The Special Characteristics of Alpha-Particle Irradiation and their Implications for Radiation Protection Dosimetry

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External Low LET Radiation

When organs and tissues are irradiated by external, ionising, low-LET electromagnetic radiation (gamma-rays and X-rays) a relatively uniform deposition of energy in tissues within the beam results. For most homogenous tissues and organs, all irradiated cells receive a similar radiation dose. This uniformity resulting from randomly distributed ionisations throughout the volume of the cell. It follows, that within such tissues, all cells have the potential to be similarly damaged. However, at low radiation doses, the level of damage sustained will be unlikely to result in cell death and most of that produced will be subsequently repaired. This is a function of the lower number of ionisations and their diffuse distribution within the cell - with no special concentrations at radiation-sensitive sites within the cell nucleus. Nevertheless, some cellular damage may remain and such damage when present in the target cells for the late effects of radiation - commonly regarded as undifferentiated stem cells - may later result in tumours. However, under the conditions of external low-LET irradiation the frequency of any late effects, induced by the radiation, will not be influenced by the

position of target cells within tissues and organs, since all cells receive a similar radiation dose. It follows, that for this type of radiation the energy deposition per unit mass of tissue, i.e., the average absorbed dose, is biologically meaningful - with respect to the prediction of the frequency of biological damage and late effects.

For the purposes of radiological protection it is assumed that, for acute, low-LET irradiations, the frequency of late effects is a linear function of the average absorbed dose received by tissues [1] - i.e., a linear dose-response relationship. Similarly, under conditions of chronic irradiation a linear dose response is assumed, but the predicted effects are discounted, to allow for the greater ability of cells to repair damage produced at a slow rate, than to repair the same total amount of damage produced at a fast rate [2]. However, radiobiological studies have shown that linear dose-response relationships, at any dose rate, are not inevitable and either curvilinear responses or sigmoid responses are possible - or even common. Such non-linear responses are interpreted as resulting from a smaller than expected effect - due to the ability of cells to repair low levels of damage with low doses of radiation and a smaller effect at very high doses, due to cell killing.

The effect of these, or similar, processes on the shape of dose-response curves has been demonstrated by Major [3] who measured the frequency of myeloid leukaemia in CBA/H mice following acute whole-body irradiation with external gamma-rays. Both a low dose shoulder, where the measured response, per unit of radiation, was lower than expected and a reduced effectiveness at high radiation doses were clearly seen. Indeed at the very highest doses employed the frequency of leukaemia returned to unirradiated-control levels. An unusual feature of this study is that the range of radiation doses employed was sufficiently large so as to reveal the shape of the complete dose-response curve. In most other studies and investigations this has either not been done or was impossible - due to competing cytotoxic effects in other tissues. Consequently, only parts of the dose-response curves have been revealed and the shape

of these will approach linearity as the fraction of the whole curve revealed decreases - even where the underlying dose-response is curvilinear or sigmoidal.

A consequence of cell killing at high radiation doses is that high dose, low-LET radiation is used by radiotherapists to treat cancer. Accordingly, only for the mid-range of doses, where the induced damage saturates repair mechanisms, but where cell killing is less likely, are linear responses expected. This is true both for the effects seen following the irradiation of whole animals and for those observed within *in vitro* cell transformation systems [4]. It follows, that many current predictions of the effects of low dose, low-LET irradiations, based on extrapolations of risk determined from the epidemiological studies of radiotherapy patients exposed to high doses of radiation, are likely to under-predict the frequency of late effects. Such variations can be seen with regard to the low-LET-derived risk-estimates for leukaemia, which are higher when derived from lower dose irradiation (e.g., received following the bombing of Hiroshima and Nagasaki) and are lower for high dose exposures (e.g., received as a consequence of the treatment of ankylosing spodylitics with X-rays). It may be concluded that even for exposures to external low-LET radiation some risk estimates used for the prediction of the consequences of irradiation are insecure.

Internal Low LET Radiation

The situation for other types of low-LET radiation including the irradiation of organs and tissues by internally deposited gamma- and beta-emitting radionuclides is likely to be more complex. Certainly, this is true for low energy beta-emitting radionuclides such as tritium (^{3}H) and carbon-14. For in such cases only those few cells located within the range of the emitted beta-particles will be irradiated and where the radionuclide is heterogeneously distributed many cells, including target cells, may be located either too remotely from the radionuclide to receive a radiation dose or so close as to receive a much greater than average dose. Under these conditions a knowledge of the relative distributions of the, often poorly defined, target cell

populations and the radionuclide is essential - in order to calculate the radiation dose received by such cells and to predict the frequency of late effects, from risk data derived from our knowledge of the toxicity of external irradiation. Similarly, a knowledge of risk resulting from intakes of radionuclides with low-LET emissions cannot easily be extrapolated back, to derive risk estimates for the uniform external radiation situation. It follows, that under these circumstances, the concept of average organ absorbed dose is likely to be inappropriate for the prediction of consequences. This will be particularly true either where a radionuclide is deposited within highly heterogeneous organs - such as the skeleton and the testes (where the radionuclide may be specifically concentrated / excluded by a target cell) or where a radionuclide is deposited in close association with chromosomes within cell nuclei. Nevertheless, in a few circumstances where high-energy beta-particles or electromagnetic radiations are emitted by deposited radionuclides then these considerations will be less important because of the long range of the emissions. However, even in these cases - where the radiation doses delivered are more homogeneous - mathematical models are required to calculate the dose received by target cells [5,6].

In other respects, the consequences of irradiation by incorporated, low-LET radiation-emitting radionuclides will be similar to the external radiation situation given that the density of ionisations within a cell is function of the LET of the emission and is independent of its source. Many curvilinear and sigmoid dose responses are thus expected. For example, non-linear dose-response curves have been demonstrated for a wide variety of tumours following the administration of beta-emitting radionuclides. Examples include osteosarcoma incidence in mice [7] and dogs [8] following protracted intakes of strontium-90 and in rats injected with both this isotope and cerium-144 [9].

High LET Alpha Radiation

In contrast to low-LET electromagnetic radiation, alpha-radiation is produced by a discrete particle - the alpha-particle - and is a high-LET radiation. Alpha-particles comprise a helium nucleus with an "atomic" mass of 4. They lack orbital electrons, consequently carry a charge of 2+ and are emitted, at high energies/velocities (typically 2 - 8 MeV) during the decay of the nucleus of some heavy isotopes, including plutonium-239 and polonium-210. Owing to their high mass and charge alpha-particles have a limited range in organs and tissues. This range, typically 20 - 60 μm, is commonly too short to penetrate the skin so most alpha-particle sources present little external radiation hazard. Also, within tissues only those cells closest to deposits of alpha-emitting radionuclides will be irradiated and at most dose levels, and for most tissues, the irradiated tissue will comprise a mixture of irradiated and non-irradiated cells. This is in marked contrast to the situation following external low-LET radiation, where the pattern of tissue / organ irradiation, within the radiation beam, is rather uniform. Also, whereas for low doses of low-LET radiations, of all types, the density of ionisations within individual cells will be low, those cells traversed by alpha-particles are intensely irradiated along the track of the particle - the particle depositing typically about 100 keV μm^{-1} of track within the irradiated cell. Therefore, it may be expected that cells hit by alpha-particles, particularly those in which the alpha-particle-track traverses the cell nucleus, will sustain substantial damage and that most cell types will be unable to repair the level of damage produced - macrophages seem to be an exception. It follows, that even at low average organ doses alpha-irradiation may result in significant levels of cell death. Again this has not been reported to occur at similar levels of organ irradiation by low-LET radiations.

Relative Toxicities of Low-LET and Alpha-Radiation

It follows from the above, that higher levels of biological damage, within small tissue volumes, will be produced by alpha-particles and other high-LET radiation types (e.g., neutrons) than are produced, within large tissue volumes, by similar average tissue doses of low-LET radiation types. To account for this difference in radiation quality

(type) radiation protection systems, to date, have specified a quality factor / dose modifying factor which should be used when predicting the frequency of late effects produced by high-LET radiation. For alpha-radiation the value of this factor was originally set at 10 (quality factor) and then subsequently revised, by ICRP 30 [3], to 20 (radiation weighting factor). This, latter, factor was specified as a general value for application in the calculation of equivalent dose to all tissues, at all radiation dose levels. It was based upon a review of the available biological information, produced under a variety of exposure circumstances and the inspection of the results of traditional calculations of ambient average dose equivalent to tissues and organs [10]. Using such criteria the value of 20 seems reasonable. For example, Griffith *et al* [11] describe a relative risk for proportional hazards, with respect to the production of bone sarcomas in dogs by the beta-emitting isotope strontium-90 and the alpha-emitting isotope plutonium-238, of 54 (based on average skeletal dose) and ratios of 60 - 170 have been described for ^{90}Sr and ^{238}Pu [12] - which are much larger than the ICRP dose modifying factor of 20. However, Hahn *et al* [13] describe a risk ratio of 10 for liver tumours produced in dogs by the beta-emitter cerium-144 and the alpha-emitting, radiographic contrast agent Thorotrast - which is smaller than 20. In other studies relative effectiveness factors of 26 for bone sarcomas in beagles (^{226}Ra vs. ^{90}Sr), 25 for bone sarcomas in mice (^{226}Ra vs. ^{90}Sr) and 30 for lung cancer in dogs (^{239}Pu vs. ^{144}Ce) have been described [14]. Similarly, relative risks of 8 - 50 have been determined for a range of mouse tumours, 19 - 70 for murine lung and mammary tumours, and 15 - 45 for life-shortening [15]. Such variations would seem to justify the ICRP factor as an average value appropriate for use in radiological protection dosimetry, where doses have been calculated as the average to a complete organ or tissue.

Recently, many more attempts have been made to identify the position of radiation-sensitive target cells within organs and tissues (e.g., the skeleton, the gastro-intestinal tract, the respiratory tract) and to specify risk on the basis of the dose received by these. Under these circumstances the ICRP dose modification factor (based, as it is, on data specified in the form of average tissue dose) becomes less useful and perhaps

even inappropriate. For example, the relative risk of 54 identified for bone sarcomas by Griffith *et al.* is easily reduced to about 5, or less, when both the different deposition patterns of the radionuclides and the importance of the bone surfaces as a target tissue for osteosarcoma are accounted for. Similarly, in the case of the liver tumours the reported risk ratio of 10 may be too high because it makes no allowance for the deposition of cerium-144 within possible target cells, but the deposition of Thorotrast within macrophages - which are radio-resistant and not target cells for liver tumours. In addition, the limited human data available, for alpha-particle toxicity, is inconsistent with high risk ratios. For example, the human data for leukaemia following irradiation by radium [16] and Thorotrast suggest low risk ratios of the order of 1 or 2 [17]. It follows, that as doses are specified to increasingly small volumes of tissues, better estimates of the relative risks from high- and low-LET radiations are required if accurate estimates of risk are to be obtained. In practice, however, obtaining such estimates is difficult, since it is almost impossible to design toxicity experiments which control for the confounding effects of the differences in the temporal and spatial distribution of dose that are characteristic of the different radionuclides used to produce irradiation of different types.

Despite the above, attempts to determine the relative effectiveness of alpha- and beta-radiation in producing tumours, under conditions where differences in the spatial and temporal distribution of dose have been minimised, have been recently reported [18]. For these studies either curium-242 (alpha, T½ = 143 days) or calcium-45 (beta, T½ = 143 days) were fused into the matrix of fused-clay spheres (diameter ~ 1.4 μm). About 80 times as much calcium was incorporated into each sphere as curium such that the energy emitted by each sphere, per unit time, was equal. Moreover, the average track length of the ^{45}Ca beta-particle (~45 μm) is not dissimilar to the track length of the ^{242}Cm alpha-particle (~40 μm) in soft tissues. Consequently, when administered to animals the fused clay spheres would be expected to locate within tissues (and, subsequently, become relocated) with patterns determined by the physico-chemical properties of the clay - i.e., independently of the incorporated radionuclide.

Also, when located within tissues the incorporated calcium or curium would irradiate the surrounding tissues, delivering a similar radiation dose, to similar cells and with a similar temporal pattern. The experiment showed that, following the inhalation of labelled particles by CBA/Ca mice, the effectiveness of the alpha-particle radiation, over a range of doses, in producing lung tumours was about 2 times greater than that the effectiveness of the beta-particle irradiation. A similar result is predicted, with respect to the production of leukaemias and liver cancer, following the intravenous injection of the particles (unpublished data). These results are consistent with the limited human data and clearly, the relative effectiveness ratio of low- and high-LET radiations, in producing tumours, may be much lower than indicated by the results of many toxicity studies that have employed average-dose, organ dosimetry and disparate radionuclides.

As implied above, the short range of alpha-particles in tissues, necessitates the use of dosimetric models, similar to those employed for beta-emitters, and a precise understanding of the spatial distribution of radionuclides and target cells for risk estimation. However, the situation is more critical for alpha-emitters given the much lower numbers of tracks for a given level of energy deposited in a tissue. For example, the same level of absorbed dose is delivered by 1 plutonium alpha-track and about 200 tritium beta-tracks. It is axiomatic that under these situations the spatial distribution of ionisations will be more uniform for the latter. Also, the distribution of target cells is poorly understood for most tissues [17] and even less is understood about their life-span and cell kinetics. It follows, that because of: the very heterogeneous dose distribution produced by alpha-particles, with some cells receiving very high doses, but adjacent cells receiving no dose; the uncertainties in radionuclide distribution (particularly as a function of time post radionuclide intake); our lack of knowledge concerning the identification, distribution and cell kinetics of target cells; the radiation dose received by target cells cannot be calculated with confidence. Clearly, if it is the radiation dose received by these cells that is important for risk estimation purposes, our knowledge of the doses that they receive from deposited alpha-emitting

radionuclides is insufficient for dose estimation purposes. Moreover, given the different levels of cellular damage produced by low and high-LET radiations and the insecure alpha-dosimetry it is most unlikely that the extrapolation of risks from external acute, low-LET situations to internal, chronic high-LET situations is scientifically justifiable. Predictions of leukaemia frequency following intakes of plutonium-239, based on risk estimates derived from our experience of the effects of atomic bomb irradiation [19] should, therefore, be either discounted or at least viewed with extreme caution. This is true even after allowance has been made for the probable overestimate of the radiation weighting factor (as described above). Similarly, if target cell dose is important, predictions based even on our experience of the toxicity of other alpha-emitting radionuclides, e.g., radium-226 and thorium-232, are unlikely to be accurate unless the radionuclides are similarly distributed to plutonium-239 - both with respect to time and space.

Dose-Response for Alpha-Emitting Radionuclides

It is important to stress that, for alpha-irradiation, at low to moderate average organ doses, most cells within a given tissue will be un-irradiated, but that those irradiated will receive a similar dose. It follows, that the principal effect of increasing the dose delivered to an organ is to increase the number of cells irradiated, but not to change the dose received by individual cells. Organ dose thus becomes a linear function of the number of cells hit. Under these circumstances it might be expected that the dose received by such cells, their probability of transformation and their ability to repair any induced damage, will be unaffected by the average tissue dose - up to the point where multiple cell hits are likely (which may induce different effects). Similarly, the probability of cell sterilisation will be unaffected by considerations of dose-rate. Linear dose-response curves without threshold are, therefore, expected. Indeed many animal studies and studies using *in vitro* cell systems seem to have confirmed such linearity for a range of effects including some cancers, chromosome damage and cell transformation. Examples include bone sarcoma induction in mice by ^{224}Ra [20] and by

^{239}Pu and ^{226}Ra in dogs [21]. Also, given that all cells hit by an alpha-particle will receive a similar dose and that this is delivered instantaneously, the rate at which dose is delivered to tissues should not effect the ability of cells to repair induced, internal damage. Dose protraction is, therefore, most unlikely to have an effect at the cellular level and where such protraction has been noted [22] to reduce the effectiveness of alpha-radiation in producing late effects this is more logically attributed to either increased time for tissue repair or to a reduction in the probability of multiple cell hits, than to increased time for cell repair.

Despite the above, our experience to date of tumour incidence in man, following exposure to alpha-irradiation, does not always demonstrate / seldom demonstrates the linear dose response predicted [23]. For example, in a population of 820, pre-1930, radium dial painters (mostly women average age 20) followed for 60 years, 46 bone tumours have been observed, but none in the 488 painters receiving average, cumulative, skeletal alpha-doses (largely from deposited radium-226) lower than 10 Gy. Similarly, the frequency of tumours in those that received the highest radiation doses was depressed [24,25]. While the latter may be explained by competitive deaths and by enhanced cell sterilisation effects, due to multiple cell hits, the lack of tumours in the low dose groups is more difficult to explain and does not accord to expectations based on assumptions of dose-response linearity. Indeed it is now widely suggested that an effective dose-threshold exists for radium-alpha-induced bone tumours and a similar threshold could exist for plutonium-induced bone tumours. (N.B. The plutonium threshold would be lower than that for radium because of its deposition near bone surfaces which results in a greater effectiveness in irradiating critical cellular structures within the skeleton [26].) Moreover, it is likely that the threshold for plutonium-239 would be sufficiently high to suggest that osteosarcoma will not be a consequence of environmental and permissible occupational plutonium exposures. This is true even for those workers exposed when the occupational dose limit for plutonium was based on a maximum permissible body burden (MPBB) of 40 nCi (1.5 kBq). Consequently, it is not surprising that, to date, only one osteosarcoma case has

been identified within the hundreds of persons with significant body burdens of occupationally-derived plutonium - an ex-Hanford worker.

From the above, it could be speculated that alpha-induced bone cancer is a special effect which is, perhaps, related in some way to a saturation of the ability of the body to repair tissue, rather than to cell damage. This suggestion is supported both by the observation that the apparent thresholds for osteosarcoma induction and for likely tissue damage (e.g., micro-fractures, cell damage, fibrosis, etc.) are similar (or at least substantially overlap) and by the known relationship between tumour induction and bone growth rate. Indeed, in the case of the radium dial painters, the distribution of induced bone-tumours throughout the skeleton closely mimics the normal distribution of spontaneous tumours within the skeleton which, in turn, are located at sites of high skeletal bone turnover - which might be expected to be particularly prone to disrepair because of their high rate of cell turnover. However, it is far from clear that alpha-induced osteosarcoma is the only special case as it is possible that similar "thresholds" exist for some types of alpha-induced leukaemia. For example, no excess leukaemias have been found in either radium dial painters or radium chemists up to the point where the level of radioactive contamination within the skeleton of such persons was sufficient to cause bone marrow failure and at this point an atypical aleukaemic leukaemia has been observed [27]. Moreover, more typical leukaemias have not been produced in the numbers expected in either the radium-226 dial-painters [16] or in patients given lower doses of radium-224 as a treatment for ankylosing spondylitis [28]. Furthermore, both myeloid leukaemia and liver cancer in Thorotrast patients occur concurrently with substantial tissue damage. Consequently, it could be argued that the irradiation of tissues close to bone surfaces presents little risk until tissue-repair mechanisms fail.

Similarly, the widely accepted concept that the alpha-emitting element, radon (as either ^{222}Rn or ^{220}Rn [commonly referred to as thoron]), induces lung tumours in humans has been based upon the excess of lung tumours observed in underground uranium miners.

Anhang/Appendix R

However, such miners also inhaled a wide variety of other toxic substances such as silica and diesel exhausts and it is far from clear that the tumours were produced as a result of exposure to radon alone. Indeed, Ishikawa *et al.* [29], in a recent study of 359 patients to whom Thorotrast was administered, and who exhaled ^{220}Rn continuously, found little evidence of an excess lung tumour incidence, compared with controls. This is an important finding since the average absorbed dose to the lungs of these patients was within the range received by the uranium miners, where tumours were seen. A similar lack of lung tumours has been noted in the larger German Thorotrast population [30]. Also, there is little evidence to suggest that exposures to environmental radon results in excess lung tumours. Indeed, a study by Blot *et al.* [31] of a large population of Chinese women found no association between radon exposure and lung cancer and the celebrated studies of Cohen [32,33] of 411 US counties showed a statistically significant negative correlation between estimated mean radon exposure and lung cancer for both men and women. Again these results may suggest that exposures to low levels of alpha-radiation, but not very high levels, present little carcinogenic risk - implying the existance of a "practical threshold". These and other studies have been reviewed by Henshaw [34]. It is suggested that the high incidence of lung tumours in uranium miners may be due to a synergistic effect between radon and silica [35] since such a synergy has been demonstrated in rats [36]. Again, silica is a substance associated with significant tissue damage.

Despite the above, it must be recognised that the appearance of tissue damage and some tumour-types, following alpha-irradiation, at similar dose levels may well be coincidental. If so, an alternative explanation is required for non-linearity in dose-response. With respect to bone tumours, Chadwick *et al.*, [37] using model predictions, suggests that the negligibly small incidence of bone tumours at low doses results from an apparent threshold which is a consequence of a quadratic dose effect relationship, where tumour incidence is proportional to exposure squared. He speculates that the apparent threshold would be absent for common cancers. Another explanation has been provided by Raabe [38] who suggests that non-linearity is related

to a dose-dependent increase in the latent period between radiation insult and the appearance of tumours, such that at low doses the latent period exceeds life-span. He suggests that it is not that the radiation is less effective at low dose, but that all the individuals in an exposed population die of other causes before they could develop an induced tumour. The case made by Raabe, on the basis of his observations of bone tumours in dogs, is compelling and, if latency lengthening is different in different species, this effect could also provide an explanation why linearity of dose response for a specific tumour is evident in some animal models, but absent in others (e.g., man).

Finally, exciting studies have been undertaken, recently, using a charged particle micro-beam [39], which allows the unambiguous irradiation of cells with a single alpha-particle. An early result of these experiments is the observation that, within a population of cells (fibroblasts), irradiated cells may induce changes in ("prime") adjacent unirradiated cells. The observation of such cell-to-cell communications is an important finding since it suggests that alpha-irradiated tissues should no longer be assumed to comprise only distinct and separate populations of irradiated and un-irradiated cells. Within the extra population of "primed cells", cell and tissue repair mechanisms may be stimulated such that subsequent mutagenic insults have a smaller than expected effect. If present, such stimulated repair/resistance to damage has the potential to modify dose response relationships - perhaps to the point where linearity is no longer present.

Despite the above, even in the absence of thresholds, sufficient differences, as detailed above, exist between low-LET ionising, electromagnetic radiations and high-LET, alpha-radiations to suggest that absorbed dose at the cellular and tissue levels is far from an unifying concept. Differences have been identified: in the distribution pattern of energy deposition at all levels - from the sub-cellular level to the organ level; in the likely ability of cells to repair damage; in the shape of dose-response relationships; in the likely effects of dose protraction; in the average dose received by irradiated cells. It is concluded that these differences are such that these radiation types be regarded as

qualitatively and quantitatively different and that low-LET risk estimates should not be extrapolated to high-LET situations e.g., for leukaemia. Moreover, taken together, the points above suggest that it is reasonable to conclude that the present intake limits for plutonium, and other alpha-emitting radionuclides, could not be justified on the basis of human experience - osteosarcoma, lung cancer and leukaemia being the predicted major effects of most such intakes. Clearly, more work needs to be undertaken to resolve the outstanding dosimetry issues including the presence / absence of dose-effect thresholds.

A Beneficial Effect of Low Dose Alpha-Radiation?

An intriguing consequence of the acceptance of possible real / practical thresholds (or even curvi-linear / sigmoidal dose-responses) for alpha-induced tumours is the possibility that, at lower doses, this type of radiation may have a beneficial effect by reducing the frequency of tumours produced by other carcinogens. A naive argument might be that at low doses, below those at which alpha-induced tumours are possible / likely, the high killing potential of alpha-particles could destroy cells which had been transformed by a wide variety of other carcinogens. In effect this would amount to a low-dose radiotherapy effect. Until recently, such a suggestion would have been met with the rebuff that at low doses such a small proportion of the total cell population within a tissue would be hit by an alpha-particle that the probability of the sterilisation of a transformed cell would be extremely unlikely. In effect the argument would be that the low-dose radiotherapy effect would be so small that it could be discounted. However, in some situations, such as at the sites of radon daughter deposition in the bronchial tree this might not be true, moreover, the observation that hit cells may stimulate protective responses in adjacent cells, and cells which are close to the irradiated cell, provides a possible mechanism for the amplification of a protective response. Perhaps, such a response could be amplified to the point where it could effectively reduce the response of a target tissue to another carcinogen - without requiring a high probability of cell hits. I would be surprised if such a possibility had

not occurred to the research team operating the charged-particle, micro-beam apparatus and, consequently, look forward to the results of some exciting experiments.

In the absence of the confirmation of a biological mechanism for a low-dose radiotherapy effect one must return to experimental evidence to glean information on its possible existence. Some such evidence does exist. For example, it is possible that a fraction of the healthy worker effect (invoked to explain why some irradiated radiation-worker populations have fewer tumours than the general population - corrected for age and sex) could result from a beneficial effect of low-dose alpha-radiation. In addition, low-dose radiotherapy may be inferred from the results of a number of epidemiological and toxicological studies. The most compelling of these are studies which have been undertaken on lung tumour induction in man and rodents and on life-shortening in NMRI mice.

As previously mentioned, the geographical epidemiological studies of Cohen [32,33] on lung cancer mortality in US. counties as a function of the mean radon concentration in homes indicate a reduction in mortality with increasing radon concentration. (A similar relationship has been claimed for the UK and a large case-control study is currently in progress to examine this possibility.) For men, mortality was reduced from about 42 deaths / 10^4 persons / y at a radon concentration of ~ 1 pCi L^{-1} to about 25 cases at 5.5 pCi L^{-1} and for woman the mortality rate, over the same range of doses was reduced from about 7 deaths / 10^4 persons / y to about 5. Although geographical studies are an ineffective tool for examining the relationships between cause and effect, the results suggest that radon may be depressing the incidence of cigarette-smoke induced lung tumours - since most lung tumours may be attributed to this carcinogen. Such a conclusion would be consistent both with dosimetric calculations of the radiation doses received from radon at lung bifurcations [34] and with results of experiments with animals which have demonstrated apparent antagonism between these carcinogens. It would also be cosistant with the results of the modelling studies of Bartstra [40] which predict that low doses of radon would have a hormetic effect

with regard to lung tumour induction. Similarly, such antagonism has been demonstrated in dogs [41] mice [42] and rats [43]. In the mouse studies, the experimental animals were exposed to ^{239}Pu oxide and / or to cigarette smoke - both by nose-only inhalation. The numbers of tumours found in the animals which received both carcinogens was half that found in the animals that received plutonium alone. The rat studies indicated that the timing and duration of exposures to radon and cigarette smoke are important since when rats were given radon alone, then smoke, no antagonistic effects were found.

Observations concerning mouse lymphoma have been made by Mueller [44]. He showed that in large (300) groups of mice, those that received a single injection of ^{224}Ra (delivering an average skeletal dose of 0.15 Gy) outlived untreated control animals. This was so even though a small number of bone tumours were induced in the radium-exposed animals. This study also illustrates the possibility that, while the incidence of a particular tumour may be reduced by exposure to high-LET radiation - so as to prolong life-span, the incidence of other tumours may be increased. The occurrence of such tumours will offset the advantages gained by reductions in prime tumour type. In this way, while it would seem that the incidence of lung tumours may be reduced following exposure to low levels of radon, the incidence of others such as leukaemia and melanoma may be increased [34].

More work, specifically designed to examine hormetic (beneficial) effects is clearly needed before a definitive judgement on their importance, or even existence, can be made. Nevertheless, sufficient evidence exists to seriously question another aspect of conventional radiological protection procedures and risk estimation processes.

Conclusion

It can be concluded that for the purposes of risk estimation in radiological protection current dosimetric procedures and risk estimation processes, for high-LET alpha

radiation, are less than ideal and that for a variety of reasons they are likely to overestimate the risk of some important radiation-induced tumours including osteosarcoma, leukaemia and lung cancer. Furthermore, given the high cost of the remediation of dwellings with high radon levels and the negative economic effects of the high perceived risk associated with the release of anthropogenic, alpha-emitting radionuclides to the environment, there exists an economic (as well as scientific) imperative for more work to be undertaken in order to derive a secure dosimetry and risk estimation process for alpha-particles

References

1. UNSCEAR. Sources, Risks and Effects of Ionising Radiation. 1993 Report to the General Assembly with annexes, United Nations (1993).

2. Stather, J. W. The use of epidemiological and experimental data in assessing health effects from internally deposited radionuclides. In: Health Effects of Internally Deposited Radionuclides. Eds., van Kaick, G., Karaoglou, A and Kellerer, A. M. Singapore: World Scientific, 407 - 419 (1995).

3. Major, I. R. Induction of myeloid leukaemia by whole-body single exposure of CBA male mice to X-rays. Brit. J. Cancer, 40, 903 913 (1979).

4. Upton, A. C. Unresolved questions on the risks from high linear energy transfer radiation. In: Risks from Radium and Thorotrast. Eds: Taylor, D. M., Mays, C. W., Gerber, G. B. and Thomas, R. G. BIR Report 21, London: British Institute of Radiology, pp 169 - 173 (1989).

5. ICRP. ICRP Publication 30, Annals of ICRP, 2, 3 - 4, Oxford: Pergamon Press (1979).

6. ICRP. ICRP Publication 56, Annals of ICRP, 20, 2, Oxford: Pergamon Press (1989).

7. McClellen, R. O. and Jones, R. K. ^{90}Sr-Iinduced neoplasia: a selective review. In: Delayed Effects of Bone-Seeking Radionuclides. Eds. Mays, C. W., Jee, W. S. S. and Lloyd, E. Salt Lake City: University of Utah Press. pp 293 - 323 (1969).

8. Raabe, O. G., Book, S. A. and Parks, N. J. Life-time bone cancer dose-response relationships in beagles and people from skeletal burdens of 226Ra and 90Sr. Health Phys., 44 (suppl. 1), 33 - 48 (1983).

9. Moskalev, Y. I., Streltsova, V. N. and Buldakov, L. A. Late effects of radionuclide damage. In: Delayed Effects of Bone-Seeking Radionuclides. Eds. Mays, C. W., Jee, W. S. S. and Lloyd, E. Salt Lake City: University of Utah Press. pp 489 - 509 (1969).

10. Muirhead, C. R., Cox, R. and Stather, J. W. Estimate of late radiation risks to the UK population. Documents of NRPB, Vol. 4, No. 4 (1993).

11. Griffith, W. C., Boecker, B. B., Gillet, N. A., Guilmette, R. A., Hahn, F. F. and Muggenburg, B. A. Joint bone biology workshop. Ed. Tomich, P. A., USDOE Report No. UCD-472-136 (1991).

12. Boecker, B. B., Griffith, W. C., Hahn, F. F., Nikula, K. J., Lundgren, D. L. and Muggenburg, B. A. Life-time risks from internally deposited, beta-emitting radionuclides. Radioprotection, 32, C1, 343 - 350 (1997).

13. Hahn, F. F., Muggenburg, B. A. and Boecker, B. B. Hepatic lessions induced by chronic beta irradiation from ^{144}Ce in dogs. In: Health Effects of Internally

Anhang/Appendix R

Deposited Radionuclides. Eds., van Kaick, G., Karaoglou, A and Kellerer, A. M. Singapore: World Scientific, 337 - 340 (1995).

14.NAS. Health risks of radon and other internally deposited alpha-emitters. BEIR IV Report. National Academy of Sciences, Washington DC: National Academy Press (1988).

15.NCRP. The relative biological effectiveness of radiations of different quality. NCRP Report No. 104, Bathesda MD: National Council on Radiation Protection and Measurements. (1990).

16.Spiers, F. W., Lucas, H. F., Rundo, J. and Anast, G. A. Leukaemia incidence in the US. Dial workers. Health Phys., 44, Supl. 1, 65 - 72 (1983).

17.Priest, N. D. Risk estimates for high-LET α-irradiation of skeletal tissues: problems with current methods? In: Health Effects of Internally Deposited Radionuclides. Eds., van Kaick, G., Karaoglou, A and Kellerer, A. M. Singapore: World Scientific, 423 - 429 (1995).

18.Kellington, J. P., Eldred, T. M., Ambrose, K., Brooks, P. N. and Priest, N. D., Relative biological effects of inhaled alpha and beta emitting particles deposited in the lung. In: Proceedings of Conference: Health Effects of Low Dose Radiation: Challenges of the 21st Century. May 1997, London: Thomas Telford Publishers, pp 44 -51 (1997).

19.Preston, D. L. and Pierce, D. A., Radiation Effects Research Foundation. Hiroshima: RERF TR 0-87 (1987).

20.Mays, C. W., Lloyd, R. D., Taylor, G. N. and Jones, C. W. Bone sarcoma induction by radium 224 in C57BL/Do mice. In: Risks from Radium and

Thorotrast. Eds: Taylor, D. M., Mays, C. W., Gerber, G. B. and Thomas, R. G. BIR Report 21, London: British Institute of Radiology, pp 40 - 54 (1989).

21. Boecker, B. B., Griffith, W. C., Guilmette, R. A., Hahn, F. F. and Muggenburg, B. A. The role of laboratory animals in studying the late-occuring effects of radionuclides deposited in the liver and skeleton. In: Health Effects of Internally Deposited Radionuclides. Eds., van Kaick, G., Karaoglou, A and Kellerer, A. M. Singapore: World Scientific, 287 - 297 (1995).

22. Mueller, W. A., Luz, A. and Linzer, U. Influence of dose rate and irradiation period on the induction of bone tumours after low radium-224 doses in mice. In: Health Effects of Internally Deposited Radionuclides. Eds., van Kaick, G., Karaoglou, A and Kellerer, A. M. Singapore: World Scientific, 307 - 313 (1995).

23. BEIR IV. Health Risks of Radon and Other Internally Deposited Alpha-Emitters. Washington DC: National Academy Press (1988).

24. Rowland, R. E. Bone sarcoma in humans induced by radium: a threshold response? Radioprotection, 32, C1, 331 - 338 (1997).

25. Rowland, R. E. Dose-response relationships for female radium dial workers: anew look. In: Health Effects of Internally Deposited Radionuclides. Eds., van Kaick, G., Karaoglou, A and Kellerer, A. M. Singapore: World Scientific, 135 - 143 (1995).

26. Thorne, M. C. Aspects of the dosimetry of alpha-emitting radionuclides in bone with particular emphasis on Ra-226 and Pu-239. Phys. Med. Biol., 22, 36 - 46 (1977).

27. Mole, R. H. Alpha-particle irradiation and human leukaemia. In: Risks from Radium and Thorotrast. Eds: Taylor, D. M., Mays, C. W., Gerber, G. B. and

Thomas R.G., BIR Report 21. London: British Institute of Radiology. pp.153 - 158 (1985)

28.Wick, R. R., Chemelevsky, D. and Gossner, W. Current status of the follow-up of radium-224 treated ankylosing spondylitis patients. In: Health Effects of Internally Deposited Radionuclides: Emphasis on radium and thorium. Eds: van Kaick, G., Karaoglou, A. and Kellerer, A. M. Singapore: World Scientific. pp 165 - 169 (1995).

29.Ishikawa, Y., Mori, T., Kato, Y., Tsuchiya, E., Machinami, R., Sugano, H. and Kitagawa, T. Lung cancers associated with Thorotrast exposure: High incidence of small cell carcinoma and implications for estimation of radon risk. Int. J. Cancer, 52, 570 - 574 (1992).

30.Hoffman, W., Johnson, J. R. and Freedman, N. Lung dosimetry of Thorotrast patients. Health Phys., 59, 409 - 419 (1990).

31.Blot, W. J., Zu, Z-Y., Boice, J. D., Zhao, D-Z., Stone, B. J., Sun, J., Jing, L-B. and Fraumeni, J. F. J. Nat. Cancer Inst., 82, 1025 - 1030 (1990).

32.Cohen, B. L. Test of the linear no-threshold theory of radiation carcinogenesis for inhaled radon decay products. Health Phys., 68, 157 - 174 (1995).

33.Cohen, B. L. Chapter 24. In: Environmental Radon: Occurrence, Control and Health Hazards. Eds: Majumbar, S. K., Schmalz, R. E. and Miller, E. W., PA: Pennsylvania Academy of Science. (1991).

34.Henshaw, D. L. Radon exposure in the home: its occurrence and possible health effects. Contemporary Physics, 34, 31 - 48 (1993).

35.Priest, N. D., Brooks, P., Eldred, T., Purbrick, W. and Kellington, J. P. European Society for Radiation Biology, Erfurt, October (1992).

36.Speithoff, A., Wesch, H., Wegener, K. and Klimisch, H-J. The effects of Thorotrast and quartz on the indiction of lung tumours in rats. Health Phys., 63, 101 - 110 (1992).

37.Chadwick, K. H., Leenhouts, H. P., Laheij, G. M. H. and Venema, L. B. The implications of a two-mutation carcinogenesis model for internal emitters. In: Health Effects of Internally Deposited Radionuclides. Eds., van Kaick, G., Karaoglou, A and Kellerer, A. M. Singapore: World Scientific, 353 - 360.(1995).

38.Raabe, O. G., Culbertson, M. R., White, R. G., Parks, N. J., Spangler, W. L. and Samuels, S. J. Life-time radiation effects in beagles injected with ^{226}Ra as young adults. In: Health Effects of Internally Deposited Radionuclides. Eds., van Kaick, G., Karaoglou, A and Kellerer, A. M. Singapore: World Scientific, 313 - 318 (1995).

39.Folkard, M., Prise, A. M., Malcolmson, A. M. and Michael, B. D. Evaluation of the risks associated with single particle effects using a charged particle microbeam. Abstract of presentation at UK Department of Health Research Seminar, NRPB, Chilton, UK. 11^{th} - 12^{th} December (1997).

40.Bartstra, R. W. Prediction of hormesis in radon carcinogenesis. Radioprotection, 32, C!, 418 (1997).

41.Cross, F. T. Radon inhalation studies in animals - Radon literature survey series. Report DOE / ER-0396 (1988).

42.Priest, N. D., Moores, S. R., Black, A., Talbot, R. and Morgan, A. The combined effects of plutonium and cigarette smoke on the production of lung tumours. In: Radiation Protection Theory and Practice, Ed. Goldfinch, E. P. Bristol: Institute of Physics, pp 433 - 437 (1989).

43.Chameaud, J. R., Perraud, R., Chretien, J., Masse, R. and Lafuma, J. Combined effects of inhalation of radon daughter products and tobacco smoke. In: Pulmonary Toxicology of Respirable Particles, Eds. Sander, C. L., Cross, F. T., Dagle, G. E. and Mahaffey, J. A., Springfield: National Technical Information Service, CONF-791002, p551 (1980).

44.Mueller, W. A. Incorporated α-emitters: low protracted doses may cause late effects with extremely long latency periods. Radioprotection, 32, C1, 371 - 373 (1997).