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Overview of epidemiological studies of nuclear workers: opportunities, expectations, and limitations*

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Abstract

Epidemiological studies of those exposed occupationally to ionising radiation offer an important opportunity to directly check the assumptions underlying the international system of radiological protection against low-level radiation exposures. Recent nuclear worker studies, notably the International Nuclear Workers Study (INWORKS) and studies of the Mayak workforce in Russia, provide powerful investigations of a wide range of cumulative photon doses received at a low dose-rate over protracted periods, and broadly confirm radiation-related excess risks of leukaemia and solid cancers at around the levels predicted by standard risk models derived mainly from the experience of the Japanese atomic-bomb survivors acutely exposed principally to gamma radiation. However, the slope of the dose-response for solid cancers expressed in terms of the excess relative risk per unit dose, ERR/Gy, differs between INWORKS and Mayak, such that when compared with the slope derived from the atomic-bomb survivors, INWORKS does not provide obvious support for the use in radiological protection of a dose and dose-rate effectiveness factor greater than one whereas the Mayak workforce apparently does. This difference could be a chance effect, but it could also point to potential problems with these worker studies. Of particular concern is the adequacy of recorded doses received in the early years of operations at older nuclear installations, such as the potential for 'missed' photon doses. A further issue is how baseline cancer

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rates may influence radiation-related excess risks. There is scope for a considerable increase in the statistical power of worker studies, with longer follow-up capturing more deaths and incident cases of cancer, and further workforces being included in collaborative studies, but the difficulties posed by dosimetry questions should not be ignored and need to be the subject of detailed scrutiny.

Keywords: cancer risk, low-level radiation exposure,
nuclear workers, dose uncertainties

(Some figures may appear in colour only in the online journal)

1. Introduction

In the current international system of radiological protection [1] the health detriment consequent to low-level exposure to ionising radiation—that is, the risk to health arising from the receipt of low doses of radiation or doses received at a low dose-rate—is posited to be due primarily to an excess risk of cancer in the exposed individual. Quantification of the radiation-related excess risk of cancer is obtained from statistical models principally derived from the experience of the Japanese survivors of the atomic-bombings of Hiroshima and Nagasaki in 1945, in particular, from the Life Span Study (LSS) cohort of ∼86 500 survivors alive in October 1950. However, not all risk models depend on the LSS data, some being derived from other exposure circumstances, notably the risk model for lung cancer following inhalation of radon and its short-lived radioactive decay products, which is obtained from studies of underground hard-rock miners. The atomic-bomb survivors were briefly and relatively uniformly exposed to mainly gamma radiation (with, in general, a small component of neutrons), so certain assumptions are necessary when other exposure conditions are under consideration, such as protracted exposure, levels of exposure that differ between organs/tissues, or exposure to other types of radiation (such as alpha-particles).

Groups of people exposed to radiation for medical purposes, in the environment and in the workplace offer opportunities for epidemiological studies to provide evidence to complement the findings of the studies of the atomic-bomb survivors [2–4]. Many of these studies are difficult to conduct or interpret for a number of reasons, such as the influence of various biases or confounding factors, poor exposure details and small numbers leading to low statistical power [5]. However, studies of those occupationally exposed to radiation offer an increasingly important source of information on the effects of protracted low dose-rate exposure to external sources of radiation, and some workers have also been exposed to internal sources of radiation as a result of intakes of radionuclides such as plutonium [6]. This paper reviews the most powerful of these worker studies, what scope there is for their expansion and enhanced power, and what problems remain to be resolved. The paper concentrates on studies of exposure to external sources of radiation although important progress is also being made in investigating the effects of exposure from internally deposited radionuclides, e.g. radon decay products [7] and plutonium [8].

2. Studies of nuclear workers in Western Europe and North America

2.1. *The International Nuclear Workers Study (INWORKS)*

For several decades, efforts have been made to combine data for workers from a number of nuclear installations to improve statistical power, initially at a national level and then

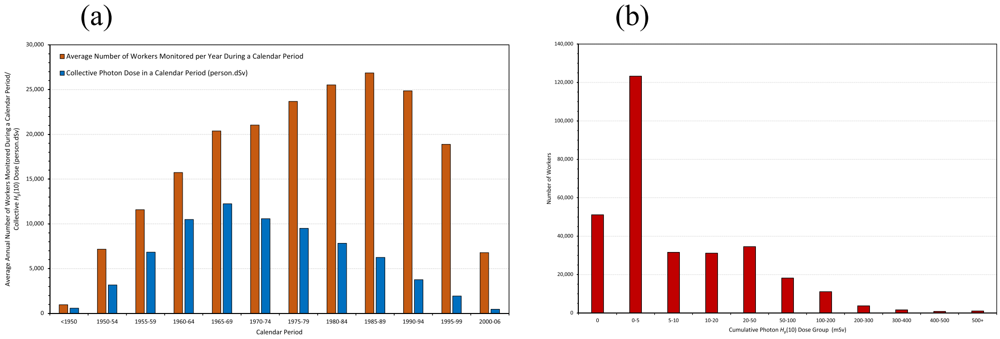


Figure 1. Distributions of (a) the annual number of workers monitored for exposure to external radiation averaged over a calendar period (generally, 5 years) and the collective photon $H_\mathrm{p}(10)$ dose (person.dSv = person.Sv × 10) received in a calendar period in INWORKS [14], and (b) the number of workers in each cumulative photon $H_\mathrm{p}(10)$ dose group in INWORKS [13].

internationally. The first international study involved workers from the USA, Canada and the UK [9], followed by the 15-country worker study [10, 11], and most recently INWORKS [12, 13]. INWORKS is a study of cancer mortality that includes ∼308 300 workers from the UK, France and five sites in the USA. This collaborative study is of particular importance because it includes workers from a number of early nuclear weapons facilities (e.g. Hanford, USA; Sellafield, UK; Marcoule, France), many of whom received annual doses in the initial years of operations that would not be acceptable today; a comparatively large proportion of these early workers accumulated occupational external doses over their working lifetimes in excess of 100 mGy.

In INWORKS, the mean cumulative photon (mainly external gamma) $H_\mathrm{p}(10)$ dose is ∼25 mSv and the collective photon $H_\mathrm{p}(10)$ dose is ∼7770 person.Sv; of this collective dose, ∼60% was received during 1960–1979 (a combination of comparatively large numbers of workers receiving, on average, annual photon $H_\mathrm{p}(10)$ doses of 2–4 mSv during this period) and ∼15% before 1960 [12, 14] (figure 1(a)); the distributions of annual doses and workers for each of the three countries have been provided by Thierry-Chef *et al* [15]. INWORKS currently includes ∼19 750 cancer deaths with follow-up to the end of 2005, 2001 and 2004 for the USA, UK and France, respectively. Importantly for power, almost 20 000 workers (6%) in INWORKS accumulated lifetime occupational photon doses exceeding 100 mSv, including more than 1000 workers with lifetime doses greater than 500 mSv [13, 14] (figure 1(b)). However, it is important to appreciate that these moderate-to-high cumulative doses consist of many small doses received at a low dose-rate over protracted periods, usually many years, and therefore these exposure circumstances are of direct relevance to radiological protection against low-level exposures.

To date, INWORKS is the most powerful study of nuclear workers from Western European and North American installations addressing the effect of protracted low-level radiation exposure on the risk of cancer mortality. However, at present, INWORKS includes workers from just five sites in the USA: Hanford, Savannah River, Oak Ridge National Laboratory (ORNL), Idaho National Laboratory and Portsmouth Naval Shipyard. Consequently, there is considerable scope for expanding the number of workers from North America included in international collaborative studies. In this respect, the Million Worker Study (MWS) currently underway in the USA [16, 17] has the potential for substantially increasing the number of US workers

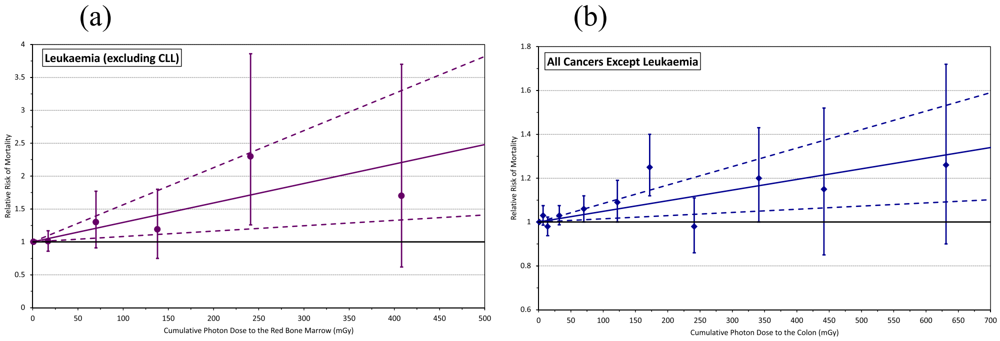


Figure 2. Dose-responses obtained from INWORKS [19, 20] in terms of the occupational photon dose accumulated over a working lifetime, for mortality from (a) leukaemia (excluding CLL) using a 2 years RBM-dose-lag, and (b) all cancers excluding leukaemia using a 10 years colon-dose-lag. Error bars and bands represent 95% confidence intervals.

included in studies of those occupationally exposed to radiation, as illustrated by the recent publication from the MWS of the results of a study of workers from Los Alamos National Laboratory [18].

The principal findings of INWORKS are linear dose-responses describing the increase of the relative risk of cancer mortality with increasing cumulative photon dose; no departures from linear dose-responses were detected. The slopes of the dose-responses (the excess relative risk (ERR) of mortality per unit organ/tissue-specific absorbed dose, ERR/Gy) are illustrated in figure 2. For leukaemia (excluding chronic lymphocytic leukaemia, CLL, now classified as a type of non-Hodgkin lymphoma), ERR/Gy = 2.96 (95% confidence interval; CI: 0.83, 5.64), based upon 531 deaths and red bone marrow (RBM) doses with a 2 years lag [19]. For all cancers excluding leukaemia, ERR/Gy = 0.48 (95% CI: 0.15, 0.85), based upon 19 064 deaths and colon doses with a 10 years lag [20], while for all solid cancers combined (all cancers excluding leukaemia, lymphoma and multiple myeloma), ERR/Gy = 0.47 (95% CI: 0.12, 0.85), based upon 17 957 deaths and colon doses with a 10 years lag [20]; a 5 years dose-lag reduces these ERR/Gy estimates by ~20% [20].

Somewhat surprising is the absence of published details of the effects of the modifications made for INWORKS to the individual databases used in the separate US, UK and French studies; for mortality from all cancers excluding leukaemia, the ERR/Sv estimates for these three national studies are 0.14 (95% CI: −0.17, 0.48) [21], 0.28 (95% CI: −0.03, 0.62) [22] and 0.34 (95% CI: −0.73, 1.58) (for all solid cancers combined [23]), respectively, which compares with the overall INWORKS ERR/Gy estimate of 0.48 (95% CI: 0.15, 0.85) [20]. The use of colon doses in INWORKS rather than $H_p(10)$ doses led to an increase of nearly 40% in the overall risk estimate from an ERR/Sv of 0.35 (95% CI: 0.10, 0.61) [20], but this ERR/Sv estimate is still larger than those from each of the national studies. There are other differences that are likely be relevant, such as the restriction in INWORKS to the inclusion of workers who had been employed for at least 1 year, a selection criterion that was not adopted by the original US and UK workforce studies [21, 22], suggesting that short-term employed workers may influence the ERR/Gy estimates for these countries. Different approaches to adjusting for various factors were also adopted in the INWORKS analyses, and this could also affect comparisons. For example, the main ERR/Gy estimate for all cancers excluding leukaemia in INWORKS, 0.48 (95% CI: 0.15, 0.85), is adjusted for neutron exposure monitoring status, but when no

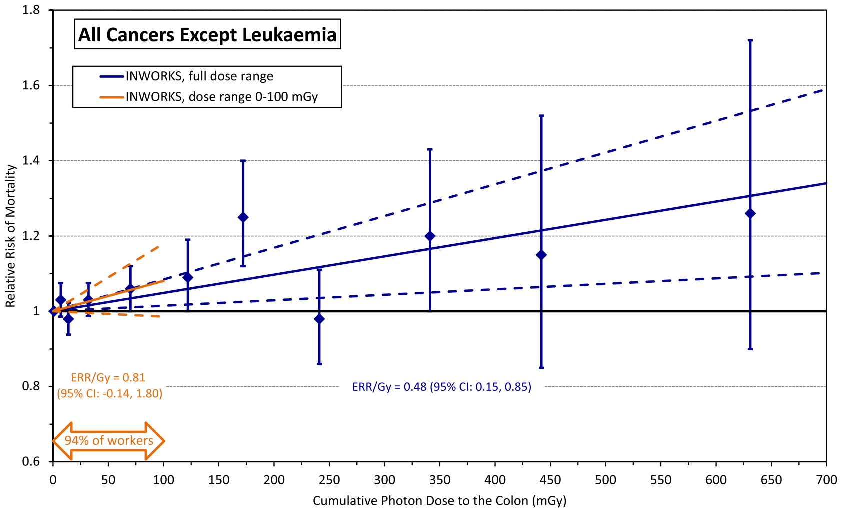


Figure 3. Dose-responses for mortality from all cancers except leukaemia from INWORKS with a 10 years colon-dose-lag, for all workers and the contribution made by the 94% of workers with cumulative photon doses to the colon <100 mGy [20]. Error bars and bands are 95% confidence intervals.

such adjustment is made, the ERR/Gy reduces by nearly 60% to 0.20 (95% CI: −0.07, 0.50). The treatment in INWORKS publications of the impacts of the various choices made in the INWORKS analyses in relation to those made in the separate national studies is disappointingly opaque.

Of some interest is the contribution to the power of INWORKS of those workers who accumulated moderate-to-high photon doses: although workers with cumulative colon doses <100 mGy represent 94% of the INWORKS study population, who generate for mortality from all cancers except leukaemia an ERR/Gy = 0.81 (95% CI: −0.14, 1.80), the 6% of workers with lifetime doses >100 mGy are influential in their downwards leverage of the dose-response, producing an overall ERR/Gy estimate for the full range of cumulative photon doses to the colon of 0.48 (95% CI: 0.15, 0.85) [20], i.e. a reduction in the slope of the dose-response of around 40% (see figure 3). It would be expected that much of the collective dose for those workers accumulating doses >100 mGy would have been received during 1960–1979 (see figure 1(a)), but it is not possible from published data to establish how much influence on the slope of the dose-response might be exerted by doses received before 1960, and these early doses could be a significant component of the cumulative doses of those workers receiving the highest lifetime doses who provide the greatest leverage on the dose-response. This could be an important issue (see discussion below on the accuracy of recorded doses).

Of importance is how the ERR/Gy estimates from INWORKS compare with the equivalent estimates obtained from the LSS. Recently, Leuraud *et al* [24] have made a detailed comparison of dose-responses for leukaemia (excluding CLL) and all solid cancers combined (and all solid cancers excluding lung cancer) that may be obtained from INWORKS and the LSS, selecting the subgroups for comparison as being as similar as possible in terms of factors such as age-at-exposure and sex, and using LSS mortality (rather than incidence) data. Doses were lagged by 5 years for all analyses. The results of fits using linear models are shown in table 1; note that significant upward curvature was reported for the leukaemia dose-response for the LSS.

Table 1. Estimates of the slopes of the dose-responses, ERR/Gy and 95% confidence intervals, obtained from INWORKS and the LSS using linear models for mortality from leukaemia (excluding CLL), all solid cancers combined, and all solid cancers excluding lung cancer. RBM doses were used for leukaemia (excluding CLL) and colon doses were used for all solid cancers combined and all solid cancers excluding lung cancer. All doses were lagged by 5 years [24].

	ERR/Gy (95% CI)		
Study cohort	Leukaemia (excluding CLL[a])	All solid cancers combined	All solid cancers excluding lung cancer
INWORKS	3.15 (0.73, 6.21)	0.29 (0.03, 0.58)	0.25 (−0.07, 0.58)
LSS	2.75 (1.53, 4.49)[b]	0.28 (0.16, 0.40)	0.25 (0.12, 0.38)

[a] The small number of deaths from CLL in the LSS cohort could not be excluded.[b] Obtained from a linear fit. A linear-quadratic model provided a significantly better fit, with a linear ERR/Gy coefficient of 0.10 (95% CI: −1.25, 1.76) and a quadratic ERR/Gy^2 coefficient of 1.61 (95% CI: 0.66, 2.88).

The current scheme of radiological protection applies a dose and dose-rate effectiveness factor (DDREF) of 2 to halve the slope of dose-responses for solid cancers obtained from the LSS [1]. The INWORKS result does not lend obvious support to the application of a DDREF of 2 to the LSS dose-response for solid cancers to obtain a ERR/Gy estimate appropriate for low-level exposures.

2.2. The UK National Registry for Radiation Workers (NRRW)

The data from the UK contributing to INWORKS were from the 3rd analysis of the NRRW, which included workers who started being monitored for exposure to external radiation during 1940–1999 and who were followed-up until the end of 2001 [22]. NRRW-3 workers represent around half of the workers, the collective dose and the workers with cumulative doses >100 mGy included in INWORKS [13]; almost 40% of the cancer deaths included in INWORKS were from the NRRW-3 database [12]. Figure 4 illustrates the importance in NRRW-3 of those workers employed in the early years of operations, with ∼23 600 of workers (14%) who started work before 1960 accounting for ∼40% of the overall collective dose and including ∼40% of the workers who accumulated lifetime occupational external doses >100 mGy [25].

NRRW-3 has now been updated [26] to include deaths among those whose monitoring for exposure to external radiation commenced during 1940–2001 and with follow-up extended a further 10 years to the end of 2011, which increased the number of deaths from all cancers excluding leukaemia contributing to the dose-response analysis by 52% from 7455 to 11 329. Nearly 35 000 workers (∼20% of all workers in NRRW-3) had died before 2012. Figure 5(a) shows the distributions by calendar period of starting radiation work and cumulative external radiation dose of all workers and of those workers who had died before 2012, and figure 5(b) shows these deaths expressed as a percentage of all workers in a particular lifetime dose/calendar period cell. Of interest is that 57% of all workers (and 37% of workers who started work before 1960) with external doses >100 mGy over a working lifetime were still alive at the end of 2011, so there is substantial information still to come from the NRRW, and by extension, INWORKS.

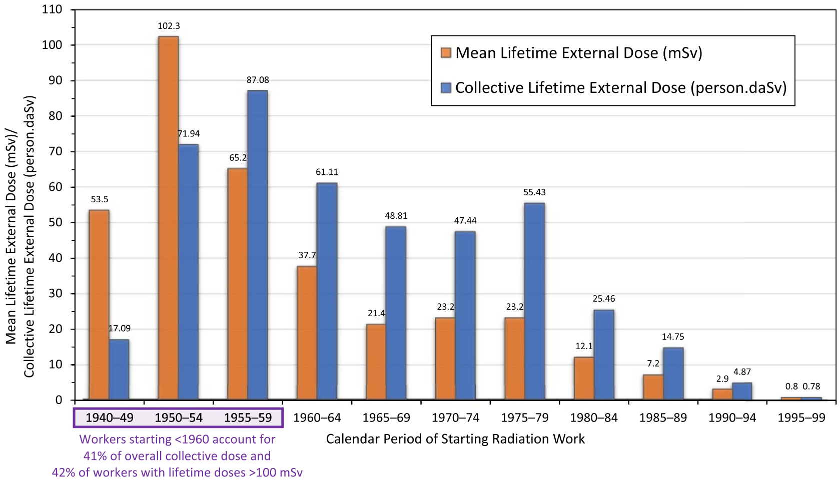
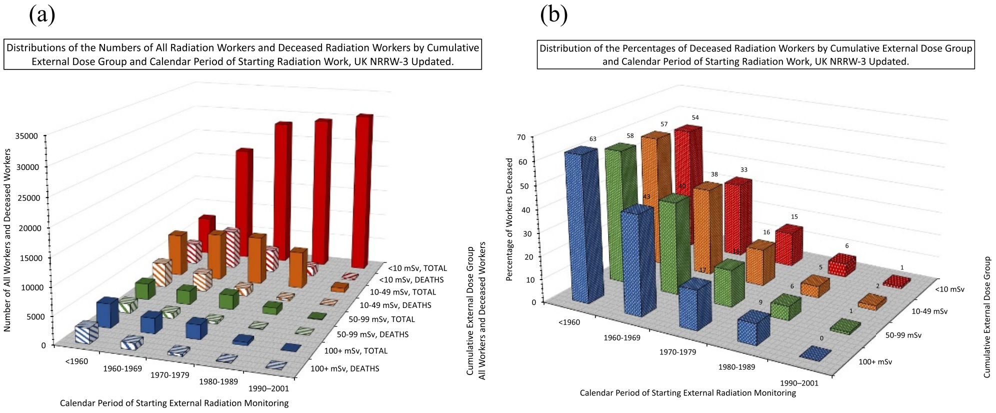


Figure 4. Distributions of mean lifetime occupational external dose (mSv) and collective lifetime occupational external dose (person.daSv = person.Sv/10) by calendar period of first monitoring for exposure to radiation, from the NRRW-3 database for follow-up to the end of 2001 [25].


(a)

Distributions of the Numbers of All Radiation Workers and Deceased Radiation Workers by Cumulative External Dose Group and Calendar Period of Starting Radiation Work, UK NRRW-3 Updated.

(b)

Distribution of the Percentages of Deceased Radiation Workers by Cumulative External Dose Group and Calendar Period of Starting Radiation Work, UK NRRW-3 Updated.

Figure 5. Distributions by calendar period of starting radiation work during 1940–2001 and by cumulative external dose group of (a) the numbers of all workers and of deceased workers, and (b) the percentages of deceased workers, from the updated NRRW-3 database with follow-up until the end of 2011 [26].

3. Studies of workers from the Mayak nuclear installation in Russia

The Mayak nuclear installation in the Southern Urals of Russia commenced operations in 1948 and was the first weapons plutonium production facility in the former USSR. Exposures to external radiation and plutonium were particularly high before 1960, and a cursory comparison of figures 6 and 1(b) is sufficient to reveal that photon doses accumulated by Mayak workers tended to be considerably larger than those by workers included in INWORKS, with almost one-fifth of the Mayak workforce receiving cumulative photon doses in excess of 1 Sv.

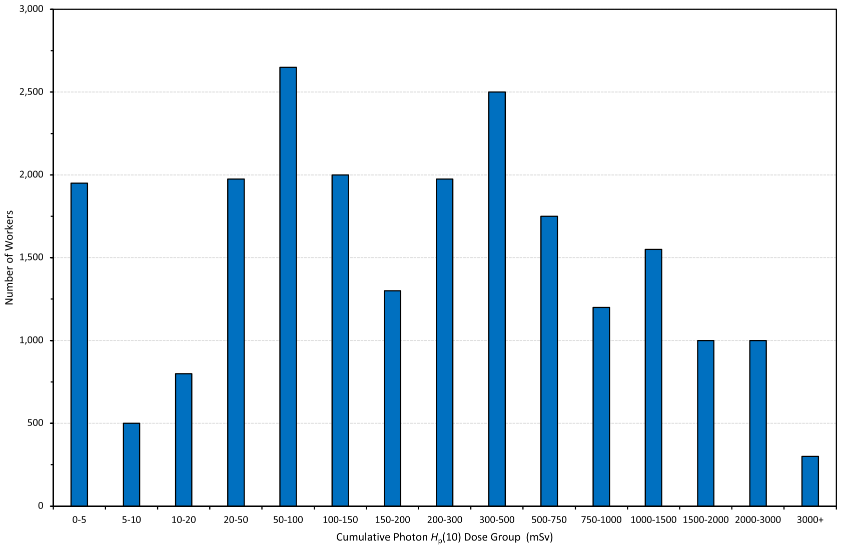


Figure 6. The number of Mayak workers in each cumulative photon $H_{\mathrm{p}}(10)$ dose group [27].

Results have been published from recent studies of the incidence of leukaemia (excluding CLL) among ∼22 400 Mayak workers [28], and mortality from solid cancers excluding lung, liver and bone cancers among ∼25 800 workers [29], in relation to photon (largely external gamma) dose—the risk of cancers of the lung, liver and bone is expected to be raised after intakes of plutonium because plutonium deposits in these organs, so these cancers were excluded from the analysis of solid cancer mortality to reduce the influence of plutonium exposures on the findings for external radiation exposure. Mean cumulative photon doses to the RBM and colon were ∼390 mGy and ∼350 mGy, respectively [28, 29]; ∼45% of the person-years of follow-up had cumulative photon doses to the colon exceeding 100 mGy and ∼10% exceeding 1 Gy [29]—the power of the Mayak studies derives from the magnitude of the doses received and their range, in combination with the number of workers accumulating moderate and high doses. The wide range of cumulative photon doses received by Mayak workers will be appreciated from figure 6, but it should be emphasised that even lifetime doses of several gray will have been accumulated as many small doses received at a low dose-rate over many years and therefore moderate and high cumulative doses received by Mayak workers are of relevance to the assessment of risks from low-level exposures.

No significant departures from linear dose-responses were found in these two studies of the Mayak workforce [28, 29] and the dose-responses are illustrated in figure 7. The ERR/Gy estimate for the incidence of leukaemia excluding CLL of 3.57 (95% CI: 1.16, 9.11) is based upon 56 incident cases and RBM doses lagged 2 years [28], while the ERR/Gy for mortality from all solid cancers excluding lung, liver and bone cancers of 0.12 (95% CI: 0.03, 0.21) is based upon 1825 deaths and colon doses lagged 5 years [29]. When the analysis of mortality from all solid cancers excluding lung, liver and bone cancers was restricted to Mayak workers who were unlikely to have experienced substantial intakes of plutonium, the ERR/Gy was 0.20 (95% CI: 0.0, 0.46) [30].

Shown in table 2 are the results of a comparison conducted by Preston *et al* [31] of ERR/Gy estimates derived from the Mayak workers and members of the LSS cohort exposed as adults;

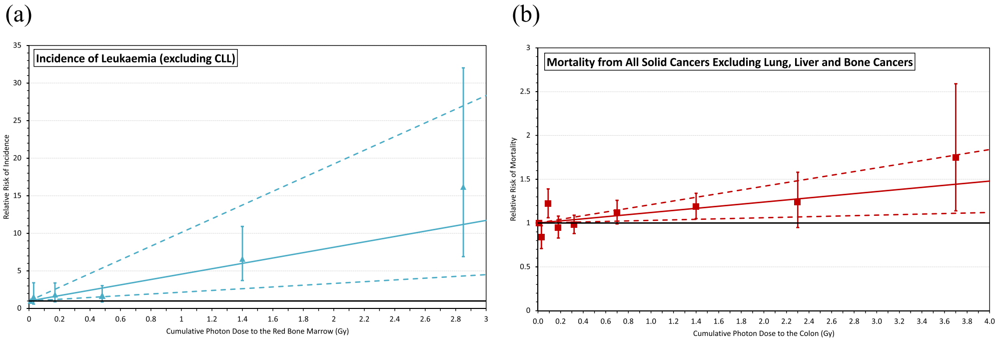


Figure 7. Linear dose-responses, ERR/Gy, derived from studies of the Mayak workforce, in terms of lifetime occupational photon doses, for (a) incidence of leukaemia (excluding CLL) with doses to the RBM lagged by 2 years [28], and (b) mortality from all solid cancers excluding lung, liver and bone cancers with doses to the colon lagged by 5 years [29]. Error bars and bands are 95% confidence intervals.

Table 2. Estimates of the slopes of the dose-responses, ERR/Gy and associated 95% confidence intervals, obtained from the Mayak workforce and the LSS cohort, for leukaemia (excluding CLL), for all solid cancers excluding lung, liver and bone cancers, and for lung cancer [31]. RBM doses are used for leukaemia and colon doses for solid cancers. Leukaemia data from the LSS were for incidence, otherwise mortality data were used.

	ERR/Gy (95% CI)		
Study cohort	Leukaemia (excluding CLL)	All solid cancers excluding lung, liver and bone cancers	Lung cancer
Mayak	0.11 (−0.2, 0.5)	0.16 (0.07, 0.26)	0.24 (0.08, 0.44)
LSS (adults, weighted averaging over sex)	0.86 (−1.4, 5.2)	0.46 (0.18, 0.85)	0.42 (0.11, 1.1)

for Mayak, mortality data only were used, while for the LSS, incidence data were used for the analysis of leukaemia and mortality data for solid cancers. The ERR/Gy estimates presented in table 2 for Mayak workers are notably lower than those for the LSS cohort. However, care in interpretation is required, because the ERR/Gy for leukaemia (excluding CLL) for the Mayak workforce using incidence data has been reported as 3.57 (95% CI: 1.16, 9.11) (see above [28]), i.e. markedly larger than that shown in table 2 for Mayak, using mortality data. Further, Leuraud *et al* [24] obtained a leukaemia ERR/Gy for the LSS cohort using mortality data of 2.75 (95% CI: 1.53, 4.49) (see table 1, but note footnote b to table 1), which is notably larger than the estimate for leukaemia incidence in the LSS shown in table 2.

4. Potential problems that need to be addressed

4.1. Implications of the INWORKS and Mayak findings for the value of the DDREF

As noted above, in the current international system of radiological protection, a DDREF of 2 is applied to solid cancer risk estimates derived from moderate-to-high doses received at a high dose-rate by survivors in the LSS cohort to generate risk estimates deemed appropriate for application to low-level exposures [1]. What evidence for such a halving of the slope of the dose-response is available from worker studies? It is rather contradictory, with INWORKS offering little support whereas the Mayak workforce provides rather stronger support. Figure 8 compares the linear ERR/Gy dose-responses for mortality from all solid cancers excluding lung cancer as derived from the LSS and INWORKS [24], and for mortality from all solid cancers excluding lung, liver and bone cancers as obtained from Mayak [31]; figure 8 summarises the results presented in tables 1 and 2.

It is unlikely that the slope of the Mayak dose-response shown in figure 8 would change materially if just lung cancer was able to be excluded from all solid cancers because liver and bone cancers make a relatively minor contribution to solid cancers [32]. Nonetheless, the impact of differences in data and modelling must be borne in mind: Leuraud *et al* [24] derived an ERR/Gy from the LSS for mortality from all solid cancers excluding lung cancer of 0.25 (95% CI: 0.12, 0.38) (table 1 and figure 8), whereas Preston *et al* [31] obtained a rather higher ERR/Gy from the LSS for mortality from all solid cancers excluding lung, liver and bone cancers of 0.46 (95% CI: 0.18, 0.85) (table 2). In a similar vein, although the ERR/Gy for leukaemia (excluding CLL) mortality obtained from INWORKS, 3.15 (95% CI: 0.73, 6.21), might appear to be compatible with that for leukaemia (excluding CLL) incidence derived from Mayak, 3.57 (95% CI: 1.16, 9.11), the INWORKS estimate is driven by the ERR/Gy for mortality from chronic myeloid leukaemia, 10.45 (95% CI: 3.34, 21.41), whereas the Mayak estimate is driven by the ERR/Gy for acute myeloid leukaemia incidence, 13.23 (95% CI: 2.53, 56.39).

The difference between the ERR/Gy estimates from INWORKS and the Mayak workforce needs to be properly understood—is this just a chance difference, given that the statistical uncertainties currently associated with the INWORKS estimate are comparatively large, or are systematic effects present, and if so, to what degree do they influence each dose-response? The answers to these questions are of some importance, since reliable conclusions concerning the appropriate DDREF to use for the purposes of radiological protection depend on a proper understanding of the apparent conflict in the inferences to be drawn from the risk estimates derived from these two nuclear worker studies [33, 34]. There are other issues that need to be considered when assessing the DDREF, such as the appropriate relative biological effectiveness (RBE) applicable to the neutrons to which the atomic bomb survivors were exposed, and how the RBE varies with the spectra of photon energies experienced during the atomic bomb explosions and occupationally [24].

One important issue that requires further scrutiny in the deliberations on DDREF and related matters is the impact on radiation dose-responses of baseline cancer rates (i.e. the cancer rates in the absence of the specific exposure(s) to radiation under consideration). The ERR expresses the proportional increase in the cancer rate in comparison with the baseline rate, whereas the excess absolute rate (EAR) is the additional rate above the baseline rate. The ERR and the EAR are alternative ways of quantifying an increased risk, but the difference in these measures becomes important when comparing radiation effects between populations with different baseline rates. Which comparison is the more appropriate depends on how radiation interacts with other risk factors: if there is a multiplicative interaction between radiation and the other major risks then ERR/Gy will be the same for the two populations, but if there is no interaction then the risks add and EAR/Gy will be the same for the two populations. The absence of an interaction between radiation and other risk factors implies that the radiation-related excess number of cases/deaths is independent of the baseline rate, but otherwise dependent (to some degree). Whether the ERR/Gy or the EAR/Gy (or some combination of the two if there is a submultiplicative interaction) is considered to be the appropriate comparison when baseline

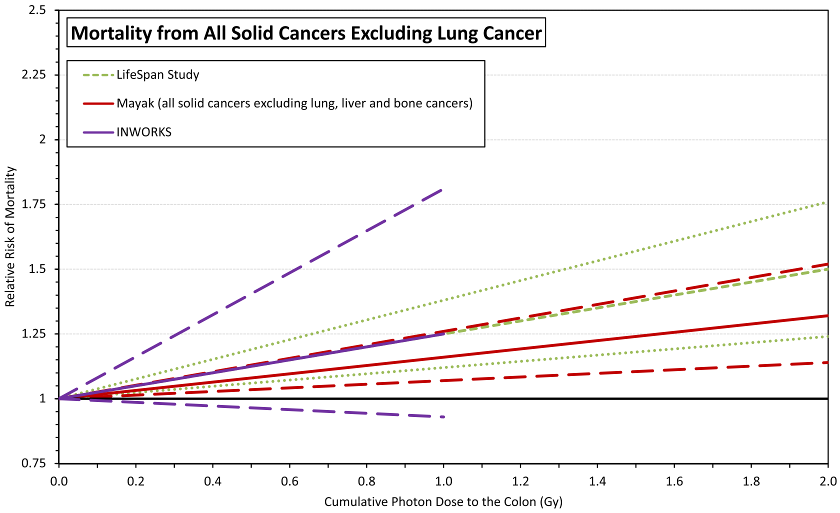


Figure 8. Linear dose-responses, ERR/Gy, for mortality from all solid cancers excluding lung cancer obtained using cumulative photon doses to the colon, for the LSS cohort [24], the Mayak workforce (for all solid cancers excluding lung, liver and bone cancers [31]) and INWORKS [24], with doses lagged by 5 years. Error bands are 95% confidence intervals.

rates differ will depend on the evidence for an interaction between radiation and other risk factors, although in most cases such evidence will be limited [35]. To illustrate the potential importance of this issue, consider the EAR/Gy for all solid cancers combined derived by Leuraud *et al* [24] from the LSS and INWORKS: respectively, 7.64 (95% CI: 2.56, 13.65) and 1.32 (95% CI: <0, 8.20) excess deaths per 10^4 person-year.Gy for an attained age <80 years. This difference contrasts with that for the ERR/Gy estimates of 0.28 (95% CI: 0.16, 0.40) and 0.29 (95% CI: 0.03, 0.58), respectively, although interpretation is not straightforward because of differences in the attained age distributions of the two cohorts. This example serves to sound a cautionary note about comparisons between risk estimates derived from populations with different baseline cancer rates, as is the case with the LSS, INWORKS and Mayak—inferences about DDREF should not be restricted to comparisons between ERR/Gy dose-responses alone, but relevant information is currently limited.

4.2. The accuracy of doses used in nuclear worker studies

Various aspects of nuclear worker studies need to be examined carefully to ensure that risk estimates are as accurate as available data permit. One important issue is the level of confidence in the suitability for use in epidemiological studies of doses recorded for the purposes of regulatory requirements and radiological protection, which has been the subject of a number of examinations [14, 36–38]. In INWORKS, recorded photon doses have been converted to $H_\mathrm{p}(10)$ doses and organ/tissue-specific absorbed doses [15], the latter being used in the epidemiological analyses [19, 20]; but it is unclear whether the adjustments to recorded doses are sufficient for some workers in the cohorts contributing to INWORKS, especially for doses received before 1960 by workers who accumulated comparatively high doses during this period [36, 39].

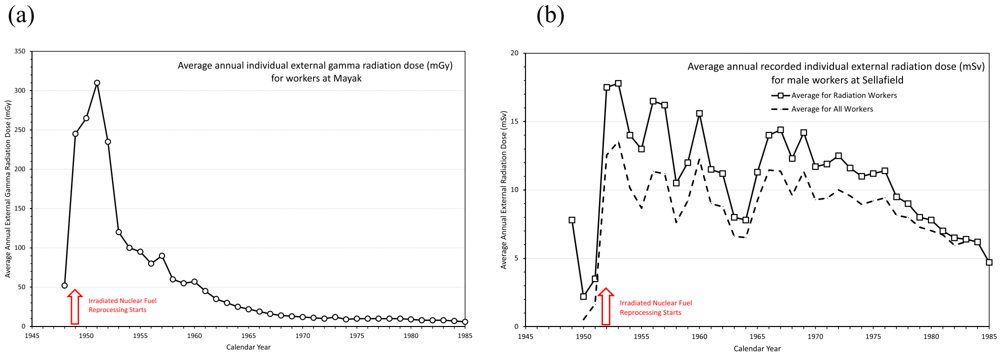


Figure 9. The distributions of average annual individual external doses received by workers during the earlier years of operations at the irradiated nuclear fuel reprocessing installations at (a) Mayak (in the former USSR) [27] and (b) Sellafield (in the UK) [42, 43], showing dose distributions in relation to when reprocessing operations began.

In this respect, the temporal distributions of annual doses from external sources of radiation in the early years of operations at certain older installations are relevant. At the Mayak and Sellafield nuclear complexes, average annual individual external doses were highest in the first few years after irradiated nuclear fuel reprocessing commenced in late-1948 and early-1952, respectively, and then steadily reduced with time [40, 41], as illustrated in figure 9 [27, 42]. The demands of familiarisation with operations requiring the large-scale handling of irradiated nuclear fuel under political pressure to rapidly extract plutonium for the production of the first nuclear weapons in the two countries upon average doses received after reprocessing commenced is clear, and is especially apparent in the high doses received at Mayak (figure 9). Sellafield workers are an important component of NRRW-3 (and therefore INWORKS): workers based at Sellafield contributed to the NRRW-3 database nearly 40% of the collective dose and 44% of the workers with lifetime doses >100 mSv [25].

These temporal patterns of average annual external doses at Mayak and Sellafield contrast with those for Hanford and Savannah River [44, 45], two of the US facilities included in INWORKS. It will be seen from figure 10(a) that in the early years of operations at Hanford (where irradiated nuclear fuel reprocessing began in late-1944) average annual recorded external doses received by monitored workers were only ∼1−2 mSv (the annual numbers of monitored workers during 1945–1950 were 4000–7000 [44]). This low level of annual doses is, perhaps, surprising when contrasted with the average annual external doses of around 15 mSv for workers monitored for exposure to external radiation (and around 11 mSv for all workers, both monitored and unmonitored) recorded at Sellafield in the mid-1950s, soon after reprocessing operations began (the annual numbers of monitored workers during 1952–1958 were 2000–4000; in this early period of operations at Sellafield the monitored workers were predominantly men [43]). It would appear that the differences in average annual external doses between Hanford and Sellafield cannot be explained just by the numbers of workers who were monitored for radiation exposure during these early periods. Similarly low average annual external doses were recorded at Savannah River following the commencement of reprocessing operations in late-1954 (figure 10(b)).

However, also shown in figure 10 are the average annual external doses reconstructed for the purposes of the US worker compensation programme [46], and there is a considerable gap between recorded and reconstructed doses at Hanford and Savannah River, but importantly,

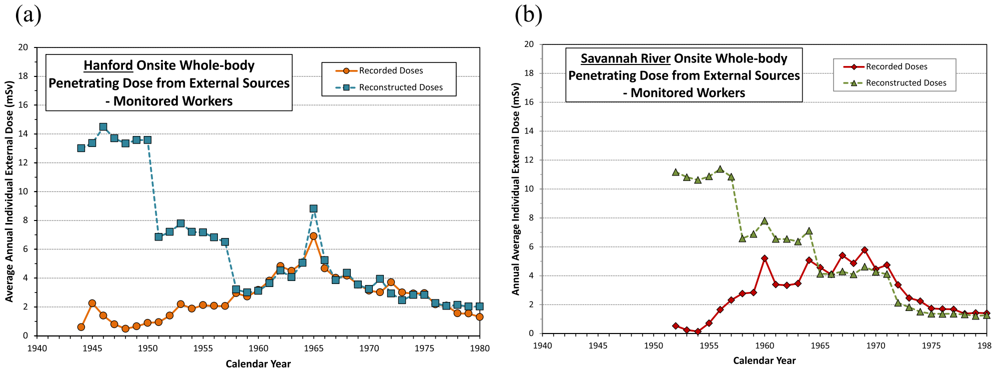


Figure 10. Comparison of the distributions by calendar year of average annual individual whole-body doses received occupationally from penetrating (primarily photon) radiation from external sources, as recorded at the US nuclear installations at (a) Hanford [44] and (b) Savannah River [45], and as reconstructed [46] for the purposes of compensating people who develop cancers that could be attributable to prior occupational exposure to radiation at these installations. Reproduced from [47]. CC BY 4.0.

only for the early years of operations at the sites. It must be expected that (possibly substantial) generosity will be built into a worker compensation programme, so the reconstructed doses would be anticipated to overestimate actual doses, but the shapes of the reconstructed external dose distributions at Hanford and Savannah River are much closer to those at Mayak and Sellafield in the early years of operations (see figure 9).

These dose reconstructions at Hanford and Savannah River beg the question as to the extent of the adjustments to early recorded external doses that may be required for epidemiological purposes when workers from older nuclear installations are included in studies. Are those dose adjustments that have already been made for INWORKS sufficient? It may be, however, that there are sound reasons for comparatively low levels of external exposure soon after irradiated nuclear fuel reprocessing began at these two US facilities, such as the design of plant in terms of radiological protection of personnel. Gilbert *et al* [48–50] scrutinised external dose uncertainties at Hanford and found indications that adjustments to recorded external doses were required, particularly in the earlier years of operations, but little evidence that substantial underestimates of external doses were widespread at Hanford.

Even so, questions have been raised about the adequacy of dose records for use in epidemiological studies at other sites, including the matter of 'missing' photon doses for early workers at ORNL [51], another US facility included in INWORKS, although the impact of this source of dose uncertainty is unclear [52]. This subject does need to be investigated in some depth, particularly those features of the dose reconstructions at Hanford and Savannah River, conducted for the purposes of worker compensation, that led to the upwards revisions in recorded doses in the early years of operations at the two sites, and whether, to some extent, these factors need to be additionally accounted for in external doses used in epidemiological studies that include US installations, such as INWORKS and the MWS. Those reviewing INWORKS dosimetry have stressed the importance of pursuing dose uncertainties and their impact upon risk estimates. Till *et al* [36] observed:

> 'The dosimetry is also quite difficult to verify from the open literature because it involves several layers of independent epidemiological studies that reach back almost four decades and because of the inaccessibility of the original dosimetry.

> The sheer technical challenge of the dosimetry and the positive findings of the epidemiology stress the importance of making the dosimetry as state-of-the-art, complete, and thorough as possible since minor variations in the cumulative dose could impact the outcome of the study. Work remains to fully verify the dosimetry methodology and to be certain that adjustments to historical doses have been properly taken into account and that uncertainties and bias have been thoroughly addressed'.

Daniels *et al* [14] remarked:

> 'Nevertheless, dose estimation errors were unavoidable, especially during the early years when contributions to individual dose from [below detection limit] doses, neutrons, and [work-related x-ray examinations] could be substantial. The potential effects on the dose-response from these sources remain unclear'.

It would be most surprising if similar dosimetry concerns were not apparent at other older nuclear installations. Indeed, the subject of Sellafield dosimetry uncertainties was addressed 25 years ago by a paper at the IRPA9 Congress [41]. In the UK, the issue of 'missing' photon doses in the early years of operations at UK Atomic Energy Authority (UKAEA) establishments was examined in some detail, finding that substantial adjustments to external dose records at certain installations were required before 1961 [53]. These adjustments were incorporated into the NRRW dosimetry database for the purposes of the NRRW-2 analysis [54], and carried over into the NRRW-3 analysis [22]. Sensitivity analyses conducted for NRRW-3 indicated that dose adjustments reduced the ERR/Sv estimates for mortality from all cancers excluding leukaemia by around 10%, although the adjustments carried out for some establishments, e.g. Sellafield, were less comprehensive than those made to historical doses at the UKAEA sites [25].

What of the accuracy of the Mayak external dose records in the early years of operations? Work examining external dosimetry at Mayak for the purposes of construction of the 'Doses-2005' database has been reported [40], but few details have been published of any further investigations for subsequent external dosimetry databases [36], including the recently published analysis of the impact on risk estimates of dosimetry uncertainties at Mayak [55], which largely concentrated on uncertainties in lung doses from plutonium. Again, it would be of value in reaching reliable inferences on risk estimates if more information on external photon doses and their uncertainties was available for Mayak, and for other older nuclear installations.

It could be argued that any revisions to early photon doses would be unlikely to influence to any significant extent the slopes of dose-responses because most of the collective dose was received in later years when dose uncertainties were less—for example, $\sim$60% of the recorded collective photon dose in INWORKS was received during 1960–1979 [14] (figure 1(a)). However, as figure 3 illustrates, the 6% of workers in INWORKS who have accumulated photon doses >100 mGy have a considerable leverage effect on the dose-response, and systematic underestimation of some historical doses for those receiving the highest lifetime doses could well affect the slope of the dose-response—although only 15% of the collective photon dose for INWORKS was received before 1960, these early doses could have a disproportionately large effect on the slopes of the dose-responses because it was mainly received by workers who accumulated the highest lifetime doses. Unfortunately, the proportion of workers in INWORKS with lifetime photon doses exceeding 100 mGy who started radiation work before 1960 has not been published, but 42% of those workers in NRRW-3 who accumulated external doses >100 mSv started to be monitored for external exposure before 1960. Given the implications for, *inter alia*, the DDREF (if any) and its use in radiological protection, it would be well worthwhile investigating this issue further.

In this respect, one initial approach to assessing the potential influence of early photon dose uncertainties upon the slopes of the dose-responses would be to perform analyses with data restricted to workers who started being monitored for exposure to external radiation either before or after 1960, given that uncertainties in photon dose records are likely to be greater in the period before 1960 [14, 36]. If photon dose uncertainties in the earlier years have a significant influence upon dose-responses, then this could be apparent from such an investigation; but of course, the problem with this approach is that the available data are divided in two, leading to a loss of statistical power and greater statistical uncertainties in the slopes of the dose-responses. Nonetheless, although addressing mortality from diseases of the circulatory system rather than from cancer, a similar division of workers by earlier and later periods of first employment at Mayak and Sellafield produced some intriguing differences in the dose-responses for the two periods [27]. Such an initial 'broad-brush' approach to investigating the impact of early doses upon dose-responses could be a useful first step.

It will have been noted that risk estimates in terms of occupational exposure from external sources have, to date, only considered photon doses in any detail; neutron doses have not been assessed quantitatively. Further, the impact upon external exposure risk estimates of doses from intakes of radionuclides has not been addressed in any comprehensive manner, although radionuclide monitoring status has been used to adjust photon risk estimates in some analyses, such as at Mayak. Uncertainties in neutron doses were considerable in the early years of the nuclear industry and persisted into the 1970s, if not later; some neutron exposures will not have been monitored and some potentially large neutron doses will not have been recorded [15, 36, 39–41]. As noted earlier, one puzzling finding from INWORKS is that the primary ERR/Gy estimate for photon doses and all cancers except leukaemia, which was adjusted for neutron monitoring status, 0.48 (95% CI: 0.15, 0.85), reduced by ∼60% to 0.20 (95% CI: −0.07, 0.51) when no such adjustment was made. This may be a chance effect, but it may also be related to inadequacies in neutron monitoring information and potential confounding effects [20, 39]. A further perplexing result from INWORKS is that when the analysis was confined to the 83% of workers who were not monitored for intakes of radionuclides, the ERR/Gy for all cancers except leukaemia increased by 50% to 0.72 (95% CI: 0.21 and 1.28); similar increases in external exposure risk estimates for workers not monitored for potential exposure to internal emitters when compared with those for workers who were monitored for internal exposures has been noted in other studies [56].

These findings indicate that it will be necessary to properly understand the impact of the inclusion of neutron and internal doses in the analyses before confident inferences may be reached on the accuracy of risk estimates for photon doses, and other sources of radiation exposure also exist that have yet to be taken into account, such as exposures to x-rays at medical examinations required for employment in the nuclear industry [14]. A point to consider is that the size of doses from sources so far unaccounted for in studies may be positively correlated with the size of recorded photon doses (and the size of photon dose inaccuracies), so that the impact of photon dose uncertainties on dose-responses may be amplified by these other dose uncertainties. The potential consequences of these additional doses for risk estimates must be assessed to be able to draw reliable conclusions, but this is likely to involve substantial work if done properly.

5. Conclusions

Large-scale radiation worker studies, such as INWORKS and the MWS, must continue because they have the potential to provide important information on radiation risks pertinent to everyday radiological protection against protracted low-level exposures.

There is a need to:

- Expand the nuclear workforces included, particularly workers from those facilities in the USA that are not currently included in international collaborations, but also, at an appropriate time, from other countries with suitable databases, such as Canada.
- Continue follow-up of workers, especially those employed in the early years of nuclear operations who received substantial cumulative doses, to achieve greater power by including more deaths and incident cases of cancer in analyses.
- Improve dosimetry, not only those components of occupational doses that are not presently included (neutrons and internal emitters), but also to ensure that photon doses are as accurate as possible, through dose reconstruction in the early years of nuclear operations, if necessary.
- In the absence of detailed dose reconstructions, examine approaches that might indicate the potential effect of dose uncertainties upon risk estimates, such as excluding from analyses those workers starting employment before 1960 who are likely to be associated with relatively greater dose uncertainties.
- In addition to examining radiation-related excess risks in terms of the usual use of ERR/Gy, explore the use of EAR/Gy when baseline cancer rates differ between the populations under study, and the implications upon inferences about DDREF and related issues (such as how radiation interacts with other major risk factors).

These considerations on continued follow-up, accurate dosimetry and other matters also apply to the Mayak workforce, which is a valuable source of information on protracted exposures; they may also be relevant to studies involving workers from other, especially older, nuclear installations.

Ultimately, it will be powerful epidemiological studies examining exposure conditions of direct relevance to radiological protection against low-level radiation exposure that will provide the most reliable evidence on the appropriateness of the assumptions currently required to generalise from the experience of the Japanese atomic-bomb survivors acutely exposed to mainly gamma radiation. This will mean addressing some difficult issues, such as the accuracy of early occupational doses and their impact on risk estimates, but unless we look, we will not know.

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