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REJ Mitchel

*Atomic Energy of Canada Limited, Chalk River, ON, Canada*

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## CANCER AND LOW DOSE RESPONSES IN VIVO: IMPLICATIONS FOR RADIATION PROTECTION

**R. E. J. Mitchel** □ Radiation Biology and Health Physics Branch, Atomic Energy of Canada Limited, Chalk River, Ontario, K0J1J0, Canada

□ The Linear No Threshold (LNT) hypothesis states that ionizing radiation risk is directly proportional to dose, without a threshold. This hypothesis, along with a number of additional derived or auxiliary concepts such as radiation and tissue type weighting factors, and dose rate reduction factors, are used to calculate radiation risk estimates for humans, and are therefore fundamental for radiation protection practices. This system is based mainly on epidemiological data of cancer risk in human populations exposed to relatively high doses (above 100 mSv), with the results linearly extrapolated back to the low doses typical of current exposures. The system therefore uses dose as a surrogate for risk. There is now a large body of information indicating that, at low doses, the LNT hypothesis, along with most of the derived and auxiliary concepts, is incorrect. The use of dose as a predictor of risk needs to be re-examined and the use of dose limits, as a means of limiting risk needs to be re-evaluated. This re-evaluation could lead to large changes in radiation protection practices.

*Keywords: risk, adaptive response, radiation protection, low dose, cancer*

### 1. THE LNT HYPOTHESIS, RISK PREDICTION AND RADIATION PROTECTION

The linear no-threshold (LNT) hypothesis is the fundamental basis for the prediction of risk from radiation exposure, and forms the basis for radiation protection practices (ICRP 1991). Dose limits for human exposure reflect this assumption that risk is proportional to total dose, without a threshold. However, radiation protection practices also utilize a number of additional concepts, derived from or auxiliary to the hypothesis, to predict the risk of a radiation exposure. The most basic concept presumes that since risk is proportional to dose, then dose (normalized as Sieverts using radiation weighting factors,  $W_R$ ) can be used as a surrogate for risk. Additionally, since each dose is assumed to create some risk, those doses, and hence risks, are treated as additive. Therefore, with the absence of a threshold, risk can only increase with each dose, and this assumption applies to low as well as high doses. Importantly however, radiation protection practices (ICRP 1991) recognize the observation that different tissues respond differently to radiation, and, based only on the tissues actu-

Address correspondence to R. E. J. Mitchel, Radiation Biology and Health Physics Branch, Atomic Energy of Canada Limited, Chalk River, Ontario, K0J1J0, Canada. Phone 613-584-8811 X4721; Fax 613-584-8217; email mitchelr@aecl.ca

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ally exposed, individually contribute different fractions to the total risk of radiation. In practice, different tissue types are assigned tissue weighting factors ( $W_T$ ) that reflect their relative fractional contribution to the total cancer and non-cancer radiation risk. The  $W_T$  for each tissue is held to be constant, independent of dose, since every tissue is assumed to obey a linear no threshold response. Another concept, also derived from observation and not the LNT hypothesis, is an assumed 2-fold reduction in the risk of a high dose/high dose rate exposure, if that exposure is received at low dose or low dose rate (ICRP 1991). Recently, serious concerns have been raised about the appropriateness of many of these assumptions (Tubiana et al. 2005, 2006).

## 2. EPIDEMIOLOGICAL BASIS FOR RADIATION PROTECTION PRACTICES

In the development of the current radiation protection system, the main source of information on radiation-induced human cancer risk has come from epidemiological data on exposed populations. However, these data are mainly from medium to large doses, and for low LET radiation epidemiological studies do not show an increased cancer risk in adult humans below about 100 mSv for an acute exposure (Tubiana et al 2005). A linear extrapolation has therefore been used to estimate the cancer risk at the lower doses relevant to the general population and radiation workers. Uncertainties in dosimetry of epidemiological studies make it more difficult to observe a dose response, which in turn tends to lead to lower risk estimates. Other problems associated with the epidemiological studies include the comparison of the results obtained for different exposure patterns (for example, acute external irradiation versus protracted internal irradiation) and/or for different types of radiation (for example,  $\gamma$  rays versus  $\alpha$  particles) and/or for exposures of mixed LET.

## 3. ADAPTIVE RESPONSE AND CARCINOGENESIS

The term adaptive response refers to biological responses whereby the exposure of cells or animals to a low dose of radiation induces mechanisms that protect the cell or animal against the detrimental effects of other events or agents, including spontaneous events or subsequent radiation exposure (Mitchel 1995). Adaptive responses occur in situations where all cells receive one or more radiation tracks at low dose rate, but also where the dose is too low for all cells to be hit. In the latter instance, the protective effect is amplified by chemical signals sent to other “bystander” cells (Broome et al. 2002; Mitchel 2004). For low LET radiation, the first ionisation track through the cell (a dose of about 1 mGy) appears to produce the maximum increase in DNA repair capacity and protective effects, and further tracks, if delivered at low dose rate, neither increase nor decrease that maximum response (Broome et al. 2002; Ulsh

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et al. 2004). For malignant transformation in human and rodent cells, the protective effect of low doses is dose *independent* for all doses up to about 100 mGy, when given at low dose rate. Above about 300 mGy, these protective effects give way to an increased risk of malignant transformation, suggesting detrimental effects outweigh protective effects at this point (Azzam et al. 1996; Redpath and Antoniono 1998). The (unknown) signal(s) for adaptation can be transmitted through the medium that surrounds the cells. In human cells, there was no difference between gamma rays and tritium beta particles for the induction of the adaptive response (Broome et al. 2002), and low doses of low LET radiation protect against the detrimental effects, including detrimental effects of high LET exposure. At least some types of high LET radiation are also able to induce the adaptive response in mammalian cells (Gajendiran et al. 2001; Iyer and Lehnert 2002).

For low doses to induce an adaptive response, cells or animals require a functional copy of the *TP53* gene, responsible for the control of several processes critical to the risk of carcinogenesis. In animals with full *TP53* function, and in cancer-prone animals with partial *TP53* function a single low, whole body dose of low LET radiation, increased cancer latency and restored a portion of the life that would have been lost due to either spontaneous or radiation-induced cancer in the absence of the low dose (Mitchel et al. 1999; Mitchel et al. 2003; Mitchel et al. 2004; Mitchel 2005). An increase in tumor latency but not frequency, suggests that adaptation to radiation *in vivo* acts primarily by slowing the multi-step process of carcinogenesis.

In *TP53* normal mice, protective effects against radiation-induced cancer occur up to at least 100 mGy (Mitchel et al. 1999). In the cancer prone mice protective effects give way to increased risk between about 10 and 100 mGy (Mitchel et al. 2004). However, different tissues appear to have different thresholds at which protection turns to detriment (Mitchel et al. 2003). The results suggest that protective adaptive responses may predominate at typical public and occupational exposure levels, but that at doses around 100 mGy detrimental effects may overcome the protection. High doses at high dose rates do not induce the protective response, although relatively high total doses received at low dose rates may be effective.

Adaptive responses to low doses (typically 1-100 mGy) have been shown to increase cellular DNA double-strand break repair capacity, reduce the risk of cell death, reduce radiation or chemically-induced chromosomal aberrations and mutations, and reduce spontaneous or radiation-induced malignant transformation *in vitro*. Elevated DNA repair capacity after low dose exposure is a response that has been tightly conserved throughout evolution, appearing in single-cell eukaryotes, simple eukaryotes, insects, plants, amphibians, and mammals including human cells, suggesting that it is a basic response critical to life (Mitchel 2006).

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#### **4. IMPLICATIONS FOR RADIATION PROTECTION**

##### **4.1 Dose additivity**

Cancer is considered to be the most important risk associated with radiation exposure. If the LNT hypothesis is correct, sequential exposures to radiation should increase cancer risk for all types of exposures. However, cell and animal experiments indicate that adaptive responses occur after low dose exposures, and that, as a consequence, responses to radiation are not linear.

A fundamental principle of radiation protection is the assumption of a linear dose response and dose additivity. The universally observed phenomenon of the adaptive response, as exemplified by the cell and animal experiments described above, indicate that for low LET radiation, the risk of cancer is not linear with dose. In fact, increasing dose by adding low doses to high doses decreases risk. The concept of dose additivity, when at least one exposure is to a low dose at low dose rate, did not hold. These data indicate that at the low doses and dose rates typical of public and occupational exposures, the radiation protection principle of dose additivity, and the concept that risk can only increase as dose increases are not justified. In general, the use of dose as a surrogate for risk needs re-evaluation. However, once past the upper dose threshold, increased dose could increase risk, as currently assumed. It is also apparent, however, that genetic variations in cancer proneness can influence these thresholds.

If different exposures (e.g. internal / external, chronic / acute, low/high, low LET / high LET, etc.) can not be summed to estimate an individual's total detriment / risk, or even if, more simply, several specific types of exposure can not be summed, then we may need to develop a new approach to radiation protection, in order to protect against each specific type of exposure separately (Mitchel and Boreham 2000). Ultimately, that approach may need to be tailored to individual genetics.

##### **4.2 Tissue weighting factors**

At high doses, different tissues are known to respond differently to radiation and are assigned constant, dose independent tissue weighting factors ( $W_T$ ) that reflect their relative fractional contribution to the total risk. However, experiments at low dose indicate that individual tissue risk is not a constant with dose, and exhibits a dose threshold below which risk is less than spontaneous risk. Different tissues appear to have different dose thresholds below which detriment turns to protection, indicating that individual tissue weighting factors ( $W_T$ ) vary from zero to positive values as dose increases. These observations indicate that tissue weighting factors are neither constant nor dose independent, and the current assumptions used for radiation protection are not appropriate.

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### 4.3 Radiation weighting factors and Sieverts

The currently accepted  $W_R$  factors have been determined by comparisons of Relative Biological Effect (RBE) at high doses, where all cells are hit by radiation and each cell receives multiple tracks of radiation. However, current animal and mammalian cell research is assessing the risk of low doses of low LET radiation down to and below a dose that represents an average of one track per cell. This is important as at these radiation levels epidemiological studies do not have sufficient power to provide risk data. Since the dose to a single cell from a single high LET track is much higher than the dose from a single low LET track, these measurements of RBE (and therefore  $W_R$ ) are valid only when there are sufficient tracks of low LET per cell to provide enough physical dose to match the effect, at a minimum, of one high LET track per cell. At lower doses, however, these concepts break down. At lower doses of high LET most cells are not hit, yet those that are hit still receive the high dose delivered by one track. At similar doses of low LET radiation all cells may still receive multiple tracks. At even lower doses, low LET radiation, like high LET radiation, will not hit all cells. At these levels, typical of public and occupational exposures, the use of  $W_R$  derived from high dose exposure assumes that the biological mechanisms responsible for the observed difference in biological response to different radiation types are the same mechanisms that operate at low doses. This has clearly been shown to be incorrect, since low doses induce protective effects. Even at the level of the response of individual genes, different genes are activated at high versus low doses. These results therefore call into question the use of current  $W_R$  factors at low doses.

Animal and cell based experiments show that low doses reduce cancer risk below the level observed in the unexposed cells or animals; i.e. below the spontaneous risk. If the radiation weighting factor ( $W_R$ ) for high doses of low LET radiation is taken as 1, then these data suggest that the  $W_R$  is a variable with dose, and can be zero at low doses. Since the  $W_R$  for high LET radiation is based on a reference to the same level of effects at low LET, the  $W_R$  for high LET also cannot be a constant. This, together with the physical impossibility of delivering the same dose per cell at low doses and the mechanistically different cellular response to high and low doses, suggests that the use of normalised dose (Sievert) at low doses is inappropriate, and that the risk or benefit of exposure to radiations of different quality needs to be understood and assessed independently, on the basis of physical dose.

The realities of human radiation exposures present an additional problem. Current cell based research indicates that a prior or concurrent exposure to low LET radiation is able to induce adaptive responses which mitigate much or all of the detrimental effect of exposure to high LET

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radiation (Wolff et al. 1991). Since virtually all public (and much occupational) exposure to high LET radiation is accompanied by exposure to low LET radiation, and if the cell based studies apply to organs and whole organisms, then radiation protection policies and risk assessments also need to consider the effect of combined exposures to these different radiation types.

#### **4.4 DDREF**

It is widely accepted that a radiation dose delivered at a low dose rate produces fewer late effects than the same dose delivered at a high dose rate. This is in a large part due to the fact that dose protraction facilitates a more effective repair of cells, including DNA damage. The ICRP therefore defines a Dose and Dose Rate Effectiveness Factor (DDREF) to allow for the reduced effectiveness of low dose rate radiation doses. The DDREF factor represents the ratio of the slope of the linear no threshold fit of high dose, high dose-rate data to the slope of the linear no threshold fit of high dose, low dose-rate data. For radiological protection the ICRP recommend a DDREF factor of 2. The utility of the DDREF coefficient depends upon the assumption that, for exposure to low doses at low dose-rate, the dose-response is linear, continuous with the slope of the high dose, low dose rate response and has a slope that is less than the corresponding slope of a linear high dose, high dose rate response.

However, low dose and low dose rate studies using low LET radiation in cells and in adult animals have shown that below a threshold dose (about 100 mGy in human cells, rodent cells and normal mice) the detrimental effects of a radiation exposure disappear and are replaced by protective effects, manifested in cells by decreases in transformation frequency and in animals by increases in cancer latency. These observations show that low dose responses are non linear and that the biological processes occurring in cells in response to low doses and dose rates can be fundamentally different from those that result from exposure to high doses, These observations undermine the concept of DDREF and indicate that at low doses DDREF becomes infinite.

These experiments indicate that the linear no threshold hypothesis, and the associated dose and dose rate reduction factors derived from high dose experiments are inappropriate for use at low doses and low dose rates. There may be no constant and appropriate value of DDREF for use in radiological protection.

#### **4.5 ALARA**

Cell and animal based experiments indicate that low doses of low LET radiation induce a protective effect that reduces the risk from spontaneous cancer and the risk of cancer from further exposure. If this is also

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true for humans, then radiation protection policies that endeavour to reduce exposures to the lowest possible dose (As Low As Reasonably Achievable, the ALARA principle), or entirely eliminate the exposure, may need to be reconsidered since they may prevent the induction of this protective response. For a public exposure, this could result in the otherwise reduced risk rising to the spontaneous level of the unexposed population. Such radiation protection policies could then be viewed as “withholding benefit”. For persons who may be occupationally exposed, prevention of the induction of protective responses would result in a higher than necessary risk if that person were then accidentally exposed to a high dose. In this circumstance, such a radiation protection policy could be viewed as increasing occupational risk.

## 5. SUMMARY IMPLICATIONS FOR THE RADIATION PROTECTION SYSTEM

At low doses,

- The conceptual basis of the present system appears to be incorrect
- The belief that the current system embodies the precautionary principle and that the LNT assumption is cautious appears incorrect
- The concept of dose additivity appears incorrect
- Effective dose (Sieverts) and the weighting factors on which it is based appear to be invalid
- There may be no constant and appropriate value of DDREF for radiological protection dosimetry.
- The use of dose as a predictor of risk needs to be re-examined
- The use of dose limits as a means of limiting risk need to be re-evaluated

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