The RBE of low-LET radiations Reply to 'The RBE of low-LET radiations' Comment on 'An etched track detector for short-term screening measurements of radon' Reply to "Comment on 'An etched track detector for short-term screening measurements of radon' " Comments on

2009 J. Radiol. Prot. 29 445

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LETTERS TO THE EDITOR

The RBE of low-LET radiations

Dear Sir

It is regrettable that Hunter and Muirhead, in their impressive review of the RBE dependence on linear energy transfer for low-LET radiations (Hunter and Muirhead 2009), failed to take mechanistic modelling into account as it provides additional reasons for the clear dependence of RBE with LET found in the radiobiological studies which they review. It also implies that the analysis of the epidemiological data made by Hunter and Muirhead is not the most appropriate for investigating a possible dependence of RBE on the LET of sparsely ionising radiations. In our opinion, this should have led them to attach much more importance to the radiobiological data and less to the epidemiology.

Some years ago, we derived a mechanistic model based on DNA double strand breaks to explain the celullar effects of radiation using a linear-quadratic dose response curve (Leenhouts and Chadwick 1978). In an extension of that model, we proposed that chromosomal aberrations are derived from double strand breaks in the DNA chromosome back-bone via a process of reciprocal recombination (Chadwick and Leenhouts 1978, 1981) which now appears to be called non-allelic homologous recombination. At that time, a considerable amount of 'microdosimetry' research in cellular radiobiology was devoted to the experimental and theoretical investigation of the RBE-LET relationship. From our point of view, the DNA double helix, with two sugar phosphate strands separated by some 2 nm, provides a well-defined, three dimensional target structure for radiation tracks so that the induction of a double strand break by a single ionising particle track will require two energy deposition events in about 2 nm along the track close to each of the two strands. The double strand breaks induced in this way will be proportional with radiation dose (αD) and radiation tracks with ionising events spaced at about every 2 nm will be most efficient in creating these double strand breaks. In the case of low-LET radiation, these tracks arise from the softer scattered electrons so that the biological efficiency of low-LET radiation will be closely related to the proportion of radiation dose deposited by the softer scattered electron tracks. Clearly, the lower the energy of the incident gamma or x-ray radiation is, the larger the proportion of dose deposited by the softer electron tracks will be and, consequently, the larger the biological effectiveness will be. Dose response curves induced by acute exposure to low LET radiations also exhibit a dose-squared component (βD^2) for double strand breaks arising, in our opinion, from two independently induced single strand breaks. This dose-squared component does not have a RBE dependence and will be closely the same for acute exposures to different low-LET radiations, but it does depend on dose rate and reduces to zero for protracted exposures.

Hunter and Muirhead use a linear-quadratic ($\alpha D+\beta D^2$) dose effect relationship to analyse the cytological data and compare the value of the linear coefficients (α) determined for different low-LET radiations with that determined using hard gamma rays to derive the RBE as a function of LET. We completely agree with this analysis and would emphasise that the RBE determined in this way is a maximum RBE which is valid at low doses. The result is as we expect and our mechanistic model provides a sound explanation for the trend of increasing RBE with LET found by Hunter and Muirhead for the cytological end-points examined. In their analysis of the epidemiological data, however, Hunter and Muirhead do not continue to use a linear-quadratic dose response but instead derive Excess Relative Risks (ERR) which assumes a linear dose

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effect relationship and with which we do not agree.

We expect that the dose effect relationship for an acute exposure to low-LET radiation, such as leukaemia in the atomic bomb survivors, will have linear-quadratic (LQ) dose kinetics at low doses but, because the mutated cells leading to cancer must survive to produce the cancer, the LQ start to the curve will be modified by a survival term and the rising part of the dose effect relationship will look like a tilted-forward 'S'. Although this type of curve can be closely approximated by a straight line to derive ERR, the straight line is not related in any way to the initial linear slope (α) of the LQ curve which does define the low dose biological efficiency of the radiation for the determination of RBE. The dose effect relationship for a chronic exposure which, except for the atomic bomb survivor study, is the situation in many of the epidemiological studies, will have an initial linear increase in effect that gradually saturates as a consequence of cell killing. The dose effect relationship for fractionated exposures will be rather complicated to analyse. The chronic exposure and fractionated exposure cases can also be approximated by a straight line although, as before, the lines will not be related to the initial linear slopes (α) which define the low dose biological efficiency. Consequently, the use of ERR to analyse epidemiological data will obscure the true determination of RBE and we are not surprised that the analysis of Hunter and Muirhead, even taking the large uncertainties in the ERR values into account, does not show anything like the trend of RBE with LET that the cytological data reveal. The epidemiological analysis made by Hunter and Muirhead is not the appropriate one to examine this problem and should not have been used to force the conclusions made by them that 'these data neither support nor disprove the hypothesis that low- and high-energy x-rays are more effective than high-energy gamma radiation.' We do not accept that their analyses permit this conclusion to be drawn.

Hunter and Muirhead have discounted the importance of their results for the cytological end points by suggesting that 'there is still some controversy as to whether chromosome aberrations and transformations are indicative of an increased risk of cancer'. We would recommend them, and any other doubters, to look at the recent cancer genomics literature and would quote the first line of a review in the 9 April 2009 issue of *Nature*, 'The cancer genome' which reads 'all cancers arise as a result of changes that have occurred in the DNA sequence of the genomes of cancer cells' (Stratton, Campbell and Futreal 2009).

In conclusion, it seems to us that the cytological data have been correctly analysed, that cytological effects are indeed relevant to the induction of cancer, and that the trend of RBE with LET revealed certainly merits careful consideration in the development of radiological protection philosophy in the future.

Note added: We would like to add a remark about the effectiveness of tritium because a similar reasoning to that applied above is relevant. The dichotomy of opinion about the effectiveness of tritium revealed in the Meeting Report on 'The assessment and control of tritium's health risk' (Bundy and Burtt 2009) in the same issue of *Journal of Radiological Protection* arises because one side of the argument is looking at the effectiveness of the low energy beta particles inducing the effect while the other side takes the ICRP approach via the epidemiology. The one side can see that the low energy beta particles will be effective mechanistically, the other sees little reason to accommodate this in the overall philosophy.

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Yours sincerely,

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Reply to 'The RBE of low-LET radiations'

Dear Sir

We welcome the letter by Dr Chadwick and Dr Leenhouts. Here are our replies to the issues raised:

The review paper has failed to take mechanistic modelling into account

We agree that mechanistic modelling should provide additional evidence concerning the RBE dependence on linear energy transfer for low-LET radiations. We did not include such modelling in our paper because few publications have examined the dose-effect relationship for double strand breaks (DSBs) in human cells using a mechanistic modelling approach. It is widely accepted that unrepaired or misrepaired DNA DSBs lead to the formation of chromosome aberrations. Hence, we did not think that it was necessary to mention mechanistic modelling based on DSBs, because there are extensive data on radiation-induced chromosome aberrations that have been used over many years and cited by bodies such as ICRP (2007) and BEIR VII (2006).

The analysis conducted of epidemiological data is not the most appropriate for investigating RBE dependence on LET of sparsely ionising radiations

Drs Chadwick and Leenhouts are concerned that our analysis of epidemiological data differs from the analysis of cytogenic data, in that we 'do not continue to use a linear-quadratic dose-response but instead derive Excess Relative Risks (ERR) which assumes a linear dose effect relationship.' The latter part of this argument is incorrect: the use of an ERR model does not imply that the dose-response relationship has to be linear. In theory, any form of dose-response model can be considered, for example using the EPICURE software (Preston *et al* 1996), and it is certainly possible to fit a linear-quadratic (L-Q) dose-relationship using an ERR model. Indeed, analyses of solid cancer risk among the Japanese atomic bomb survivors have adopted such an approach (Preston *et al* 2003; UNSCEAR 2008).

However, these analyses show little evidence for a quadratic term in the solid cancer dose-response, whereas analyses of leukaemia risk—using either an ERR or an Excess Absolute Risk model (UNSCEAR 2008)—do show evidence for a quadratic term.

The published findings from studies of occupational exposures are generally based on the fit of a linear, rather than a L-Q dose-response model. The relatively low doses received by workers mean that these studies generally have low statistical power to detect deviations from a linear dose-response relationship. At the same time, the narrow range of doses means that the impact of any quadratic term in the dose response would be low and that the linear term obtained from fitting an L-Q model should be similar to that based on a linear dose-response analysis.

The studies of medically exposed groups to which we referred related to cancers of the thyroid and female breast. In some studies, there was an indication of a flattening in the dose response at very high doses (>10 Gy). However, pooled analyses of these studies (Ron *et al* 1995; Preston *et al* 2002) indicated that the trend in risk with dose is consistent with linearity and provided no evidence against a linear dose-response model. Hence, we used the ERR estimates based on a linear model for comparisons both amongst studies of medical exposure and between these studies and the A-bomb study.

In summary, the comparison of risk estimates based on linear dose-response models is unlikely to have had a marked influence on our examination of the possible impact of LET.

The review paper casts doubt on whether chromosome aberrations and transformations are indicative of an increased risk of cancer

We are not disputing that the statement that cancer can arise as a result of changes that have occurred in the DNA sequence of the genomes of cancer cells. However, the nature of the association between the frequency of chromosomal aberrations and the risk of cancer in humans continues to be controversial.

Whilst some cancers tend to have specific rearrangements—in particular, translocations—there are valid reasons to doubt whether dicentrics would lead to cancer, because the cells are unlikely to form colonies.

Associations have been identified between specific stable translocations and certain cancers. However, whether these aberrations are directly induced by low radiation doses and whether they are directly causal is still the topic of debate.

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Yours sincerely,

Nezahat Hunter and Colin Muirhead
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Comment on 'An etched track detector for short-term screening measurements of radon'

Dear Sir

We are writing to note that the use of short-term measurements for radon in homes was the subject of a major DEFRA project, which was published in late 2003 [1]. This report, and subsequent papers by our group [2–4] gave clear guidance on the accuracy of the track etch, charcoal and electret detectors for 1-week and 1-month exposures, compared to the standard 3-month exposures. Subsequent analysis of the results prompted our group to recommend 14-day exposures, rather than 7-day exposures, because of potential distortions due to tidal effects [5].

One important feature of our results, which Ibrahimi and Miles [6] appear to ignore, is that the 3-month exposure in itself has some uncertainty in estimating the long-term average radon level (taken as the annual average) which is required to estimate the extent of the long-term health risk from radon.

The full set of our results, which compared 228 weekly, 228 monthly and 76 three-monthly readings to the annual average radon level in the tested houses, are reproduced in Table 1. In our case, a detector measurement at or below the lower bound indicates, with at least 95% certainty, that the long term average radon level in the houses is below the Action Level; while a measurement at or above the upper bound indicates, again with at least 95% certainty, that the long term average radon level in the houses is definitely above the Action Level.

Table 1. Equivocal ranges of various radon detectors exposed for different durations.

	1-Week Track-Etch	1-Month Track-Etch	3-Month Track-Etch	1-Week Electret	1-Week Charcoal
Lower Bound	75	109	112	59	68
Upper Bound	519	478	356	667	522

Our published analysis went on to suggest the circumstances in which a short-term measurement was of value, as indicated in Table 2. This gives more detail to Ibrahimi and Miles' statements about the value of results in low and high radon areas, and we suggest that the HPA could adopt this methodology, which would obviate the need to always send a set of three-month exposure detectors to the householder at the same time.

Table 2. Protocols for use of short-term radon measurements.

Area	Initial Test	Repeat if equivocal
New Homes in radon affected areas *or* < 5% existing houses over Action Level	1-week	1-week
> 5% and < 10% existing houses over Action Level	1-week	3-month
> 10% existing houses over Action Level	3-month	3-month

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Yours sincerely,

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Reply to "Comment on 'An etched track detector for short-term screening measurements of radon'"

Dear Sir

Denman *et al* suggest that in our paper we appear to ignore the uncertainty on the use of 3-month measurements in estimating long-term average radon concentrations. In fact we have long recognised such uncertainties—see, for instance Cliff *et al* (1994) and Miles (2001). As stated in the paper, measurement results are not reported to the homeowners, but rather 'all results are corrected to the estimated annual mean radon concentration...using correction factors based on typical seasonal variation in radon concentrations in UK homes.'

Denman *et al* further suggest that other work (Phillips *et al* 2004) provides clearer guidance on the uncertainties on the results of measurements across the UK with different types of detectors over different durations. That study reported results of radon measurements of 37 homes over one year in Northamptonshire. We note that the report concluded that 'St

Gobain detectors exhibited a large offset, which varied with exposure length.' These detectors constituted 65% of the etched-track detectors used in their study. We suggest that this variable bias in the results makes the conclusions regarding uncertainties on different measurement durations less reliable. The Health Protection Agency (and its predecessor, the National Radiological Protection Board) applies quality control measures to prevent such effects from occurring (Miles *et al* 2004).

One of the most important factors contributing to uncertainties in estimates of long-term average concentrations is differences in patterns of seasonal variation between houses. We are currently analysing the results of a study of 120 homes in five areas of the UK, in which radon concentrations were measured over eight 3-month periods, to determine how patterns of seasonal variation in radon concentration differ. We hope to submit this study for publication within the next few months.

Denman *et al* also suggest that HPA could avoid the need to issue a set of 3-month detectors alongside a set of 14-day detectors in some cases, depending on the probability of finding high radon concentrations in the area where the house to be measured is situated. We agree that a scheme such as this could limit the number of 3 month detectors issued. However, we believe that the practice of issuing 3-month detectors alongside 14-day detectors is helpful because it avoids the need for householders to take further action to start a new measurement in the case of an equivocal result from the 14-day measurement, since the 3-month measurement is already under way.

We would like to take the opportunity to point out an error in equation (1) of our paper. This should read:

$$\text{Annual mean radon concentration} = (\mathrm{C} - 4) \times (1/[1.645 - 0.063t]) + 4 \qquad (1)$$

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Yours sincerely,

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Comments on 'Impact of tritium around EDF nuclear power plants'

Dear Sir

We read with interest the paper of Le Guen (2009). The conclusions of Le Guen (2009) in relation to environmental transport and biological incorporation are very much in line with those of recent reviews by the Advisory Group on Ionising Radiation (AGIR) of the UK Health Protection Agency (AGIR 2007) and a related open literature publication (Little and Lambert 2008). Le Guen (2009) remarked on the meta-analysis conducted by Little and Lambert (2008), and implicitly also the recent review by the AGIR (2007), that 'the method used by these authors to ascertain [relative biological effectiveness (RBE)] may be criticised, especially concerning the method of calculation and of selecting the studies used in the calculation. The RBE of tritium depends on its location in cells. If tritium is incorporated in DNA precursors (e.g. thymidine, deoxycytidine, etc), it can deliver doses to the DNA that are more substantial than if it is located outside a cell nucleus, as is the case after incorporation of HTO. The strategy is therefore to define the RBE then the weighting factors for these different cases.'

Implicit in this statement is that studies involving tritiated thymidine (^{3}HTdR) should be considered separately from those involving tritiated water (HTO), and that the RBE for the former should be higher than the latter. There were only two studies with ^{3}HTdR that met our quality control criteria and were included in the review (AGIR 2007, Little and Lambert 2008), namely those of Lambert (1969) and Carr and Nolan (1979); both studies assessed the effects of ^{3}HTdR and HTO in relation to reference (X or γ) irradiation. Lambert (1969) assessed spermatogonial survival in DBA2 male mice injected at the age of 10–12 weeks with HTO or ^{3}HTdR and in a reference group exposed to 200 kVp x-rays. Lambert (1969) ascertained an RBE of 1.3–1.6 for ^{3}HTdR, or 2.3–2.4 for HTO (Little and Lambert 2008). Carr and Nolan (1979) assessed testis weight loss in male CBA mice injected intraperitoneally with 0.037–0.74 MBq/gram body mass ^{3}HTdR or 0.37–1.5 MBq/gram body mass HTO at about 100 days of age, and a reference group exposed to chronically delivered ^{60}Co γ-rays given at a decreasing dose rate matching the dose rate from HTO (tritium simulator). They ascertained an RBE of 2.07 (95% CI 1.58, 2.56) for ^{3}HTdR, or 1.43 (95% CI 1.06, 1.80) for HTO (Little and Lambert 2008).

These data do not suggest a consistent pattern of variation of RBE by type of tritium (^{3}HTdR vs HTO) used—in particular the RBE for ^{3}HTdR is not consistently higher than that of HTO. Taken together with our response (Little and Lambert 2009) to comments made by Paquet and Métivier (2009) in the same issue, we therefore see no reason to modify our methods of analysis or conclusions (AGIR 2007, Little and Lambert 2008).

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Yours sincerely,

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Reply to "Comments on 'Impact of tritium around EDF nuclear power plants'"

Dear Sir

I would like to express my appreciation for the insights provided by Little and Lambert into their highly informative publication on retrospective research (Little and Lambert 2008). The only point of divergence between the paper and the authors' of these comments is the relative weight of the results of studies concerning tritiated thymidine when calculating RBE. In their comments, Little and Lambert go back over the two studies selected for their review and included in the AGIR 2007 report (AGIR 2007). A notable point is that both these relatively old studies concern the same organ, i.e. the testicle, and practically the same tissue, responsible for gametogenesis.

The tissue in question is a fast-regenerating tissue where numerous cells constantly proliferate. It is therefore very tricky to extend results obtained using this tissue to all other tissues of an organism, and in particular to more slowly-regenerating tissues. Indeed, inside the proliferating cells, tritiated thymidine will be directly incorporated into DNA during replication. In-situ damage to DNA will therefore be substantial and confined to the latter.

Tritium in the form of tritiated water propagates in all cells, regardless of their replicative status. All cells will then build up damage in all compartments (including the nucleus). It is therefore hard to imagine a comparable effect between HTO and OBT (h^3-thymidine) in all tissues except some fast-regenerating tissues like the testicle.

It was in an attempt to answer this type of question that we decided, 3 years ago, to support research into tritium (Saintigny *et al* 2008) and to resume studies by using tritium in various forms, i.e. tritiated water (HTO) and tritiated thymidine ^{3}HDTR. For example, research not as yet published and currently being conducted in Yannick Saintigny's laboratory (CEA, France) is showing that the contamination of proliferating cells with HTO or h^3-thymidine does not produce the same biological effects on hematopoiesis.

While Little and Lambert's results and conclusions should not be called into question *per se*, we feel that their extension to the entire organism with a view to defining a total RBE is still a tricky matter.

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Yours sincerely,

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Comments on 'Are the risks from tritium exposures being underestimated?'

Dear Sir

We read with interest the paper of Paquet and Métivier (2009). The main conclusions are very much in line with those of recent reviews by the Advisory Group on Ionising Radiation of the UK Health Protection Agency (AGIR 2007) and two related open literature publications (Little and Lambert 2008, Little and Wakeford 2008). Paquet and Métivier (2009) remarked on the meta-analysis conducted by Little and Lambert (2008) (incorporated also in AGIR (2007)) that 'the method used by these authors to define a standard RBE may lay itself open to criticism, particularly as regards the calculation method and the selection of studies used in this calculation. In fact, the ICRP—in its latest publication—preferred to use all published data as a basis, and to estimate the range of predominant RBEs. It concluded that the majority of RBEs, all effects combined, range between 1 and 3 with regard to gamma rays and between 1 and 1.5 with regard to x-rays (ICRP 2007).'

For certain of the experimental studies, in particular those of Gragtmans *et al* (1984), Matsuda *et al* (1986), Zhou *et al* (1986), Satow *et al* (1989), Kamiguchi *et al* (1990a, b), Tanaka *et al* (1994), Johnson *et al* (1995) and Kozlowski *et al* (2001), where the original statistical analysis was suboptimal, or in which the relevant quantity, RBE^{max}, was not estimated, Little and Lambert (2008) attempted re-analysis; for some studies (Gragtmans *et al* (1984), Johnson *et al* (1995)), when the re-analysed results were close to the original estimates the original estimates were employed for the purposes of the meta-analysis. We judge that to do as we did was better than to use the original analysis, which was in many cases suboptimal, for example using the wrong error structure (e.g., assuming normal rather than binomial or Poisson errors), which would have yielded the wrong uncertainty range. The method used by Little and Lambert (2008) to aggregate risks, the best linear unbiased estimator (BLUE), is a standard statistical technique, with well known optimality properties (Mood *et al* 1974). In particular, among linear unbiased combinations of estimators it has the lowest variance (Mood *et al* 1974).

The implicit preference of Paquet and Métivier (2009) for considering all studies without regard to experimental quality (which was not in fact what ICRP (2007) did) we regard as

scientifically unjustified. The main selection criteria for our meta-analysis were that the report had to have concurrent X- or γ-irradiated reference group, and that estimates of RBE^{max} be given (or computable from the published data) together with uncertainties. The dangers of using non-concurrent controls are well known—it was judged that inclusion of studies with non-concurrent controls in the meta-analysis would lead to possible bias. As above, we gave priority to use of an inverse-variance weighted (BLUE) approach to combine estimates and uncertainties from individual studies in developing pooled estimates of RBE^{max}. The reason for doing this was to obtain statistical uncertainties in aggregate estimates. We took the view that a parameter estimate without an associated estimate of uncertainty is of little use, and in particular cannot be used to derive an aggregate measure of RBE^{max} and its uncertainty.

In summary, whilst we do not substantially differ from the conclusions of Paquet and Métivier (2009) we judge that the techniques of study selection, and in some cases re-analysis, performed by AGIR (2007) and Little and Lambert (2008) are fully justified.

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Yours sincerely,

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Comment on "Response to 'More on the risk of cancer among nuclear workers'"

Dear Sir

In the June issue of this journal, Professor Simmons (Simmons 2009) responded to an editorial published in the previous issue (Wakeford 2009). This editorial was prompted by the publication in the *British Journal of Cancer* earlier this year of the 3rd analysis of the National Registry for Radiation Workers (NRRW) (Muirhead *et al* 2009). I shall not address Professor Simmons' comments on the more general points made in the editorial. However, I would like to respond to his comments that relate specifically to the NRRW analysis.

First, Professor Simmons queries the existence of a 'healthy worker effect' (HWE) in the NRRW, based on findings for radiologists. It is hard to think why the evidence for or against a HWE in radiologists would affect the interpretation of findings for the NRRW, which includes very few workers from the medical sector. Standardised mortality ratios (SMRs) below 100% have been observed in various occupational groups, including workers in non-nuclear sectors (Fox and Collier 1976) and even among non-radiation workers employed in the nuclear sector (e.g. Atkinson *et al* 2004). Furthermore, SMRs that are statistically significantly less than 100 were seen in the NRRW not only for cancer but also for various non-malignant diseases and for the category of all accidents and violence (Muirhead *et al* 2009). Consequently, it is very clear that there is a HWE in the NRRW.

Secondly, in discussing the NRRW analysis of cancer risk in relation to external radiation dose (Muirhead *et al* 2009), Professor Simmons comments on the relatively small number of data points that are statistically significantly greater than a relative risk of 1. However, it should be borne in mind that as data are divided more finely, the statistical precision of individual data points will be reduced. Our objective was not to analyse individual data points, but rather to assess the evidence for any trends in risk with dose in the NRRW and to see whether this was consistent with trends estimated from the Japanese A-bomb survivors. Not only did we find statistically significant trends with dose in both mortality and incidence for non-CLL leukaemia and for cancers other than leukaemia (with or without lung and pleural cancers), but also these trends were highly consistent with the trends estimated at low doses from the A-bomb study. Thus our findings do strengthen the evidence for raised cancer risks associated with occupational radiation exposures.

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Yours sincerely,

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Comment on 'Mammography—oncogenecity at low doses'

Dear Sir

We read with considerable interest the paper by Heyes *et al* entitled 'Mammography—oncogenecity at low doses' recently published in your journal [1].

In their paper, the Heyes *et al* assert that 'evidence highlighting the increase in relative biological effectiveness (RBE) of mammography x-rays to a range of x-ray energies implies that the risks of radiation-induced breast cancers for mammography x-rays are potentially underestimated by a factor of four.' They then extrapolate their alarming conclusion by stating 'the risk/benefit analysis (of the UK NHS breast screening programme), however, implies the need for caution for women screened under the age of 50, and particularly for those with a family history (and therefore a likely genetic susceptibility) of breast cancer.'

The authors do note that there is potentially some uncertainty in their conclusion by acknowledging that 'recent low dose in vitro data have indicated a potential suppressive effect at very low dose rates and doses.' However, they then apparently discount the uncertainty and this suppressive effect by stating that 'whilst mammography is a low dose exposure, it is not a low dose rate examination, and protraction of dose should not be confused with fractionation.'

In this letter, we wish to point out some data, not noted by the authors, that calls into question their conclusions. The suppressive effect to which the authors refer is the data of Azzam *et al* [2] and the data of Redpath *et al* [3–5] showing that low doses of gamma radiation or x-rays reduce the neoplastic transformation frequencies of a mouse cell system (C3H 10T1/2) and a human hybrid cell system (CGL1) to values below that of their spontaneous frequencies. This latter system was the same cell system used by Heyes *et al* [1] to determine their quoted RBE values. Of particular importance to the question at hand (and noted by the authors) is data showing that this suppressive effect is also seen with low doses of mammographic energy x-rays [6]. Like the study of Heyes *et al* [7], these experiments were carried out at high dose-rate as were the experiments with fluoroscopy energy x-rays [5]. The earlier studies of Azzam *et al* [2] and Redpath *et al* [3, 4] used low dose-rate for the low dose exposures. Subsequent studies at much lower dose-rates [8, 9] also show a suppressive effect at low doses. In summary, the collective experience is that suppression of neoplastic transformation in vitro by low doses (<100 mGy) occurs over a wide range of dose rates (0.1–>1000 mGy/min). It is perhaps important to note that such protective effects of low doses of radiation have apparently

been tightly conserved throughout evolutionary history [10]. Recently the nature of the various protective mechanisms induced by low doses, and their influence on radiation risk predictions and outcomes, has been reviewed [11].

In their paper, the authors further elaborate on the reason for their dismissal of these apparently ubiquitous, protective cellular responses. They '...suggest that the J-shaped model of transformation suppression at low doses may be compromised by this significantly higher background transformation rate, and that the observations of Ko *et al* [6] should be confirmed under experimental conditions in which the spontaneous transformation frequency is much lower before such models are adopted for radiological protection purposes.'

Apparently the authors are unaware that Redpath and Elmore have considered the impact of background transformation rate on the shape of the dose response curve [12]. In that publication, they combined all their data for low-LET radiation sources, even though, as they acknowledge, the data are for radiation sources of different energy that potentially have different biological effectiveness. Redpath and Elmore pointed out that 'the experiments were performed over a period of years using different batches of serum, and since serum batch is well known to influence background frequency, this combination had to be done for two groups separated by level ('low' and 'high') of spontaneous background frequencies.' Even though the spontaneous background frequency of transformation varied by more than 2-fold in the 'low' and 'high' cases, transformation frequency was clearly suppressed in both instances, at doses <100 mGy. Indeed, the mean of the 'low' values was $3.10 \pm 0.2 \times 10^{-5}$, a value essentially the same as that of $2.8 \pm 0.4 \times 10^{-5}$ seen by Heyes *et al* [7]. This analysis contradicts the current suggestion of Heyes *et al* [1] that high spontaneous transformation frequency compromises the general conclusion that low doses suppress rather than increase risk.

We would additionally point out that these protective effects of low doses, and dose thresholds for harm, are not confined to cells in culture, but have been repeatedly observed in cancer studies in animals [13, 14]. Additionally, those observations have been repeated in mice that were cancer prone for genetic reasons [15, 16], a point bearing directly on the authors special concern for 'those with a family history (and therefore a likely genetic susceptibility) of breast cancer.'

In summary, for the reasons stated, we believe that the existing data do not support the somewhat alarming conclusions of Heyes *et al* [1], not withstanding apparent RBE increases for mammographic x-rays seen at doses higher than 200 mGy.

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Yours sincerely,

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