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INVITED EDITORIAL

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Questions have been raised (Wakeford 2005, Shigematsu 2005, Lagarde 2005, McGeoghegan 2005) about the validity of the radiation risk estimates reported in the large-scale ‘15-country IARC’ study of nuclear workers (Cardis *et al* 2005), and in particular the anomalously high outlier risk coefficient from the country of Canada (Ashmore *et al* 2007, UNSCEAR 2008). These concerns included bias, confounding, the selection of workers to include (or exclude) from study, analytical issues and low statistical power. In this issue of the journal, J P Ashmore and colleagues provide a comprehensive, if not exhaustive, evaluation of one facility in Canada (Atomic Energy of Canada Limited, AECL) which was responsible for the anomalously high Canadian radiation risk coefficient for all cancers excluding leukemia, which was six times higher than estimated for the 15-country study (Ashmore *et al* 2010). Their paper should be recommended reading for those conducting radiation studies because it focuses on the quality and integrity of the data collected and analyzed, and the potential pitfalls and uncertainties involved.

The authors conclude that the anomalously high radiation risk for AECL is related to missing dosimetry information, including dates of hire, that occurred when the transfer of dosimetry data was made from the AECL worker records to the National Dose Registry (NDR). Prior to this transfer, epidemiologic studies relied on the dosimetry information obtained directly from the AECL worker records. It appears that the incomplete data had a significant effect on the risk coefficient for the AECL cohort which unduly influenced the risk coefficient for the total Canadian cohort, which in turn unduly influenced the risk coefficient for the 15-country study. The impact of this one facility, with only 11 907 workers, within one country is truly remarkable since excluding it from the 15-country analysis reduced the size and the precision of the risk estimate (based on well over 100 facilities) so that it was no longer statistically significant.

Ashmore *et al* present a stunning figure showing the abrupt change in the estimates of radiation risk from various Canadian and international studies when the NDR, and not the AECL, dosimetry data were used in epidemiologic studies. Before 1995 there was little evidence for an association between occupational exposure and cancer based on the AECL dosimetry data (Gribbin *et al* 1993, Cardis *et al* 1995). After 1995 the radiation risk estimates for the Canadian studies and the 15-country study that incorporated the Canadian data were all elevated, and most significantly so. The graph supports the view that studies published after 1995 were adversely affected by a problem in the transfer, processing and incorporation of the dosimetry data from the AECL worker cohort into the NRC database. Potential problems with the NDR were hinted at earlier by E S Gilbert (2001) in an informative commentary on the unusually high radiation risk estimates based on NDR data and on the potential distortions that can arise from small biases and confounding in studies of low statistical power, i.e. when the predicted increase in risk is likely to be at most a few per cent.

Ashmore *et al* raised another issue concerning the exclusion of certain subsets of workers and the influence of such exclusions on the study results. The two major exclusions in the 15-country study involved workers with the potential for internal exposures to radionuclides or neutrons and the exclusions based on socioeconomic status (SES). Ashmore *et al* conclude that the exclusions based on internal and neutron exposures had little effect on the Canadian risk coefficient, in large part because the numbers were small. Of the 88 AECL workers excluded from the 15-country study because of potential exposure to internal radiation, it appeared that only 21 (or 23.9%) had positive measurements high enough to warrant removal from work, implying that 76.1% of those excluded may have had inconsequential intakes of radionuclides, if any. While such exclusions seem reasonable and were apparently protocol-based, they nonetheless are somewhat subjective (particularly for workers without bioassay measurements or with null or low measurements) and slightly different assumptions on what constitutes a potential for internal exposures might have influenced results if exclusions were as substantial as they were in the 15-country study (n = 58 771). There seemed to be some inconsistencies in excluding workers based on internal contamination in that the AECL workers exposed to tritium (which contributed 20% of the total collective dose) were included but workers in Slovakia exposed to tritium apparently were not (Vrijheid *et al* 2007). Workers with the potential for internal intakes of radionuclides or neutron exposure had been included in the 3-country study and their exclusion in the analysis had no effect on the cancer or leukemia risk estimates (Cardis *et al* 1995, table VII). All workers (n = 6 638) at Rocky Flats were also excluded from the 15-country study because of the potential for internal contamination (Cardis *et al* 2007), although they had been included in the 3-country study (Cardis *et al* 1995). The Rocky Flats cohort also showed little evidence for an association between cancer and cumulative occupational dose (Gilbert *et al* 1993).

Ashmore *et al* noted that the AECL cohort, with indicators of SES missing for 40% of the workers, was not that different from the Ontario nuclear utility cohort with 50% missing SES; however, the AECL cohort was included in the 15-country cancer analysis and the Ontario cohort was not. Other exclusions based on SES included the Idaho nuclear facility with 21% missing SES (Schubauer-Berigan *et al* 2005) and the Japanese facilities with apparently no measures of SES. Ashmore *et al* noted differences in the effect of adjusting for SES, which increased the radiation risk estimate for the AECL cohort but decreased the risk estimate in the 15-country study (as well as in the 3-country study), suggesting opposite effects of possible confounding factors. Also, when SES was not considered and the Ontario, Japanese and Idaho cohorts are included in the 15-country analysis, all risk estimates were reduced (Cardis *et al* 2007, table 6). It is not entirely clear why adjustments had such divergent effects but emphasizes the importance of good measures of SES in studies of low statistical power. SES is often used in epidemiologic studies to control for unknown confounding factors associated with lifestyle, such as cigarette smoking which is more prevalent in blue-collar (hourly) workers than white-collar (salaried) workers (Lee *et al* 2004).

Another issue raised by Ashmore *et al* concerned the possibility of confounding, and in particular cigarette smoking and lung cancer. They concluded that deaths from lung cancer contributed to the high AECL risk coefficient, and though smoking may have played a role, it was not the sole reason for the high risk in Canada, implying that the missing dosimetry was of more or equal import. Lung cancer was the only site-specific risk that was statistically significant in the 15-country study and it was unusually high (twice as high as among the atomic bomb survivors). It also had a remarkable influence on the all-cancer risk estimate. Removing this one cancer from the analysis diminished the size and removed the statistical significance of the all-cancer risk coefficient. The authors in the 15-country study evaluated the possibility of confounding by smoking to the extent possible by looking at the radiation risk for nonmalignant respiratory disease and ‘smoking-related cancers’ (which were elevated but not significantly) and non-smoking-related cancers. The authors concluded that smoking may have played a role but would be unlikely to explain all the excess cancer risk observed. This analysis is somewhat difficult to interpret because ‘smoking-related cancers’ included cancers of the uterine cervix, stomach, liver, kidney and others that may very well be linked to cigarette smoking, but not strongly or close to the strength of the association with lung cancer, and the association between radiation and nonsmoking-related cancers was not statistically significant. Similar to the 3-country study (Cardis *et al* 1995), the recent update of the United Kingdom worker study considered only cancers ‘strongly’ related to smoking in their analyses and, in contrast to the 15-country study (Cardis *et al* 2007) reported a nonsignificant negative correlation with cumulative dose (Muirhead *et al* 2009).

Ashmore *et al* also raised concerns about the computed confidence interval about the risk estimate for the Canadian cohort in that it was notably narrow and, remarkably, did not overlap with the confidence interval for the risk estimate from the overall 15-country study. They speculated that the incomplete dosimetry data may be an explanation, possibly by placing workers in incorrect duration of employment categories (used as a stratification factor in the analysis) since year of first hire would be incorrectly estimated based on monitoring data in the NDR.

Ashmore *et al* also noted that the adjustment for duration of employment had a minimal effect on the risk coefficient for the AECL cohort whereas it led to a substantial increase in the 15-country cohort. In fact, the statistical significance for the cancer risk estimate in the 15-country study appears to be due entirely to this adjustment (Cardis *et al* 2007). It is not entirely clear whether stratification on duration of employment is warranted in general as a method to adjust for the healthy worker effect (Checkoway *et al* 1989), and it might have been informative to learn whether the radiation risk estimates were different for workers with long (>10 yr) versus short (<10 yr) durations of employment. The duration of employment was associated with both cumulative radiation dose and cancer risk in the 15-country study (Cardis *et al* 2007), and thus an adjustment for the duration of employment might be expected to diminish the risk estimate for cumulative exposure, not increase it substantially as was observed. The 15-country study adjusted for duration of employment (in addition to sex, age, calendar period, SES and facility) whereas the 3-country study did not. An analysis in the 3-country study adjusting for duration of employment, however, found little effect on the cancer or leukemia risk coefficients (Cardis *et al* 1995, table VII). When the duration of employment is not included as a stratification factor in the 15-country study, all of the estimates of excess risk (cancers excluding leukemia, lung cancer, and leukemia excluding CLL) were reduced by a factor of two to three and none of the associations remained statistically significant (Cardis *et al* 2007, table 6). The recent update of the United Kingdom worker study (many workers of which were included in the 15-country study) found that adjustment (or stratification) by duration of radiation work tended to reduce the estimates of radiation risk and that even among those employed for over 30 years the adjustment had little effect (Muirhead *et al* 2009). So again a conundrum as to why adjustment in the 15-country study had such a remarkable effect, whereas it had no or minimal effect in the 3-country and the United Kingdom and Canadian studies.

The 15-country study was much larger (n = 407 391) than the earlier 3-country study (n = 95 673), and both studies included workers from the United States, the United Kingdom and Canada, yet the 15-country study had much lower statistical power to detect a radiation effect, had there been one, than the 3-country study. How can this be? The mean dose of workers in the 15-country study (19.3 mSv) was lower than the mean dose in the 3-country study (40.2 mSv), but equally important, the dose distribution was much narrower, i.e. there were fewer cancer deaths among workers with exposures over 100 mSv (239 vs 413, table 1). Despite the overlap in the two studies, the substantial numbers of exclusions based on the potential for internal radionuclide or neutron exposures and on SES in the 15-country study essentially reduced the number of workers with relatively-high occupational doses and reduced the statistical power of the study. The excess risk for leukemia, the malignancy most strongly and most frequently linked with radiation (NRC 2006, UNSCEAR 2008), was no longer statistically significant in the 15-country study because, it seems, the workers with relatively high external doses in the 3-country study (from the Sellafield facility in the United

Table 1. Comparison of occupational radiation studies with the atomic bomb survivor study.

Study	Mean dose (mSv)	No of subjects	No of solid cancer deaths	No of solid cancer deaths with cumulative dose exceeding 100 mSv	400 mSv
IARC 15-country study cancer analysis (Cardis *et al* 2007)[a]	19.3	277 400	4770	239	10
IARC 3-country study (Cardis *et al* 1995)[b]	40.2	95 673	3976	413	56
UK National Registry of Radiation Workers (Muirhead *et al* 2009)[b]	24.9	174 541	7891	888	169
US 3-facility study (Gilbert *et al* 1993)[b]	27.4	44 943	1906	112	9
Atomic bomb survivors (Preston *et al* 2004)	∼ 210	86 611	10 127	2470	878

[a] 129 991 (31.9%) of the total 407 391 workers in the 15-country study were excluded in the cancer analyses from Japan (83 740), Idaho (25 570) and Ontario (20 681).

[b] All cancers excluding leukemia.

Kingdom) were excluded based on their potential exposure to internal radionuclides. Because the predicted relative risk at 100 mSv for solid cancers based on atomic bomb survivor data is so small and of the order of 1.02 (Preston *et al* 2004), the low mean dose and the few workers with cumulative doses over 100 mSv in all the large occupational studies to date (table 1) indicate the substantial difficulty in directly detecting a radiation effect when the predicted excess is only about 2% above the normal expectation, i.e. statistical uncertainties and the potential for confounding are substantial.

Both the Canadian and the 15-country solid cancer risk coefficient appear to be anomalously high. If the AECL data are removed from the 15-country analysis, the statistical significance disappears. If one cancer (lung) is removed from the analysis, the statistical significance disappears. If the duration of employment is not included as an adjustment variable, the statistical significance disappears. If different selection or exclusion criteria based on SES and monitoring for internal exposures or from neutrons are chosen, the risk estimate is decreased. The comprehensive 15-country study is a major tour de force in radiation occupational epidemiology and will be the standard for years to come. The quality of data, exposition of analyses and many other strengths have not been touched on (e.g. Gilbert *et al* 2006). However, the Canadian evaluation indicates that even large studies of low statistical power are susceptible to slight biases, confounding and selection that have the potential to distort study findings. Even a study of millions of workers exposed to very low doses (below 100 mSv), no matter how carefully conducted, would be inadequate to produce precise and uncertain estimates of risk in part because of the dominating influence of any subtle biases or unknown confounding factors (UNSCEAR 2008, Land 1980). Thus, studies of populations exposed to both moderate doses and a range of doses from low to high will remain the primary source of data for risk estimation (Gilbert 2001, ICRP 2007, UNSCEAR 2008). Except for the unusually high occupational exposures experienced by radium dial painters, Russian plutonium workers and underground miners exposed to radon, the main utility of occupational studies has been to confirm the validity and appropriateness of the estimates from the higher dose and higher dose rate studies of atomic bomb survivors and medically exposed populations (ICRP 2005).

The main unanswered question in radiation epidemiology is the potential risk associated with chronic low dose and low dose-rate exposures experienced over long periods of time (Shore 2009). Occupational studies clearly are important in providing information in this area (Jacob *et al* 2009). However, studies of current workers are unlikely to be informative since today's radiation protection culture appears to have controlled worker exposures to a meaningful degree (about 2 mSv per year currently in the United States, NRC 2007). Such low doses are also reflected in the 15-country study for which many of the workers were young with low cumulative doses, too low it seems to provide precise estimates of radiation risk and well below what they received from natural background sources of radiation. Looking to the past and obtaining high-quality radiation dosimetry and occupational data may be a way to obtain more precise estimates of radiation effect (Hall *et al* 2009). The recent United Kingdom dosimetry registry worker study (Muirhead *et al* 2009) goes a long way in this regard by analyzing workers with a wide range of doses up to and above 400 mSv, although the mix of tumors showing marked elevations (pleural cancer, rectum, uterus, testes) were not the ones expected following low-dose radiation exposure. Nonetheless, the pattern of risk over dose categories, particularly the risk of leukemia excluding chronic lymphocytic leukemia supports a low-dose risk, at least for cumulative doses above about 100 mSv. The follow-up of the early worker cohorts in the United States (Wakeford 2009) would be of value. Studying the early nuclear power plant workers (1960–1979) in the United States would be a contribution, because numbers are large and allowable doses were high (up to 120 mSv per year) (Muirhead *et al* 1996). Other contributions may come from continued study of the Chernobyl accident and the Techa River contamination (UNSCEAR 2008, Shore 2009) or even military veterans who participated in nuclear weapons tests (IOM 2000). The study of patients treated with radiation and the evaluation of organs outside the primary radiation field and exposed to low-dose scatter would be valuable given the large numbers and potential for high quality dose reconstruction. Studies of high-background radiation may also have the potential to provide upper limits on risk (Hendry *et al* 2009, Nair *et al* 2009).

The careful and comprehensive evaluation of the Canadian AECL data by Ashmore *et al* has provided a platform to emphasize the need for high quality data in studies of low statistical power. Studies of low statistical power, i.e. with small numbers of excess cancers to be detected atop a large number due to other causes, are susceptible to small biases that may creep in and distort study outcomes by creating or masking an exposure effect. Continued vigilance to reduce and evaluate these uncertainties from bias and confounding, in addition to statistical and dosimetric uncertainties, in radiation studies is applauded and encouraged.

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John D Boice Jr
Professor, Vanderbilt University, Nashville, TN, USA
Scientific Director, International Epidemiology Institute, Rockville, MD, USA