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A reanalysis of cancer mortality in Canadian nuclear workers (1956–1994) based on revised exposure and cohort data

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Background: A 15-country study of nuclear workers reported significantly increased radiation-related risks of all cancers excluding leukaemia, with Canadian data a major factor behind the pooled results. We analysed mortality (1956–1994) in the updated Canadian cohort and provided revised risk estimates.

Methods: Employment records were searched to verify and revise exposure data and to restore missing socioeconomic status. Excess relative risks per sievert (ERR/Sv) of recorded radiation dose and 95% confidence intervals (CIs) were estimated using Poisson regression.

Results: A significant heterogeneity of the dose–response for solid cancer was identified ($P=0.02$), with 3088 early (1956–1964) Atomic Energy of Canada Limited (AECL) workers having a significant increase (ERR/Sv = 7.87, 95% CI: 1.88, 19.5), and no evidence of radiation risk for 42 228 workers employed by three nuclear power plant companies and post-1964 AECL (ERR/Sv = -1.20, 95% CI: < -1.47, 2.39). Radiation risks of leukaemia were negative in early AECL workers and non-significantly increased in other workers. In analyses with separate terms for tritium and gamma doses, there was no evidence of increased risk from tritium exposure. All workers had mortality lower than the general population.

Conclusion: Significantly increased risks for early AECL workers are most likely due to incomplete transfer of AECL dose records to the National Dose Registry. Analyses of the remainder of the Canadian nuclear workers (93.2%) provided no evidence of increased risk, but the risk estimate was compatible with estimates that form the basis of radiation protection standards. Study findings suggest that the revised Canadian cohort, with the exclusion of early AECL workers, would likely have an important effect on the 15-country pooled risk estimate of radiation-related risks of all cancer excluding leukaemia by substantially reducing the size of the point estimate and its significance.

Ionising radiation is a known human carcinogen (International Agency for Research on Cancer (IARC), 2000, 2012) and has been studied extensively in various population groups, including nuclear workers occupationally exposed to radiation. In Canada, radiation doses are measured by licensed dosimetry services and submitted to both the National Dose Registry (NDR) and to employers. 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) ((National Dose Registry (NDR), 2007). The first

Canadian study of nuclear workers was based on one facility (Atomic Energy of Canada Limited (AECL)) and used radiation doses provided directly by AECL (Gribbin *et al*, 1993). Analysis was based on workers monitored between 1956 and 1980, and doses for workers exposed before 1956, for which records had been destroyed in the February 1956 fire, were reconstructed for those still in employment in 1956. Study data were included in the pooled analysis of mortality of nuclear workers from three countries (Cardis *et al*, 1995). Several later NDR-based studies

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included radiation-exposed workers from a variety of occupational settings and are outside the focus of this paper (Ashmore *et al*, 1998; Sont *et al*, 2001). The most recent study of Canadian nuclear workers (Zablotska *et al*, 2004) included post-1956 workers from AECL, and workers from Hydro-Québec (HQ), New Brunswick Power Corporation (NB) and Ontario Hydro (OH), all of which started monitoring after 1956. The study reported a sizeable, although statistically non-significant, increased risk of solid cancer mortality (excess relative risk per sievert (ERR/Sv) = 2.80, 95% CI: -0.038, 7.13). Table 1 presents the chronology of Canadian studies, as well as international studies which included Canadian nuclear workers, and highlights this important change of the source of radiation dose information, which occurred in the late 1990s.

The data from the last Canadian study (Zablotska *et al*, 2004) (hereafter referred to as 'the original Canadian study') were provided to the International Agency for Research on Cancer (IARC) for the 15-country pooled mortality analysis (Cardis *et al*, 2005, 2007). This pooled study showed statistically significantly increased risks per unit of occupational ionising radiation dose for mortality from solid cancer and from all cancers excluding leukaemia (Table 2, models 1-3), which were three times as high as the ERR estimate for solid cancer mortality in Japanese atomic bomb (A-bomb) survivors exposed to higher doses (ERR/Sv = 0.32, 95% CI: 0.01, 0.50, males exposed at age 35 years) (Cardis *et al*, 2007). In the pooled analysis (Cardis *et al*, 2007), Canadian workers had the highest cancer radiation risk estimates among the 15 countries (Table 1, study 6) and were a major factor behind the significant pooled results. None of the other 14 country cohorts individually had significantly raised cancer mortality risk estimates. The exclusion of the Canadian workers (4% of the sample) from the pooled analysis changed the findings to statistically non-significant with a reduction of the pooled risk estimate by 40% (Table 2, model 4) (Cardis *et al*, 2007). The apparent difference in the results between the Canadian and the 15-country studies attracted a lot of attention and raised questions as to the data and analytical validity (Wakeford, 2005; United Nations Scientific

Committee on the Effects of Atomic Radiation (UNSCEAR), 2008; Wakeford, 2009; Boice, 2010).

Radiation risk estimates for leukaemia were not significant for Canada in the 15-country study (Cardis *et al*, 2007). In contrast, previous Canadian studies (Gribbin *et al*, 1993; Cardis *et al*, 1995; Zablotska *et al*, 2004) and the A-bomb and other studies (National Research Council (NRC), 2006) reported significantly raised radiation risks for leukaemia. A recent independent study of UK radiation workers, which did not contribute in its entirety to the 15-country study, reported significantly increased risks of mortality from leukaemia and from all cancers excluding leukaemia (ERR/Sv = 1.712, 90% CI: 0.06, 4.29 and ERR/Sv = 0.275, 90% CI: 0.02, 0.56, respectively; Muirhead *et al*, 2009).

To better understand the radiation risks of Canadian nuclear workers, the Canadian Nuclear Safety Commission (CNSC) initiated a study with the following objectives:

1. Create a revised cohort based on a detailed review of employment and dose records, various corrections and improvements, and updated socioeconomic status (SES) information for nuclear workers.
2. Assess cancer risks for Canadian nuclear workers from whole-body radiation exposures based on the revised cohort.
3. Assess tritium-specific cancer risks for Canadian nuclear workers. (In Canada, CANDU heavy water moderated nuclear power reactors are a potential source of occupational tritium exposure for nuclear workers. No studies to date have reported tritium-specific risks for nuclear workers (Little and Wakeford, 2008)).

MATERIALS AND METHODS

Review of the differences between the 15-country and original Canadian studies. The data from the original Canadian cohort

Table 1. Epidemiological studies of all cancers excluding leukaemia in the Canadian cohort of nuclear workers

No.	Study	Reference	Source of exposure information	Cohort description	No. of deaths ^a	Mean cumulative whole-body gamma dose, mSv	ERR/Sv (90% CI)
1	AECL workers	(Gribbin <i>et al</i> , 1993)	AECL	8977 M	221	15	0.049 (-0.68, 2.17)
2	AECL workers in the IARC 3-country study	(Cardis <i>et al</i> , 1995)	AECL	11 355 M,W	234	NR	0.13 (<0, 2.1)
3	NDR workers	(Ashmore <i>et al</i> , 1998)	NDR	105 456 M 101 164 W	1136 ^b 496 ^b	10.6 1.7	3.0 (1.1, 4.9) ^b 1.5 (-3.3, 6.3) ^b
4	NDR workers	(Sont <i>et al</i> , 2001)	NDR	95 643 M 191 333 M, W	2030 ^c 3639 ^c	11.5 6.64	2.5 (1.1, 4.2) ^c 2.3 (1.1, 3.9) ^c
5	Canadian nuclear workers	(Zablotska <i>et al</i> , 2004)	NDR	45 468 M, W	474 ^d	13.5	2.80 (-0.038, 7.13) ^{d,e}
6	Canadian nuclear workers in the IARC 15-country study	(Cardis <i>et al</i> , 2007)	NDR	15 955 M, W, excluding OH	204	NR ^f	6.65 (2.56, 13.00) ^f
7	Canadian nuclear workers in the IARC 15-country study	(Cardis <i>et al</i> , 2007) (Vrijheid <i>et al</i> , 2007)	NDR	38 736 M, W, including OH	400	19.5 ^f	3.60 (1.03, 7.27) ^f

Abbreviations: AECL = Atomic Energy of Canada Limited; CI = confidence interval; ERR/Sv = excess relative risk per sievert; IARC = International Agency for Research on Cancer; M = men; mSv = millisievert; NDR = National Dose Registry; NR = not reported; OH = Ontario Hydro; W = women.

^aAll cancers excluding leukaemia, unless otherwise noted.

^bAll cancers.

^cIncidence.

^dSolid cancer.

^e95% CI.

^fColon dose.

Table 2. Radiation risk estimates for all cancers excluding leukaemia from various models from the 15-country pooled analysis of mortality of nuclear workers

Reference	Model No.	Model description	No. of deaths	ERR/Sv (95% CI)
(Cardis <i>et al</i> , 2005)		All cancers excluding leukaemia		
	1	Standard analysis ^a	5024	0.97 (0.14, 1.97)
		Solid cancer		
	2	Standard analysis	4770	0.87 (0.03, 1.88)
			No. of deaths	ERR/Sv (90% CI)
(Cardis <i>et al</i> , 2007)		All cancers excluding leukaemia		
	3	Standard analysis	5024	0.97 (0.27, 1.80)
	4	Standard analysis excluding Canada	4820	0.58 (–0.10, 1.39)
	5	Standard analysis plus OH	5220	0.89 (0.21, 1.69)

Abbreviations: CI = confidence interval; ERR/Sv = excess relative risk per sievert; OH = Ontario Hydro; SES = socioeconomic status.

^aStandard analysis includes 15 countries, with adjustment for SES. OH is not included because of lack of SES data.

study (Zablotska *et al*, 2004) were provided to IARC for the 15-country pooled analysis (Cardis *et al*, 2005, 2007). Although both studies used the same data and similar protocols for eligibility and exclusions, several potentially important differences have been identified. One difference was in the determination of those monitored > 1 year. Based on the *a priori* protocol, the 15-country study excluded 13 990 workers with only one annual dose record from the Canadian cohort, while the original Canadian study excluded only 7444 workers and retained the remaining 6546 workers who had monthly employment records (obtained from the nuclear facilities), which showed that they were monitored for > 1 year. A less important difference was the use of colon doses in the 15-country analysis, which on average were 9.1% lower compared with the recorded doses used in the original Canadian cohort study (range: –3, 33%). Finally, in the original Canadian study, solid cancer and leukaemia mortality risk estimates with and without adjustment for SES were similar; thus workers with missing SES information were included in the analysis (Zablotska *et al*, 2004). In the 15-country study, according to the *a priori* protocol, cohorts with large numbers of workers with missing SES information were excluded from analyses of all cancers excluding leukaemia, approximately a third of the pooled cohort. The 15-country study excluded OH workers ($n = 22\,769$, 58.8% of the Canadian cohort, SES missing for 49.7% of workers or 14% of total OH person-time) but retained AECL workers ($n = 11\,382$, SES missing for 25.7% of workers or 29% of total AECL person-time) (Vrijheid *et al*, 2007). Pooled radiation risk estimates with and without OH were significantly increased (Table 2, models 5 and 3, respectively), suggesting that the unusually high Canadian dose-related risk estimate in the 15-country study was most likely driven by AECL workers, who represented the majority of the Canadian cohort, had the longest follow-up and the highest radiation doses.

Creation of the original Canadian cohort. Formation of the original Canadian cohort is described in detail in Zablotska *et al* (2004). In brief, the NDR contains all available information on radiation exposure for > 500 000 workers who have potential radiation exposure (Ashmore *et al*, 1997). In order to be eligible for the current cohort, participants had to be monitored in a nuclear facility in Canada for ≥ 1 year, registered in the NDR and had to have a minimum of identifying information to ensure reliable linkage with the death records (see below). The 1-year minimum monitoring was to avoid including individuals with very short-term employment who often demonstrate irregular mortality patterns (Howe *et al*, 1988).

The first reactor at AECL came on line in 1949 but a fire destroyed AECL dose records in 1955. Hence, only employees whose monitoring started in 1956 or later were included in the cohort. The power generating companies (OH, HQ, NB) all started nuclear operations after 1956. A further 188 potential subjects were excluded for irregularities in their records, leaving a cohort of 45 468 for analysis (Table 3).

Revisions and updates of the original Canadian cohort and creation of the revised cohort. As our initial evaluation pinpointed an important change in exposure information for AECL workers over time (Table 1), an extensive evaluation of the AECL facility and NDR dose records and their cross-verification was initiated (Ashmore *et al*, 2010). This process involved careful review of dosimetric practices at AECL and the protocols for data validation, verification, storage and transfer to the NDR. We used the roster of AECL workers from Gribbin *et al* (1993) and the list of AECL workers from the NDR to recreate a more complete roster of workers monitored at AECL before 1981. Although it was possible to recreate the employment roster, dose files created for the Gribbin *et al* (1993) study have been lost. After correcting for mistakes and resolving duplicates, the resultant file of 14 768 workers was linked to the NDR dose records for 1956–1980 and to the Statistics Canada mortality file created for the original Canadian study. A total of 2871 workers could not be linked to the NDR, although some had worked up to 15 years at AECL. The reasons why they do not have records in the NDR remain uncertain. It is important to underscore that these workers contributed to the first studies of AECL workers (Gribbin *et al*, 1993; Cardis *et al*, 1995) but did not contribute to the NDR-based studies (Zablotska *et al*, 2004; Cardis *et al*, 2007).

During the search of AECL dose records and their comparison with the NDR dose records, we found 505 workers who were employed before 1956 and thus were not eligible to participate in the study by Zablotska *et al* (2004) or Cardis *et al* (2007) and were excluded from the revised cohort (Table 3). We restored missing zero-recorded doses for 5336 workers that were not reported to the NDR between 1956 and 1970. Finally, original SES assignments were done in 2001 for OH workers employed at the time. We computerised job classifications at the time of hire for all OH workers and used this information to assign SES status of workers in the revised cohort. The details of these and other data revisions are summarised in Supplementary Table S1.

Dosimetry. The NDR database contains annual summary doses for whole-body external and internal radiation exposure for each monitored individual from each organisation where he/she was

Table 3. Demographic and exposure characteristics of the original and revised Canadian cohorts of nuclear workers, 1956–1994

	Analytical cohort	
	Original ^a	Revised ^b
Original size of the cohort	45 656	45 656
Exclusions		
Nuclear monitoring at AECL before 1956	0	505
Irregularities in records	188	196
Additions		
Monitoring > 1 year ^c	0	147
Monitoring in nuclear facilities ^d	0	166
Cumulative whole-body dose \geq 500 mSv	0	48
Size of the cohort used in the analysis	45 468	45 316
Sex (%)		
Male	37 735 (83.0)	37 697 (83.2)
Female	7733 (17.0)	7619 (16.8)
Facility (%)		
AECL	16 361 (36.0)	15 937 (35.2)
Hydro-Québec	2283 (5.0)	2358 (5.2)
New Brunswick Power Corporation	2154 (4.7)	2154 (4.8)
Ontario Hydro	23 217 (51.1)	23 414 (51.7)
Multiple facilities	1453 (3.2)	1453 (3.2)
SES (%)		
1—Professional	5519 (12.1)	4870 (10.7)
2—Other 'white collar'	15 462 (34.0)	20 322 (44.8)
3—'Blue collar' skilled	3761 (8.3)	9943 (21.9)
4—'Blue collar' unskilled	1348 (3.0)	2492 (5.5)
9—Unknown	19 378 (42.6)	7689 (17.0)
Radiation doses^e		
Mean person-time weighted total dose lagged by 10 years (range, SD), mSv	19.13 (0–491.40, 40.30)	21.64 (0–678.78, 47.00)
Mean person-time weighted tritium dose lagged by 10 years (range, SD), mSv	NA ^f	3.02 (0–169.24, 10.55)
Solid cancer deaths and person-years by radiation dose category, mSv		
< 1	306/431 363	270/486 426
1–49	118/152 521	118/101,165
50–99	23/13 338	18/10 230
100 +	27/10 758	31/15 827

Abbreviations: AECL = Atomic Energy of Canada Limited; mSv = millisievert; NA = not applicable; SD = standard deviation; SES = socioeconomic status.

^aThe data from the last study of Canadian workers (Zablotska *et al*, 2004).

^bCurrent analysis based on the revised and refined data set.

^cAECL workers with missing zero recorded doses for 1956–1970 in the NDR, which showed that they worked for > 1 year.

^dAECL workers listed in the NDR as monitored in non-nuclear facilities only but found in the AECL employment roster for 1956–1981.

^eDose in this and subsequent tables refers to the cumulative person-time weighted lung dose.

^fSome tritium doses were missing and hence not included in the analysis.

monitored during the year. External doses were penetrating (whole-body) gamma doses expressed as equivalent doses given in millisievert (mSv). Workers with neutrons ($n=15$) or high internal exposures ($n=10$) were excluded from the cohort. The latter group included workers with internal doses from various radiation types other than neutrons and tritium, and their doses may not have been estimated systematically in a suitable way for epidemiological analyses.

Internal doses for workers in Canada were primarily from tritium. Tritiated water distributes quickly throughout soft tissues and results in a (nominal) whole-body dose. Tritium doses were assessed using routine urinalysis of workers. The urinalysis measurements were converted into equivalent doses expressed in mSv using the biokinetic model and dose conversion factors taken from ICRP (International Commission on Radiological Protection (ICRP), 1994, 1997). Quality factors for gamma rays and tritium were assumed equal to 1. Some pre-1969 records of tritium doses in AECL workers were missing from the NDR (Ashmore *et al*, 2010) and were not included in the original Canadian study. These were included in the current analysis of the revised cohort and are described in more detail in Supplementary Table S1.

Mortality ascertainment. No changes in the mortality ascertainment (described in detail elsewhere, (Zablotska *et al*, 2004)) were undertaken. In brief, the cohort was linked to the Historic Summary Tax File (HSTF) and to the Canadian Mortality Data Base (CMDDB) to ascertain mortality until the end of 1994. The HSTF includes identifiers and the minimal amount of data required to ascertain the vital status and location of individuals since 1984. The HSTF was used to enhance the mortality linkage by filling in data gaps, to confirm the vital status of the cohort members at the end of the follow-up period and to evaluate the results of the mortality linkage. The CMDDB (1950 to present) is based on the vital statistics programme at Statistics Canada, which routinely collects demographic and cause of death information from all provincial and territorial vital statistics registries on all deaths in Canada. Some data are also collected on Canadian residents who died in some states of the United States. Registration of deaths is a legal requirement through the Vital Statistics Acts (or equivalent legislation) in each Canadian province and territory, so reporting is virtually complete. Under-coverage is thought to be minimal ($\leq 1\%$) (Goldberg *et al*, 1993).

Linkage of the worker data to the mortality data was based on a probabilistic approach (Howe and Lindsay, 1981; Howe, 1998), which allows fast and relatively precise linking of the identifying data for a cohort to mortality data from the CMDDB. For the present study, manual inspection was used to examine links close to the threshold to resolve any ambiguity or uncertainties. A study comparing the accuracy of ascertaining mortality through computerised record linkage with CMDDB found 96.4% completeness, equivalent to high-quality manual searches (Shannon *et al*, 1989). Individuals without a social insurance number, who did not link to the HSTF and who did not have a death link in the CMDDB had their termination date at work as the last date alive. Vital status ascertainment was complete for 97.6% of workers and cause of death was known for 99.9% of deaths.

Statistical analysis. The methods used for this reanalysis were as close as possible to those used for the original Canadian study. Both the original and the revised cohorts included workers monitored in one of the nuclear power plant (NPP) companies (HQ, NB or OH) or in the AECL nuclear research and development facility. Individual workers contributed person-years at risk from the date when they had completed 1 year of monitoring until their date of death, last date known alive or 31 December 1994, whichever occurred earlier.

In the categorical analysis, dose was categorised into four categories with cut points similar to those used in the original

Canadian study (<1, 1–49, 50–99, ≥100 mSv). The person-year weighted mean total dose in each cell was used in the regression analysis. For comparability with previous studies (Zablotska *et al*, 2004; Cardis *et al*, 2007), dose was lagged by 2 years for the analysis of leukaemia and by 10 years for all other cancers. A similar 10-year lag was used for whole-body external and tritium doses based on a recent report (Little and Lambert, 2008), although other lag periods were also considered.

For the cancer mortality analyses, the underlying causes of death were recoded from the original International Classification of Disease (ICD) codes in use at the time of death to the ICD, Ninth Revision (ICD-9) (World Health Organization (WHO), 1998). Cancer mortality analyses were conducted for all solid cancers combined, that is, all cancers except leukaemia, lymphoma and multiple myeloma (ICD-9 140.0–199.9), and all leukaemia (204.0–208.9). Less detailed analyses were conducted for eight individual cancers with >10 deaths. Additional exploratory analyses were conducted for (a) all cancers excluding leukaemia (140.0–203.9) and leukaemia excluding CLL (204.1) to compare with the 15-country study (Cardis *et al*, 2007), (b) solid cancer excluding lung cancer and/or rectal cancer to verify that the results for solid cancer were not solely dependent on these outcomes and (c) solid cancer by individual facilities and within facilities by start of radiation monitoring to understand the time pattern of radiation risks.

Observed and expected deaths, based on Canadian population death rates (1956–1994) specific for sex, age and calendar year, were used to estimate standardised mortality ratios (SMRs) by means of indirect standardisation. We also conducted internal dose–response analyses without the use of external cancer rates. For these analyses, a linear model was used to estimate excess relative risk per sievert (ERR/Sv):

$$R_D = R_0 * (1.0 + \beta D \exp(\sum_i \gamma_i z_i)), \quad (1)$$

where R_D is the rate at dose D , R_0 is the background rate (stratified to adjust for potential confounders), β is the ERR/Sv, D is the cumulative lagged continuous dose, z_i are potential effect modifiers, and γ_i are the corresponding coefficients.

When tritium dose was investigated as a potential risk factor, it was entered into the model simultaneously with the whole-body gamma exposure (both as separate linear terms):

$$R_D = R_0 * \left(1 + (\beta_1 D_{\text{gamma doses}} + \beta_2 D_{\text{tritium doses}}) \exp(\sum_i \gamma_i z_i) \right), \quad (2)$$

Stratification variables for each analysis were selected based both on *a priori* considerations and empirical results, that is, all variables used in the original Canadian study (sex, attained age, year at risk, duration of monitoring, facility, monitoring status and SES) were not only considered but also verified that they continued to produce a sizable (≥10%) change in the point estimate of the ERR. Person-time tables were cross-classified by all confounders, cumulative radiation dose and monitoring status (still being monitored or no longer monitored). Duration of monitoring was used as a surrogate for duration of employment, to adjust for a healthy worker effect (Gilbert, 1992). Monitoring status was lagged by 5 years to account for individuals who ceased to be monitored, because they had developed cancer, left employment or died within a 5-year period.

We evaluated possible effect modifiers of the dose–response (facility of monitoring, sex, attained age, age at first monitoring and time since first monitoring) using tests of heterogeneity, for categorical variables, and tests of linear trend, for continuous variables. We also evaluated *a priori* the dose–response by start of monitoring (in 5-year intervals from 1956 to 1994) because of the under-reporting of zero doses to NDR before 1971 (see Supplementary Table S1).

Maximum likelihood point and interval estimates were obtained using the module AMFIT from the computer package EPICURE (Preston *et al*, 1993). Tests of significance were based on the likelihood ratio test. 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 $-1/D_{\text{max}}$, where D_{max} was the maximum dose.

The study was conducted in accordance with accepted ethical practices and was approved by Health Canada's Research Ethics Board.

RESULTS

Demographic and exposure characteristics of the original and revised cohorts. A total of 607 979 person-years at risk were accumulated by the 45 468 members of the original cohort with a mean period of follow-up of 13.4 years (not shown). The majority of workers from the original cohort were included in the revised cohort (Table 3). Most workers were male (83.2%), and except for the lowest dose group (<1.0 mSv), women contributed negligibly to the follow-up (not shown).

Some 513 workers previously included in the original Canadian and 15-country studies were excluded and 361 workers were added as a result of information discovered during evaluation of the AECL facility and NDR dose records (Table 3). The details of these and other data revisions are summarised in Supplementary Table S1. Updates of the revised cohort resulted in the wider dose range compared with the original Canadian study, but mean doses were similar (21.64 vs 19.13 mSv). Although the cumulative person-time in the revised cohort was larger than in the original cohort, the total number of deaths was reduced, primarily due to exclusion of AECL workers with pre-1956 radiation exposures.

Comparison of the revised cohort with the general Canadian population. Canadian workers (revised cohort) had lower all-cause (Supplementary Table S2) and solid cancer (Supplementary Table S3) mortality compared with the similar age-, sex- and calendar-time-adjusted general Canadian population. AECL workers' all-cause mortality and solid cancer mortality were similar to that of all other workers and were significantly lower compared with the general Canadian population. There was no difference between SMRs for all-cause mortality and solid cancer mortality by sex or start of first monitoring. Mortality from all leukaemia, leukaemia excluding CLL, and non-Hodgkin lymphoma was also lower compared with the general Canadian population (Supplementary Table S4). Hodgkin's disease and multiple myeloma had <10 deaths in the cohort in 1956–1994, so were not included in the analysis. We noted an increased SMR for all leukaemia among early AECL workers, but it was not statistically significant and was based on a small number of cases.

Dose–response analyses of the revised cohort and comparisons with the results of the original cohort

Solid cancers. AECL workers represented approximately half of follow-up time and deaths from solid cancer in the revised cohort. The majority, however, were in the lowest cumulative dose group <1 mSv (233 136 person-years, 110 deaths, not shown). OH workers had the second largest contribution, with the majority of follow-up time and deaths also in the lowest cumulative dose group (196 802 person-years, 138 deaths, not shown). In the categorical analysis of solid cancer mortality in the original and revised cohorts, trends in risk with increasing dose were not statistically significant (P -linear trend = 0.11 and 0.97, respectively, Figure 1). In the original cohort, there was a significant deficit in risk in the

lowest positive dose group. In the revised cohort, all relative risk estimates were above unity, and workers with cumulative doses ≥ 100 mSv had slightly elevated risks compared with workers with cumulative doses < 1 mSv (relative risk = 1.34, 95% CI: 0.82, 2.14), but confidence intervals for all dose categories included unity, indicating compatibility with no increase in risks (Figure 1).

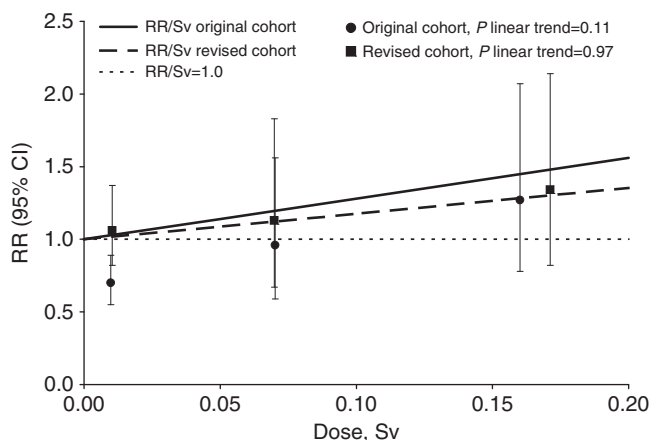


Figure 1. Categorical relative risks and fitted dose–response lines for solid cancer mortality in the original and revised cohorts. Data points and error bars represent category-specific RRs and 95% CIs for mean recorded dose per category. The fitted linear dose–response was adjusted to pass through the lowest dose category. Dose–response models were adjusted for sex, attained age, socioeconomic status, calendar time and duration of monitoring by stratification.

In analyses using continuous doses, a positive border-line significant increase in risk of solid cancer mortality was estimated in the original Canadian study (ERR/Sv = 2.80, 95% CI: -0.038, 7.13, $P=0.05$, Table 4). A much smaller and statistically non-significant increase in risk was estimated in the revised cohort (ERR/Sv = 1.77, 95% CI: -0.42, 5.30, $P=0.13$), a 37% decrease in the point estimate. Risks of all cancers excluding leukaemia were lower than risks of solid cancer and were also not statistically significant (ERR/Sv = 1.20, 95% CI: -0.73, 4.33, $P=0.27$). When women were excluded from the cohort (11% of all deaths), the risk estimates remained unchanged (not shown).

The observed elevation in solid cancer mortality radiation risks was only observed in AECL workers (Table 4). Risk estimates for AECL workers were statistically significant and unusually high in both the original (ERR/Sv = 4.50, 95% CI: 0.60, 11.1, $P=0.02$) and revised (ERR/Sv = 3.25, 95% CI: 0.11, 8.85, $P=0.04$) cohorts. All solid cancer mortality radiation risks among workers from the three NPP companies were negative.

Solid cancer mortality radiation risks were statistically significantly increased for AECL workers first monitored before 1960, were lower in magnitude and no longer significant for those first monitored in 1960–1964 and were negative for all other 5-year periods separately and combined starting 1965 (Table 5). No dose–response of solid cancer mortality was observed when the 27 926 workers from the three NPP companies were combined (Table 5), whether first monitored in the early years when facilities became operational (1960 for OH, 1971 for HQ and 1982 for NB) or later.

The observed positive solid cancer radiation dose–response among AECL workers was due to the positive radiation

Table 4. ERR/Sv and 95% CI for mortality from various causes in the original and revised Canadian cohorts of nuclear workers, 1956–1994

Cause of death	N deaths	Original			Revised		
		ERR/Sv (95% CI) ^{a,b}	P-value ^c	N deaths	ERR/Sv (95% CI) ^{a,b}	P-value ^c	
Solid cancer	474	2.80 (-0.038, 7.13)	0.05	437	1.77 (-0.42, 5.30)	0.13	
AECL	248	4.50 (0.60, 11.1)	0.02	208	3.25 (0.11, 8.85)	0.04	
Hydro-Québec	14	-4.65 (< -4.66, 56.5)	0.59	15	-4.62 (< -4.63, 51.6)	0.62	
New Brunswick Power Corporation	9	-6.44 (< -6.44, 445)	0.78	9	-6.42 (< -6.44, 701)	0.81	
Ontario Hydro	184	-2.40 (< -2.41, 4.40)	0.30	188	-0.13 (< -1.90, 9.34)	0.97	
Multiple facilities	19	-2.02 (NE)	0.75	17	NC		
Cancer of buccal cavity and pharynx	13	7.52 (< -2.08, 77.6)	0.40	12	0.91 (< -1.47, 43.3)	0.87	
Esophageal cancer	14	-2.00 (< -2.08, 55.0)	0.86	13	-1.45 (< -1.47, 48.2)	0.88	
Colon cancer	40	10.7 (< -2.08, 48.4)	0.17	37	14.4 (< -1.47, 70.9)	0.11	
Rectal cancer	16	34.1 (1.41, 165)	0.03	15	6.99 (< -1.47, 64.2)	0.36	
Pancreatic cancer	22	-2.03 (< -2.08, 34.4)	0.59	20	-1.46 (< -1.47, 45.2)	0.72	
Lung cancer	183	4.34 (-0.19, 12.7)	0.07	174	3.13 (-0.45, 10.4)	0.11	
Prostatic cancer	26	0.78 (< -2.08, 19.2)	0.85	22	0.43 (< -1.47, 17.7)	0.91	
Brain and other CNS cancer	25	-2.04 (< -2.08, 8.99)	0.34	22	-1.45 (< -1.47, 5.83)	0.32	
Other solid cancers	35	-2.04 (< -2.08, 12.2)	0.42	31	-1.47 (< -1.47, 4.26)	0.26	
All leukaemia	22	18.9 (< -2.08, 138)^d	0.25	21	5.06 (< -1.49, 57.8)^d	0.54	
Leukaemia excluding CLL	18	52.5 (0.205, 291) ^d	0.05	17	9.79 (< -1.49, 107) ^d	0.37	
All cancers excluding leukaemia	509	2.37 (-0.37, 6.60)	0.10	468	1.20 (-0.73, 4.33)	0.27	

Abbreviations: AECL = Atomic Energy of Canada Limited; CI = confidence interval; CLL = chronic lymphocytic leukaemia; CNS = central nervous system; ERR/Sv = excess relative risk per sievert; NE = could not be estimated; NC = no convergence after maximum iterations.

^aModels adjusted for sex, attained age, socioeconomic status (SES), calendar time and duration of monitoring by stratification.

^bDoses lagged by 10 years.

^cP-value from the likelihood ratio test for departure of ERR/Sv from zero.

^dModels additionally adjusted for monitoring status at a facility by stratification and doses lagged by 2 years.

Table 5. Modification of radiation-related risks of mortality from solid cancer by start of nuclear monitoring in the revised cohort of Canadian nuclear workers, 1956–1994

	N subjects/PY	N deaths	Mean dose (SD), mSv	ERR/Sv (95% CI) ^{a,b}	P-value ^c
Risks by facility and by start of first monitoring					
AECL	15 937/298 462	208	20.29 (47.83)	3.25 (0.11, 8.85)	0.04
First monitored 1956–1959	1355/46 016	74	37.04 (71.19)	7.78 (1.52, 21.5)	<0.01
First monitored 1960–1964	1733/52 899	39	20.15 (46.06)	3.75 (< –2.02, 70.3)	0.81
First monitored 1965–1994	12 849/199 547	95	13.61 (32.72)	–1.03 (< –1.66, 5.76)	0.63
Hydro-Québec, New Brunswick Power Corporation, Ontario Hydro^d	27 926/287 338	212	19.47 (41.02)	–0.32 (< –1.90, 8.20)	0.91
First monitored 1965–1994	27 907/286 771	212	19.56 (41.20)	–0.68 (< –1.91, 7.45)	0.81

Abbreviations: AECL = Atomic Energy of Canada Limited; CI = confidence interval; ERR/Sv = excess relative risk per sievert; mSv = millisievert; PY = person-years; SD = standard deviation.
^aModels adjusted for sex, attained age, socioeconomic status (SES), calendar time and duration of monitoring by stratification.
^bDoses lagged by 10 years.
^cP-value from the likelihood ratio test for departure of ERR/Sv from zero.
^dDoes not include 1453 nuclear workers (17 solid cancers) who were monitored in multiple facilities, because most of them were monitored at AECL after 1965.

Table 6. Best estimates of radiation-related risks per unit of occupational radiation exposure in the revised Canadian cohort of nuclear workers, 1956–1994

Cause of death	AECL workers first monitored 1956–1964 (3088 workers/98 915 PY)			All NPP workers and AECL workers first monitored starting 1965 (42 228 workers/514 729 PY) ^a		
	N deaths	ERR/Sv (95% CI) ^c	P-value ^b	N deaths	ERR/Sv (95% CI) ^c	P-value ^b
All cancers excluding leukaemia	121	6.00 (1.02, 15.8)	<0.01	347	–1.36 (< –1.47, 1.98)	0.34
Solid cancer	113	7.87 (1.88, 19.5)	<0.01	324	–1.20 (< –1.47, 2.39)	0.42
All leukaemia	8	NC		13	14.4 (< –1.49, 146)^d	0.28
Leukaemia excluding CLL	5	–1.50 (NE) ^d	0.85	12	14.4 (< –1.49, 146) ^d	0.28

Abbreviations: AECL = Atomic Energy of Canada Limited; CI = confidence interval; CLL = chronic lymphocytic leukaemia; ERR/Sv = excess relative risk per sievert; NE = could not be estimated; NC = no convergence after maximum iterations; NPP = nuclear power plant; PY = person-years.
^aIncludes 1453 nuclear workers (17 solid cancers) who were monitored in multiple facilities, because most of them were monitored at AECL after 1965.
^bP-value from the likelihood ratio test for departure of ERR/Sv from zero.
^cModels adjusted for sex, attained age, socioeconomic status (SES), calendar time and duration of monitoring by stratification and doses lagged by 10 years.
^dModels additionally adjusted for monitoring status and facility by stratification and doses lagged by 2 years.

dose–response observed in 3088 workers first monitored in 1956–1964 (ERR/Sv = 7.87, 95% CI: 1.88, 19.5, Table 6). The dose–response for the remaining workers from the three NPP companies and AECL workers first monitored starting 1965 (42 228 workers and 514 729 PY) was negative (ERR/Sv = –1.20, 95% CI: < –1.47, 2.39). A formal test of the difference in slopes between AECL workers first monitored 1956–1964 ($N = 3088$ AECL workers; 113 solid cancer deaths) and all other workers in the revised cohort ($N = 42 228$ workers; 324 solid cancer deaths) was highly statistically significant (P -heterogeneity = 0.02, not shown). A significant heterogeneity between the two subcohorts was also observed for all cancers excluding leukaemia (P -heterogeneity < 0.05, not shown).

Increased dose-related risks of solid cancer mortality among early AECL workers were not modified by age at first monitoring or time since first monitoring (both P -linear trend > 0.2, not shown) or by attained age ($P > 0.5$). Risks per unit of dose for all other Canadian workers remained negative and did not vary by sex (P -heterogeneity > 0.5, not shown) or age at first monitoring or time since first monitoring (both P -linear trend > 0.5, not shown).

Leukaemia. There were few leukaemia deaths in the original and revised cohorts (22 and 21, respectively) and included only 4 CLL deaths (Table 4). There were increased leukaemia radiation risks in higher dose groups in both cohorts; however, no clear linear trend in risk with increasing dose was observed (not shown).

The radiation risk estimate for all leukaemia (ERR/Sv = 5.06 (95% CI: < –1.49, 57.8, $P = 0.54$) was much smaller than the estimate without CLL deaths (ERR/Sv = 9.79, 95% CI: < –1.49, 107, $P = 0.37$) in the revised cohort, but both were not statistically significant. Risks of all leukaemia excluding CLL were negative among early AECL workers but non-significantly increased among the remaining 42 228 workers (Table 6).

Various cancer sites. None of the eight individual solid cancer sites with > 10 deaths showed significant association with dose in the revised cohort (Table 4). The pattern of risks for lung cancer mortality were similar in both cohorts, that is, elevated but not statistically significant and compatible with no increase in risk. Based on 263 non-lung cancer solid cancers, an ERR/Sv = 0.80 (95% CI: < –1.47, 5.23, $P = 0.60$) was estimated in the revised cohort (not shown). The pattern of risks of solid cancer mortality excluding lung cancer by facility resembled that observed for all solid cancers (i.e., positive although no longer significant risks for early AECL workers and negative risk for workers from all other facilities, not shown).

In the original Canadian study, the only solid cancer outcome with a significantly increased dose-related risk was rectal cancer. In the revised cohort, the risk estimate for rectal cancer was substantially reduced and no longer statistically significant (Table 4). Removal of lung and rectal cancers resulted in a

substantially reduced risk of solid cancer ($ERR/Sv = 0.40$, 95% CI: < -1.47 , 4.77, not shown). Examination of individual cancer sites among early AECL workers showed that risks were significantly increased for lung and colon cancer and increased for rectal cancer, which jointly contributed 52% of all solid cancer deaths.

Radiation-related risks of exposure to tritium. The contribution of tritium to the total whole-body dose in the revised cohort was small (mean tritium dose = 3.02 mSv, Table 3). Only a small number of workers had tritium doses ≥ 50 mSv ($n = 809$, 1.8%). Tritium doses varied widely by facility and were significantly higher among workers from the three NPP companies compared with AECL workers (mean dose = 4.70, range: 0–149.32 and mean dose = 0.64, range: 0–81.61 mSv, respectively).

When tritium doses were added to the model with gamma doses as a second linear term (equation (2)), the fit of the model did not improve ($P = 0.39$, not shown). We estimated $ERR/Sv_{\text{gamma doses}} = 2.56$ (95% CI: -0.11 , 6.79) and $ERR/Sv_{\text{tritium doses}} = -4.71$ (95% CI: < -5.92 , 8.58) in the model with two separate dose terms. Analyses of lung and other individual solid cancers as well as leukaemia using two linear dose terms showed that risks were due solely to gamma doses and that the addition of tritium doses did not improve the fit of the model (not shown). Despite higher tritium doses for workers from the three NPP companies, the estimate of radiation risk of solid cancer mortality for this group remained negative when workers with non-zero tritium doses were excluded from analyses or when a linear term for tritium dose was added to the model with a linear term for gamma doses (not shown). Estimated risks of solid cancer for AECL workers (both all workers and early workers) remained significant when workers with non-zero tritium doses were excluded from analysis (not shown).

DISCUSSION

The current reanalysis is based on the verified and revised exposure and cohort information and contains more complete information than either (Gribbin *et al*, 1993; Cardis *et al*, 1995) or (Zablotska *et al*, 2004; Cardis *et al*, 2005, 2007). It should be considered the most accurate analysis to date of radiation risks among Canadian nuclear workers. The exclusion of AECL workers monitored before 1956, addition of zero-dose records for AECL workers monitored from 1956 to 1971 and other corrections to the original Canadian study (Zablotska *et al*, 2004) reduced the statistically non-significant solid cancer mortality risk estimate from $ERR/Sv = 2.80$ to $ERR/Sv = 1.77$ in the current analysis (Table 4). However, we showed that the combined estimate was not an accurate representation of risks per unit of radiation dose for all Canadian nuclear workers in the revised cohort because of identified significant heterogeneity in risks between 3088 AECL workers first monitored in 1956–1964 and 42 228 workers at three Canadian NPP companies and post-1964 AECL workers. The estimate of radiation risk of solid cancer for the latter group of Canadian nuclear workers is $ERR/Sv = -1.20$ (95% CI: < -1.47 , 2.39) and is much lower than either risk estimate excluding OH workers ($ERR/Sv = 6.65$) or including OH workers ($ERR/Sv = 3.60$) estimated for Canadian workers in the 15-country study (both significant, Table 1); (Cardis *et al*, 2007). Risks of leukaemia were increased but not statistically significant in the revised cohort. Tritium doses were generally low and analyses of all outcomes showed that risks were due solely to gamma doses.

We observed a significant dose-related increase in risk of solid cancer mortality among early AECL workers first monitored in 1956–1964. The highest attained age and the longest time since first monitoring in this group could provide a better opportunity to detect radiation effects compared with other workers with lower

attained age and shorter follow-up. However, increased risks in this group did not vary by time since first monitoring or attained age, and radiation risks of solid cancer were negative for all those first monitored starting 1965. The observed dose-related increase in risk of solid cancer mortality among early AECL workers is also not likely to be due to differential ascertainment of deaths. The SMRs for all-cause mortality and solid cancer mortality among AECL workers, by start of monitoring, were all statistically significantly lower than the Canadian general population. It is also unlikely to be due to missing SES data as risk estimates among early AECL workers were significantly increased both among those with known and those with missing SES information. The increased dose-related risk of solid cancer in this small group of workers was mostly due to a positive radiation dose-response for colon, lung and rectal cancer, but rectal cancer has not been linked to radiation in the A-bomb survivor studies (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2008; Preston *et al*, 2010).

Although leukaemia is usually thought to be most strongly related to radiation (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2008), no dose-response was observed among early AECL workers. A previous study including pre-1956 AECL workers (Gribbin *et al*, 1993) based on AECL records reported a significantly increased risk of leukaemia, although it was based on a small number of cases and included workers with pre-1956 radiation doses. Significantly increased radiation risks of leukaemia were also reported in other previous Canadian studies (Cardis *et al*, 1995; Zablotska *et al*, 2004).

Although the subgroup of 3088 early AECL workers had statistically significantly higher mean doses compared with other AECL workers first monitored starting 1965 or workers from the NPP companies (29.21 vs 13.61 vs 19.47 mSv, respectively, $P < 0.001$), the differences were relatively modest and cannot explain the observed differences in estimated solid cancer mortality risks. Mean doses for early AECL workers were also higher compared with the first study of AECL workers (Gribbin *et al*, 1993), even though the latter included workers with reconstructed pre-1956 doses (not included in this analysis) (29.21 vs 15.0 mSv, respectively). It is not possible to directly compare the two analyses, because dose data for Gribbin *et al* (1993) study have been lost. This suggests the possibility of missing AECL workers with zero doses before 1971 in the revised cohort. It is likely that the 2871 workers from the reconstructed AECL roster who could not be linked to the NDR had only zero doses and were not reported to the NDR before 1971. If indeed present, this bias would have resulted in the decrease in the number of workers with zero doses and a likely increase in mean cumulative doses. If there was a systematic bias in inclusion of records of AECL employees with zero doses in the NDR in the pre-1971 period, it could explain the differences in solid cancer risk estimates between the studies based on the AECL facility records, which were essentially negative (Gribbin *et al*, 1993; Cardis *et al*, 1995), and the studies based on the NDR records (Zablotska *et al*, 2004; Cardis *et al*, 2005, 2007). Questions about differences in solid cancer risk estimates between Canadian studies have been raised previously (Gilbert, 2001). Our findings for early AECL workers are the likely reason for the high solid cancer risk estimates in the other NDR-based studies (Ashmore *et al*, 1998; Sont *et al*, 2001).

These facts discovered during this reanalysis reinforce our concerns that there remains a data problem in the early AECL workers, most likely missing dose information due to incomplete transfer of AECL dose records to the NDR, as opposed to a true increase in the dose-related risk of solid cancer mortality. Based on our analyses and the identified problem with early AECL dose records, we believe it is not appropriate to use the early AECL data until they can be verified. The CNSC, AECL and NDR discussed the findings of our study for the 3088 early AECL workers and

agreed on the importance of having accurate and complete records for these workers. At the same time, we have confidence in the data for NPP workers and for AECL workers first monitored starting 1965 as no inconsistencies have been identified during numerous checks (Gale and Doerffer, 2000; Gale, 2002, 2003). The CNSC is starting to make plans to initiate an updated analysis of the Canadian nuclear workers cohort for mortality and cancer incidence. Preparations for an updated analysis will include consideration of the remaining issues with the 1956–1964 AECL workers.

The strengths of the revised Canadian cohort and this study include substantial follow-up (up to 38 years), a large cohort of nuclear workers ($N = 45\,316$) and reasonably accurate and precise dose information for the majority of workers (93.2%). Study findings are limited by lack of information on potential confounders, although current analysis improved SES information for a substantial proportion of the cohort. The pattern of risks and the size of dose-related risk estimates of solid cancer excluding lung cancer, a cancer most strongly related to smoking, resembled that of the whole group of solid cancer. Thus, it is unlikely that our results were severely confounded due to missing smoking information. In contrast, in the 15-country study radiation-related risks of lung cancer were significant and very high ($ERR/Sv = 1.86$, 90% CI: 0.47, 3.81) (Cardis *et al*, 2007) and could have biased 15-country study estimates for all cancer excluding leukaemia upward. Thus, there is a strong possibility that the 15-country estimates have been confounded by smoking.

Although analyses for separate facilities and by start of monitoring did not have adequate power to test hypotheses, they provided insight into the nature of the risks of solid cancer observed in this study. As with other studies of occupational exposures of nuclear workers (Thierry-Chef *et al*, 2007), quality and completeness of dose measurements, especially tritium doses, could have contributed to uncertainties in dose estimation. These errors are expected to be random and would likely result in underestimation of risks. However, previous evaluations of Canadian dosimetry, notwithstanding missing dose records, concluded that measurement error in dosimetry would have had little impact on the results (Thierry-Chef *et al*, 2002, 2007).

A recent independent study of about 175 000 nuclear workers from the United Kingdom (Muirhead *et al*, 2009) was based on a large number of deaths from all cancer excluding leukaemia (7455 vs 468 in the current study and 5024 in the 15-country study). The mean cumulative radiation dose among the 42 228 Canadian workers was comparable with the UK cohort, and although point estimates for risks of all cancers excluding leukaemia were quite different ($ERR/Sv = -1.36$, 95% CI: < -1.47 , 1.98 and $ERR/Sv = 0.275$, 90% CI: 0.02, 0.56, respectively), the confidence intervals overlapped, suggesting compatibility. Both were compatible with the risk estimated for male A-bomb survivors exposed at age 35 years ($ERR/Sv = 0.32$, 90% CI: 0.07, 0.47) (Cardis *et al*, 2007).

It is important to consider the potential effects of using verified and revised exposure and cohort information from the current study on the pooled estimate of risk from all cancers excluding leukaemia in the 15-country study. The Canadian cohort was a major factor behind the finding of a statistically significant dose-related increase in risk for all cancers excluding leukaemia mortality (Cardis *et al*, 2005, 2007). Our review of the differences in analytical strategies between the original Canadian cohort study (Zablotska *et al*, 2004) and the 15-country study (Cardis *et al*, 2007) showed that the unusually high dose-related cancer risk estimate in the latter study for Canada was most likely driven by a single facility, AECL. Our analysis of the revised cohort and exposure data suggests that a small group of 3088 early AECL workers first monitored 1956–1964 had a consistent and significant dose-related risk of solid cancer mortality but not leukaemia. The findings of this study suggest that the revised Canadian cohort, with the exclusion of early AECL workers, would likely have an important effect on the pooled risk

estimate of radiation-related risks of all cancer excluding leukaemia by substantially reducing the size of the point estimate and its significance.

In summary, the present study provides the most accurate data to date on mortality in the cohort of Canadian nuclear workers. Some 42 228 workers from Ontario Hydro, Hydro-Québec and New Brunswick Power Corporation NPPs and AECL workers first monitored starting 1965 had no dose-related increase in risk of solid cancer mortality due to radiation exposure. A small group of 3088 AECL workers first monitored in 1956–1964 showed a consistent and significant dose-related risk of solid cancer mortality but not leukaemia. Although a genuine difference in response between the two groups cannot be ruled out, inconsistencies in dose information for AECL in that early period appear to be causing a systematic error that cannot be explained at this time. Overall, the results of analyses of the revised Canadian data are compatible with the current radiation risk estimates from low-dose radiation exposures that form the basis of radiation protection standards.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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