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EDITORIAL

Cancer risk among nuclear workers

The framework of radiological protection recommended by the International Commission on Radiological Protection (ICRP) is based on a dose–response model for radiation-induced cancer that is linear at low doses and has no threshold—the linear no-threshold (LNT) model. The slope of this linear dose–response provides the risk coefficient (cancer risk per unit radiation dose received) appropriate for low level exposures. The low dose risk coefficient is obtained from groups exposed to moderate-to-high doses, principally the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki, with the high dose/high dose-rate risk coefficient being halved (a dose and dose-rate effectiveness factor, DDREF, of two) to account for the reduced carcinogenic efficiency of low dose/low dose-rate exposures that are the primary concern of radiological protection. The nominal lifetime excess absolute risks (EAR) per sievert for fatal cancer currently adopted by the ICRP for the purposes of radiological protection are 5% per Sv for a general population and 4% per Sv for a population of working age (i.e. excluding children) exposed to low doses/low dose-rates.

Clearly, it is of some importance to check the assumed risk coefficients that underlie radiological protection through direct study of those exposed to low doses/low dose-rates of ionising radiation. This is, however, easier said than done. The excess radiation-related risk of cancer predicted to be produced by low doses is small and easily hidden among random and systematic variations in the background risk of cancer, so that large numbers of exposed people must be included in a study to have a realistic chance of being able to detect the excess risk. Nuclear industry workers are particularly suitable subjects for epidemiological study because of the generally good personnel and dosimetry records that are available, and a number of studies of such workers have been carried out. Even so, it is only studies that combine large numbers of workers from many facilities that will have sufficient power to properly investigate the predicted small increase in risk, one such study being the second analysis of the UK National Registry for Radiation Workers (NRRW), the results of which were published in this journal (Muirhead *et al* 1999 *J. Radiol. Prot.* **19** 3–26).

The largest nuclear worker study to date, co-ordinated by the International Agency for Research on Cancer (IARC), has just been published in the *British Medical Journal* (Cardis *et al* 2005 *BMJ* **331** 77–80). It includes radiation workers from 154 facilities of the nuclear industries of 15 countries, all but one of these (Lithuania) being members of the OECD. In all, nearly 600 000 workers were available for study; but after excluding workers employed for less than one year ($\sim$110 000), those not monitored for exposure to external sources of radiation ($\sim$40 000), and those with potential for substantial exposure ($\geqslant$10% of the effective dose) to internal emitters or neutrons ($\sim$40 000 and $\sim$20 000, respectively), just over 400 000 radiation workers were included in the analyses. Approximately 24 000 (6%) of these workers had died during the study period, 6519 of cancers other than leukaemia and 196 of leukaemia other than chronic lymphocytic leukaemia (CLL, which is considered to be only weakly linked to radiation exposure, if at all). Over five million person-years of follow-up were included in the study and the collective external radiation dose was 7892 person Sv, the mean cumulative individual dose being 19.4 mSv (with 90% of workers having a dose <50 mSv). Men accounted for 90% of the workers and 98% of the collective dose, so the study can provide little information on

the risks to women. Considerable effort has been expended in deriving appropriate doses from dosimeter records, and individual red bone marrow and colon doses have been calculated for the leukaemia and other cancers analyses, respectively.

Risk estimates are given as excess relative risk (ERR) coefficients—the ERR per unit cumulative external dose received—taking due account of latent periods by appropriately lagging doses and adjusting for risk modifying factors such as age, calendar period, facility and (where available) socioeconomic status. The ERR is the proportional increase in the risk of cancer mortality in comparison with the background absolute risk, and the ERR coefficient describes the degree of variation of the ERR with dose—it is the slope of the linear dose–response relationship. It is important in studies such as this, especially when the predicted excess risk is small in comparison with the background risk, to attempt to deal, as far as is possible, with biases (systematic errors) and confounding factors. So, if there is a correlation between dose and some background risk factor (such as smoking), confounding is a possibility because an association with the background factor could be mistakenly interpreted as an association with dose. A limitation of large cohort studies is that comprehensive data on possible confounders is usually unavailable, and methods must be adopted in an attempt to overcome this difficulty. For this reason, the authors only included in the analysis of cancer other than leukaemia those workers with adequate socioeconomic information, and this necessitated the exclusion of the Japanese and some US and Canadian workers, reducing the number of deaths to 5024. Socioeconomic status is known to be correlated with some background risk factors for cancers other than leukaemia, such as smoking, so it is important to adjust for socioeconomic status to try to eliminate possible confounding, although realistically, this adjustment cannot be expected to be completely successful in its objective.

For all cancers other than leukaemia the ERR coefficient was 0.97 (95% confidence interval (CI): 0.14, 1.97) Sv^{-1} (dose lagged ten years), and for leukaemia other than CLL the ERR coefficient was 1.93 (95% CI: <0, 8.47) Sv^{-1} (dose lagged two years). In a short summary paragraph in the *British Medical Journal* that accompanies the paper by Cardis *et al* it is baldly asserted that 'these estimates [derived by Cardis *et al*] are higher than the risk estimates used for current radiation protection standards'. This may be referring to the results of an analysis of Life Span Study (LSS) data for adult male Japanese atomic bomb survivors carried out by Cardis *et al*: ERR coefficients of 0.32 (95% CI: 0.01, 0.50) Sv^{-1} for all cancers other than leukaemias, lymphomas and myelomas (cf 0.87 (95% CI: 0.03, 1.88) Sv^{-1} for the nuclear workers), and 1.54 (95% CI: -1.14, 5.33) Sv^{-1} for leukaemia other than CLL. It must be borne in mind, however, that while this LSS leukaemia risk estimate is based upon a linear–quadratic dose–response that effectively incorporates a DDREF of two, the LSS other cancers risk estimate requires a reduction by a factor of two to provide an ERR coefficient that is appropriate for low doses. Ostensibly, then, the ERR coefficient for all cancers other than leukaemia obtained by the IARC study of nuclear workers is six times greater than that obtained by halving the ERR coefficient obtained from the group of adult male Japanese survivors of the atomic bombings—the risk estimate obtained by the IARC study is a factor of six greater than the low dose/low dose-rate risk estimate derived under the assumptions made by ICRP for the purposes of radiological protection. This inference is compatible with a rough calculation of the EAR coefficient that may be undertaken (although this was not done by Cardis *et al*): the approximate lifetime cancer mortality absolute risk in OECD countries is $\sim$25%—about a quarter of people in these countries die of cancer—so an ERR coefficient of $\sim$1 Sv^{-1} gives an EAR coefficient of $\sim$25% per Sv, which is about six times greater than the nominal EAR coefficient of 4% per Sv assumed by ICRP for a working population.

Should we conclude, as a consequence, that the current framework of radiological protection underestimates the radiation-induced risk of cancer mortality by a factor of around

six? Well, not on the basis of this study alone. First, even for a study as large as the IARC study statistical uncertainties are still relatively big: the lower 95% confidence limit on the ERR coefficient for all cancers other than leukaemia is 0.14 Sv^{-1}, giving an EAR coefficient of ~3.5% per Sv, so that the study findings are statistically compatible with the ICRP assumption, although only just.

Second, and more importantly, there is evidence in the results of the study of Cardis *et al* that residual confounding, in particular by smoking, may have inflated the radiation risk estimates. The ERR coefficient for all cancers other than leukaemia, 0.97 (95% CI: 0.14, 1.97) Sv^{-1}, is strongly influenced by that for lung cancer, 1.86 (95% CI: 0.26, 4.01) Sv^{-1}—the ERR coefficient for all cancers other than leukaemia and cancers of the lung and pleura is 0.59 (95% CI: −0.29, 1.70) Sv^{-1}—pointing to a possible role for smoking. However, the ERR coefficient for smoking-related cancers other than lung cancer is not particularly noteworthy at 0.21 (95% CI: <0, 2.01) Sv^{-1}—although this category includes sites of cancer (such as the uterine cervix) that are less strongly associated with smoking than lung cancer—and the ERR coefficient for cancers unrelated to smoking is positive, but statistically non-significant, at 0.62 (95% CI: −0.51, 2.20) Sv^{-1}. Nonetheless, it is of some interest that mortality from all non-malignant respiratory diseases and from chronic obstructive bronchitis and emphysema, groupings of diseases that are related to smoking, produce ERR coefficients of 1.16 (95% CI: −0.53, 3.84) Sv^{-1} and 2.12 (95% CI: −0.57, 7.46) Sv^{-1}, respectively. Cardis *et al* conclude: 'Taken together, these findings indicate that a confounding effect by smoking may be partly, but not entirely, responsible for the estimated increased risk for mortality from all cancers other than leukaemia.' This is an entirely reasonable conclusion; but the big question is to what degree smoking might be responsible for the positive association with radiation, and this question cannot be answered on the basis of the results of this study as reported.

Third, the Canadian data have a surprisingly large influence on the ERR coefficient for all cancers other than leukaemia: even though there are just over 200 Canadian cancer deaths (i.e. 4% of the total number of cancer deaths) contributing to the analysis, exclusion of the Canadian data leads to a 40% reduction in the ERR coefficient to 0.58 (95% CI: −0.22, 1.55) Sv^{-1}. No further details are provided by Cardis *et al* (apart from a figure indicating that the Canadian point estimate for the ERR coefficient is >6 Sv^{-1}, and the lower 95% confidence limit is >2 Sv^{-1}), but it would be of interest to know more about the Canadian data, for example how much lung cancer mortality contributes to the high ERR coefficient.

Finally, the ERR coefficient for leukaemia other than CLL, 1.93 (95% CI: <0, 8.47) Sv^{-1}, is indicative of an excess radiation-related risk of leukaemia mortality, and this would be the cancer grouping for which an association with radiation would be expected to be strongest given the evidence for the greater sensitivity of leukaemia to induction by radiation. However, of some interest is why the association is not statistically significant, especially since some previous studies (such as the second analysis of the NRRW) with smaller numbers of deaths gave positive ERR coefficients that were of marginal statistical significance. This could, of course, just be due to a chance downward fluctuation in the number of observed deaths; but I wonder if there is more to it than this. It is well established that the risk of acute leukaemia following brief exposure (as during the atomic bombings) is expressed as a 'wave' with time-since-exposure, the risk rising rapidly a couple or so years after exposure and then falling away less steeply from a peak about five years post-exposure. Now, as noted by Cardis *et al*, most of the high doses in the IARC study were received by nuclear workers in the early years of the industry, and one would anticipate that the excess risk of leukaemia induced by these doses would be concentrated within the next decade. Perhaps an early temporal 'wave' of leukaemia excess risk has been hidden by considering only the total follow-up period? This is not just an academic question. In the study by Shilnikova *et al* (2003 *Radiat. Res.* **159** 787–98) of the

Russian Mayak nuclear facility workers (who received much higher doses than the workers in the IARC study) the leukaemia ERR external dose coefficient for the entire period of follow-up (excluding the initial two years after first exposure) was 1.0 (90% CI: 0.5, 2.0) Sv^{-1}, but the excess risk was markedly concentrated in the period 3–5 years after the dose was received when the ERR coefficient was 7.6 (90% CI: 3.2, 17) Sv^{-1}. It would seem that the temporal distribution of the leukaemia risk among the workers included in the IARC study might be well worthwhile exploring.

So, the study of Cardis *et al* is a worthy effort to investigate cancer mortality among the large numbers of nuclear workers that are necessary to provide meaningful estimates of the risk arising from protracted exposure to low doses of radiation. The authors are to be applauded for the substantial effort that has been expended in establishing a cohort of around half a million workers and then accurately determining individual doses, vital status and causes of death. However, the study also illustrates how difficult it is to eliminate the effect of significant extraneous influences when the predicted radiation-induced excess risk is so small. That is not to say that such studies should not be attempted, and it is of some interest that only 6% of the workers had died—there is much information still to come from this cohort. It might be fruitful for the authors to further examine the currently available data to identify possible anomalies, in particular why the Canadian data have such an impact on the results. In the longer term, a case–control study of lung cancer nested within the cohort that uses detailed individual smoking (and other relevant) data could better quantify the effect of residual confounding upon the radiation risk estimates. What can be concluded at the moment is that it is necessary to conduct and interpret worker studies with considerable care if we are not to be misled by an overly simple view of complex results. The IARC study probably does indicate that repeated exposure to small doses of radiation increases the risk of cancer, but to infer that current risk estimates are underestimates is premature.

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