	100%	246,586	100%		
		IHD					
12 categories		No.	%	No.	%	RR[b, c]	95% CI
0	0	12	1%	42,649	17%	1	
0-0.001	0.001	23	2%	17,549	7%	1.49	0.73-3.03
0.001-0.005	0.003	63	5%	34,293	14%	1.387	0.74-2.61
0.005-0.010	0.007	69	5%	35,729	14%	1.137	0.61-2.13
0.010-0.018	0.014	81	6%	27,812	11%	1.565	0.84-2.92
0.018-0.032	0.022	121	10%	32,155	13%	1.444	0.78-2.66

0.032-0.058	0.044	103	8%	22,188	9%	1.241	0.67-2.30
0.058-0.102	0.077	76	6%	12,946	5%	1.462	0.78-2.73
0.102-0.240	0.147	63	5%	11,081	4%	1.369	0.73-2.58
0.240-0.500	0.334	50	4%	5,849	2%	1.621	0.85-3.10
0.500-1.000	0.651	24	2%	2,692	1%	1.3	0.64-2.65
1.000-5.097	1.605	21	2%	1,643	1%	1.421	0.68-2.96
Total	0.137	706	100%	246,586	100%		

Abbreviations: CVD, cardiovascular diseases; CI, confidence interval; DOF, degrees of freedom; IHD, ischemic heart diseases; RR, relative risk; Sv, sievert.

[a] *P* heterogeneity =0.314 (DOF=11); *P* linear trend 0.256 (DOF=1).

[b] Model adjusted for calendar time, age at risk and cohort by stratification.

[c] *P* heterogeneity =0.612 (DOF=11); *P* linear trend 0.319 (DOF=1).

Supplementary Table S3. Radiation risk estimates and 95% confidence intervals for **CVD and IHD mortality** by category of **cumulative gamma dose**, male Port Hope and Wismut workers.

Dose Categories, Sv	Mean Dose, Sv	Cases		Person-years		RR[a, b]	95% CI
		CHD					
6 categories		No.	%	No.	%		
0	0	36	3%	42,649	17%	1	
0-0.09	0.03	959	76%	17,549	7%	1.217	0.86-1.72
0.10-0.19	0.14	101	8%	34,293	14%	1.223	0.83-1.81
0.20-0.49	0.33	90	7%	35,729	14%	1.485	1.00-2.21
0.50-0.99	0.65	42	3%	27,812	11%	1.213	0.76-1.93
1.00-5.10	1.61	35	3%	32,155	13%	1.397	0.86-2.27
Total	0.137	1,263	100%	246,586	100%		
		IHD					
6 categories		No.	%	No.	%	RR[b, c]	95% CI
0	0	22	3%	42,649	17%	1	
0-0.09	0.03	526	75%	17,549	7%	1.226	0.79-1.91
0.10-0.19	0.14	61	9%	34,293	14%	1.217	0.74-2.01
0.20-0.49	0.33	52	7%	35,729	14%	1.447	0.86-2.43
0.50-0.99	0.65	24	3%	27,812	11%	1.166	0.64-2.12
1.00-5.10	1.61	21	3%	32,155	13%	1.275	0.68-2.38
Total	0.137	706	100%	246,586	100%		

Abbreviations: CVD, cardiovascular diseases; CI, confidence interval; DOF, degrees of freedom; IHD, ischemic heart diseases; RR, relative risk; Sv, sievert.

[a] *P* heterogeneity =0.498 (DOF=5); *P* linear trend 0.311 (DOF=1).

[b] Model adjusted for calendar time, age at risk and cohort by stratification.

[c] *P* heterogeneity =0.807 (DOF=5); *P* linear trend 0.755 (DOF=1).

Supplementary Table S4. Radiation risk estimates and 95% confidence intervals for **CHD and IHD mortality** by category of **cumulative RDP exposure**, male Port Hope and Wismut workers.

Dose Categories, WLM	Mean Dose, WLM	Cases		Person-years		RR[a, b]	95% CI
		CHD					
8 categories		No.	%	No.	%		
0	0	97	8%	74,669	30%	1	
0-0.9	1	106	8%	26,251	11%	1.478	1.11-1.96
1-2	2	154	12%	38,564	16%	1.164	0.89-1.52
3-7	5	272	22%	47,801	19%	1.492	1.16-1.92
8-23	14	408	32%	44,660	18%	1.315	1.02-1.69
24-49	33	120	10%	9,270	4%	1.438	1.08-1.92
50-99	68	59	5%	2,865	1%	1.781	1.26-2.52
100-623	221	47	4%	2,506	1%	1.439	0.99-2.09
Total	17	1,263	100%	246,586	100%		
		IHD					
8 categories		No.	%	No.	%	RR[b, c]	95% CI
0	0	69	10%	74,669	30%	1	
0-0.9	1	67	9%	26,251	11%	1.412	1.00-2.00
1-2	2	84	12%	38,564	16%	1.045	0.75-1.46
3-7	5	151	21%	47,801	19%	1.439	1.05-1.97
8-23	14	208	29%	44,660	18%	1.242	0.91-1.70
24-49	33	65	9%	9,270	4%	1.391	0.96-2.01
50-99	68	33	5%	2,865	1%	1.537	0.99-2.39
100-623	221	29	4%	2,506	1%	1.328	0.83-2.12
Total	17	706	100%	246,586	100%		

Abbreviations: CVD, cardiovascular diseases; CI, confidence interval; DOF, degrees of freedom; IHD, ischemic heart diseases; RR, relative risk; WLM, working level months.

[a] *P* heterogeneity =0.007 (DOF=7); *P* linear trend 0.491 (DOF=1).

[b] Model adjusted for calendar time, age at risk and cohort by stratification.

[c] *P* heterogeneity =0.807 (DOF=7); *P* linear trend 0.755 (DOF=1).