LETTERS TO THE EDITOR

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LETTERS TO THE EDITOR

What is a low dose?

Dear Sir

Volume 29, issue 2A of Journal of Radiological Protection includes many very interesting and useful papers on radiation risks, covering a wide range of exposure circumstances, types and levels. The use of the term ‘low dose’ by individual authors is usually clear in the context of each paper, but collectively, they add up to quite a confusing picture. For example:

- Martin et al [1] describe low doses as ‘those received in medical and occupational exposures’. Surely that is so wide a definition as to be meaningless, especially if you include some therapies.
- Hendry et al [2] describe a low dose as being 5 mSv/y, commenting that this is about twice average natural background. Put against the observation that this natural background is apparently the second highest cause of lung cancer, this makes a small dose sound quite significant. The paper goes on to refer to attempts to classify different levels of dose (Sohrabi), with a very high dose being one greater than 50 mSv/y. Perhaps this was a helpful suggestion, but the Sohrabi papers quoted are now quite old—what happened to the proposals? Hendry et al answer the question by quoting the French Academy of Sciences, in the mean time, as saying low dose means less than 100 mSv!
- Heyes et al [3] refer to a (non-linear!) response effect at low dose, 1–10 mGy. They also have high doses as >0.1 Gy and ultra-low doses as 5–10 μGy.
- Harrison [4] then has a paper suggesting that uncertainty analysis in prospective dosimetric assessment for protection purposes is of questionable value. This is said to be because the prospective doses in such cases are small fractions of dose limits, and the uncertainty ranges on low values of effective dose are likely to be misleading unless the basis and scope for the calculations is clearly explained. The caveat given at the end is a truism, but its inclusion is justified because such an explanation has often not been provided when it should have been. The upshot would appear to be, yes uncertainty analysis would be useful, it should be done (in some cases at least), but only if it is done properly. In any event, Harrison is calling low dose something which is less than the dose limit, say, less than 1 mSv.
- The paper by Little [5] then offers the succinct, low dose range: 0–2 Sv. Being risk averse, I think I would prefer to get a low dose from Sohrabi, or better yet, from Harrison!
- Wakeford then has a paper [6] which presents a schematic of stochastic health risks at low dose, but without any indication of the scale of dose. Any scale would surely have been controversial, but an order of magnitude would be very helpful, and more or less necessary given the variant definitions of low dose given above.

So individually the papers are self-consistent, but collectively they create some real difficulties for those having to describe the significance (in terms of health risk) of radiation exposure at different levels. Something is needed for wider risk communication to all sorts of non-specialists, but also to stop the specialists confusing each other.

Something like the INES scale to describe accidents would be about the right level of sophistication and INES has been shown to be effective and successful in a similarly complex communication situation. Seven levels, as in INES, should be sufficient to cover the range...
from central nervous system failure in 24 h to so small an increment above the ambient that we cannot measure it nor see any effects, even if millions of people are receiving that increment. Such a scale has been proposed to describe the hazard associated with quantities of radioactive material, in terms of activity levels and external dose rates [7]. It could be extended, with just some thought, to describe levels of dose, from say ultra low, to very high—i.e. the kinds of terminology used above, for use in normal communication, but standardised.

The final paper in the issue by Hall [8] illustrates why the above is perhaps important. In reference to decisions on CT scanning, he suggests that even a very small individual risk when multiplied by a very large and increasing number is likely to produce a significant long-term public health concern. The ICRP has said ([9], paragraph 66) that because of uncertainties at low doses, it judges that it is not appropriate for public health planning, to calculate the hypothetical number of cases of cancer or heritable disease that might be associated with very small radiation doses received by large numbers of people over long periods of time. The ICRP’s recommendation here seems to assume knowledge of an awful lot of radiation exposure situations which are locally specific, and to make judgements which go beyond radiation protection. Perhaps Hall would prefer to do the uncertainty analysis himself, then make the technical judgements himself, and then make decisions in discussion with the relevant stakeholders, but based, among other things, on a common understanding of very small radiation doses.

In any event, it is bizarre that a single issue of Journal of Radiological Protection can contain so many definitions of low dose. Unless the health physics community is collectively clearer about the meaning of low dose, I suggest that all the small individual confusions produced by different usages add up to something significant.

References


Yours sincerely,

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Response to “Reply to ‘The RBE of low-LET radiations’ ”

Dear Sir

We appreciate the opportunity to respond to the letter from Drs Hunter and Muirhead. The basis for the mechanistic modelling is not important, although the use of a molecular lesion with direct links to the three cellular end points, aberrations, mutations and cell killing does have distinct advantages. What is important is the widely accepted linear-quadratic dose effect relationship which can be used to analyse these cellular effects and the equally well accepted conclusion that the linear term is dependent on radiation quality (Goodhead 1987, Chadwick et al 1992). The derivation of this linear term from experimental cellular data provides an opportunity to derive maximum RBEs of different radiations at very low doses, obviously of interest to radiological protection.

Although the analysis of epidemiological data using ERR is not restricted to linear dose responses, there is little evidence of attempts to use other response forms except in the case of leukaemia in the atomic bomb survivors (Preston et al 1994, Little et al 1999, UNSCEAR 2000). Consequently, we maintain our claim that the analyses of the epidemiological data made by Drs Hunter and Muirhead are not appropriate for the detection of variations of RBE for low-LET radiations at very low doses of interest for radiological protection. Indeed, it may well be, taking account of the large uncertainties in the ERR values from epidemiological data, that we should conclude that the epidemiological data themselves are not useful for this sort of study.

It seems rather clear that DNA sequence changes, or mutations, are implicated in the development of cancer (Stratton et al 2009) and that specific chromosomal rearrangements found in some cancers are evidence of these DNA changes. Consequently, as radiation induces cytological damage in the form of chromosomal rearrangements and mutations, it seems logical to associate this with radiation induced cancer and thus analyse dose responses appropriately. Although we agree that dicentrics are unlikely to lead to the development of cancer, other aberration types certainly might. Thus, we can see no reason why the fact that dicentrics are unlikely to lead to a cancer should disturb in any way this association of cytological damage and cancer induction nor can we see any reason to expect that the specific stable translocations associated with certain cancers should, of necessity, have been induced by low dose radiation. We regret to say, therefore, that the reasoning used by Hunter and Muirhead about dicentrics and the role of low dose radiation to cast doubt on whether cytological damage is involved in cancer induction is, in our opinion, unconvincing.

References

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Dear Sir

We welcome the opportunity to reply to Dr Chadwick’s and Dr Leenhouts’s response to our previous letter.

We disagree that epidemiological data are not useful for investigating the RBE of low-LET radiations. Epidemiological studies provide a basis for directly evaluating the risk of cancer mortality and incidence in humans following radiation exposure. In making judgements as to whether x-rays and other low-energy photons are more effective than high-energy gamma rays in inducing health effects in humans, it is important to consider the evidence obtained from all relevant radiobiological and epidemiological studies. In our paper (Hunter and Muirhead 2009), we initially considered radiobiological studies in human lymphocytes, which clearly indicate a higher biological effectiveness of x-rays relative to the high-energy gamma rays. We then investigated whether useful information on the RBE of low-LET radiations can also be obtained from epidemiological studies. However, the evidence obtained from epidemiological studies does not provide clear evidence of a difference in the effectiveness of cancer induction between x-rays and gamma rays. Although large uncertainties exist in the epidemiological data, we should not rule out this sort of comparison.

We also disagree with the statement by Dr Chadwick and Dr Leenhouts that ‘...nor can we see any reason to expect that the specific stable translocations associated with certain cancers should of necessity, have been induced by low dose radiation’. When considering the relative effectiveness of low doses of differing radiation qualities in inducing cancer, the RBE calculation must be for an endpoint or process that is caused by the radiation. Therefore it must be assumed that DSB-initiated translocations are the key action of radiation in causing cancer for the Chadwick/Leenhouts model to be of any relevance. If the translocations have a different (spontaneous) origin, this model becomes irrelevant. There does of course remain uncertainty on the origin (spontaneous/ radiation-induced) of translocations observed in specific cancers and indeed the aetiology of individual cancers arising in irradiated persons. Some supporting evidence for a radiation origin is available from animal studies.

References

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Yours sincerely,

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Comment on ‘Updated estimates of the proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionising radiation’

Dear Sir

This is an excellent paper (Little et al 2009) on a topic of considerable interest to those of us wishing to understand the extent to which radiation exposures may be responsible for childhood cancers. The authors refer to a recent paper in which they estimated that 20% of childhood leukaemias in Great Britain are attributable to natural background radiation (Wakeford et al 2009). Using revised estimates of background radiation doses (Kendall et al 2009), they have now revised this estimate to 15–20%. While the authors caution that this estimate is subject to considerable uncertainties, the revision from 20% to 15–20%, referred to as a ‘best estimate’, may give a misleading impression of our current understanding of this topic.

One cause for concern is that the analysis employs estimates of equivalent doses to red bone marrow (RBM) in microsieverts (μ Sv), calculated using a radiation weighting factor of 20 for alpha particles. As pointed out by the authors, equivalent dose is a radiation protection quantity; radiation weighting factors are chosen by the ICRP (1991, 2007) to take account of the relative biological effectiveness (RBE) of different radiation types, in this case alpha particles compared with gamma rays, for all radiation-induced cancers. For scientific applications, the best available information should be used, including RBE data specific to the cancer type under consideration. The authors are aware of the evidence from human and animal studies of RBE values for alpha-induced leukaemia of closer to 1 than 20. The best estimate of the proportion of childhood leukaemias attributable to natural background radiation is then closer to 10% than 20%, according to the analysis presented by the authors.

A further cause for concern is the treatment of in utero doses. It is noted that doses received by the embryo/fetus and the infant in the first year of life are particularly important in determining the fraction of childhood leukaemia attributable to background radiation, primarily because of the background peak of incidence of leukaemia in young children. However, the leukaemia risk models used were based primarily on follow-up of the Japanese atomic bomb survivors which began in 1950 and therefore do not provide quantitative information on leukaemia occurring in the first few years of life. Little and colleagues are, of course, aware of this problem and refer to the similarity in risk coefficients derived from the Japanese data and from the Oxford Survey of Childhood Cancer (OSCC) following in utero exposures resulting from diagnostic radiography. A useful addition to the paper would have been quantitative estimates based on the OSCC data.

A complication in the assessment of in utero doses of relevance to the induction of leukaemia is the multiple and changing sites of haemopoiesis during embryonic and fetal development.

Comments on Comment on ‘Updated estimates of the proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionising radiation’

Dear Sir

This is a well-considered response to the paper by the authors. The authors have acknowledged that their estimates of the proportion of childhood leukaemia attributable to natural background radiation are subject to considerable uncertainties, and the revision from 20% to 15–20% may give a misleading impression of our current understanding of this topic. However, the authors point out that the analysis employs estimates of equivalent doses to red bone marrow (RBM) in microsieverts (μ Sv), calculated using a radiation weighting factor of 20 for alpha particles. This is a radiation protection quantity, and radiation weighting factors are chosen by the ICRP (1991, 2007) to take account of the relative biological effectiveness (RBE) of different radiation types, in this case alpha particles compared with gamma rays, for all radiation-induced cancers. For scientific applications, the best available information should be used, including RBE data specific to the cancer type under consideration. The authors are aware of the evidence from human and animal studies of RBE values for alpha-induced leukaemia of closer to 1 than 20. The best estimate of the proportion of childhood leukaemias attributable to natural background radiation is then closer to 10% than 20%, according to the analysis presented by the authors.

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A complication in the assessment of in utero doses of relevance to the induction of leukaemia is the multiple and changing sites of haemopoiesis during embryonic and fetal development.
development (Metcalf and Moore 1971, Medvinsky et al 1993, Campagnoli et al 2000). The red bone marrow is the recognised target for leukaemia induction in children and adults, or more precisely, haemopoietic stem cells within bone marrow. In the embryo and fetus, however, although the bone marrow becomes established as the main site of haemopoiesis in the last few months of fetal life, the liver is an active site of haemopoiesis in mid-gestation. The stem cells that seed the liver and bone marrow may originate in the yolk sac or in an intra-embryonic site. The doses from internal emitters used by Little et al (2009), calculated by Kendall et al (2009), rely on methods developed by the ICRP (2001, 2004), considered appropriate for protection purposes. In utero RBM doses are calculated from 8–38 weeks using simplified biokinetic and dosimetric models. No account is taken of dose to other tissues or of possible changes in sensitivity of different precursor cells. Although the estimated in utero doses from background radiation are dominated by contributions from external radiation (Kendall et al 2009, Little et al 2009), uncertainties in dose and risks from in utero irradiation must remain an important source of uncertainty in their analysis of childhood leukaemia causation.

A unique opportunity for assessing risks from radiation exposure in utero and in childhood is afforded by follow-up studies of people exposed as a result of radioactive discharges to the Techa River from the Russian Mayak plutonium production plant (Krestinina et al 2005, Degteva et al 2007). The dominant contributions to radiation doses were external sources and ingestion of radionuclides, principally strontium-90 (Degteva et al 2007, Shagina et al 2007).

Good measurement data are available on which to base estimates of exposures and work is in progress to improve dosimetric models. There is also potential to study the children of female workers employed at the Mayak plant and combine these cohorts.

Having based their analysis on RBM doses, Little and colleagues end their paper with an appendix on lymphatic tissue doses, not referred to in the main paper. There has been conjecture that irradiation of lymphoid cells in tracheobronchial lymph nodes and other lymphatic tissue may contribute to risks of leukaemia induction (COMARE 1996, Harley and Robbins 2009). While this possibility cannot be dismissed, the most appropriate approach on current evidence is to assume that the risk is of stable genetic mutations in haemopoietic stem cells and lineage committed precursor cells. These cells are located primarily, from the third trimester of in utero development, in specific microenvironments within red bone marrow. Attempts to provide estimates of doses to lymphatic tissue in different organs are of questionable value.

Until we know more about doses and risks from radiation exposure received in utero and early childhood, care is needed in the interpretation of assessments of the type provided by Little and colleagues.

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Yours sincerely,

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**Reply to “Comment on ‘Updated estimates of the proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionising radiation’”**

Dear Sir

We thank Dr Harrison for his interest in and comments on our paper (Little *et al* 2009). Many of his points echo those made in our discussion in this paper and in the related earlier paper (Wakeford *et al* 2009).

Harrison (2010) points out, as do we, that there is uncertainty in the relative biological effectiveness (RBE) which should be applied to the absorbed dose from alpha-particles when calculating the risk of radiation-induced childhood leukaemia. We presented results for a range of RBES: table 5 of our paper shows that the percentage of childhood leukaemia calculated to be attributable to natural background radiation is 19.2% if a RBE of 20 is used for alpha particles, falling to 13.1% with a RBE of 1. (The calculations underlying table 5, like those
of table 3 referred to below, use the UNSCEAR (2008) leukaemia risk model and the 70% ERR/30% EAR model for transferring risks between populations.) As stated in our paper (Little et al 2009), the ICRP recommended radiation weighting factor (\(w_R\)) for alpha-particles of 20 (ICRP 2007) is intended for general radiation protection purposes, and we also pointed out (Little et al 2009) that there is evidence that a RBE lower than that implied by a \(w_R\) of 20 may be appropriate for the induction of adult leukaemia by alpha-particles. Harrison (2010) argues that the same should apply to childhood leukaemia; this may be the case, but we noted that, unlike the situation with adult leukaemia, there is no direct evidence relating to children, and that other factors (such as the distribution of red bone marrow, bone dimensions and type of leukaemia) may provide important differences between adults and children. Further, we note that the leukaemia risk models presented in the BEIR VII (US NRC 2006) and UNSCEAR (2008) reports are expressed in terms of the equivalent dose to the red bone marrow, i.e. an implicit RBE of 20 for alpha-particles.

Harrison (2010) points out that our results indicate that the dose to the fetus is relatively important: setting it to zero reduces the percentage of childhood leukaemias calculated to be due to natural background radiation from 19.2% to 15.5% (table 3 of Little et al (2009)). Harrison (2010) correctly notes that broad-brush methods were specified by ICRP (2007), and were applied by Kendall et al (2009) for calculating doses to the fetus, since more detailed modelling taking account of the different sites of haematopoiesis with fetal age was not available. However, the importance of this point should not be overemphasised: more than two-thirds of the fetal equivalent dose is due to penetrating radiation which will give a similar dose to all fetal organs and tissues. The contribution from penetrating radiation would be even higher if alpha-particles were assigned a RBE of less than 20.

Harrison (2010) suggests that it would be useful to present quantitative results based on in utero risk estimates for childhood leukaemia using data from the Oxford Survey of Childhood Cancers (OSCC), as well as those from the Japanese atomic bomb survivors exposed after birth. In fact, as we pointed out, the excess relative risk (ERR) coefficients from the two datasets are statistically compatible and do not differ materially. We would not therefore anticipate any substantial difference being made to our overall conclusions by use of an ERR derived from the OSCC to estimate attributable proportions following exposure in utero—in fact, this may slightly increase the attributable proportion—and use of the excess absolute risk (EAR) coefficient from the OSCC would almost certainly increase the attributable fraction given the difference in baseline rates of childhood leukaemia between the two populations (Wakeford and Little 2003). The Techa River cohort (Ostroumova et al 2006) is undoubtedly of potential value for estimation of risk from internally deposited radionuclides, but as yet reliable in utero risk estimates for childhood leukaemia based on individually-estimated doses have not been derived.

As we point out, and as Harrison (2010) acknowledges, there have been suggestions (COMARE 1996, Harley and Robbins 2009) that dose to lymphatic tissue may be of relevance to the induction of childhood leukaemia (especially given that the commonest type of childhood leukaemia is acute lymphoblastic leukaemia, particularly in young children). Our discussion in section 4.3 of the main paper and in the appendix updates the calculations of dose to lymphatic tissue presented by Simmonds et al (1995). While emphasizing that even greater uncertainties apply to estimates of doses to lymphatic tissue than to red bone marrow, our conclusion is that the active marrow receives a dose that is comparable with those received by other of the more highly exposed organs and higher than the doses to many organs with a significant proportion of lymphatic tissue. Thus more recent dose estimates would not suggest that concentrating attention on the red bone marrow is seriously underestimating the contribution that natural background radiation makes to the burden of childhood leukaemia in Great Britain.
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Wakeford R, Kendall G M and Little M P 2009 The proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionizing radiation Leukaemia 23 770–6

Yours sincerely,

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