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LOW FLUENCE

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ABSTRACT

The question of the appropriate extrapolation to low dose has long been a subject of controversy. A linear no-threshold model is favored by regulatory bodies as the basis of RBE assignments and estimates of radiation hazards to the general population. This model is largely supported by extensive application of the linear-quadratic survival formula "fitted" statistically to a wide variety of experimental data obtained at doses typically exceeding 1 Gy, and then extrapolated to mGy for practical applications, and even to the prediction of hazards from single electrons. Such extrapolations are questionable at best, and may even prove hazardous for risk evaluations. Fluence and geometry rather than dose based data are proposed as a basis for a limiting "threshold" for a "low dose" extrapolation. The proposed threshold is one where the fluence of particles is one per square micron, where on average only 2/3 of the 1 μm^2 pixels covering an irradiated area are traversed by one or more particles. The corresponding dose threshold is determined by the LET of the bombarding radiation. For relativistic electrons this dose is about 0.032 Gy. © 2003 COSPAR. Published by Elsevier Science Ltd. All rights reserved.

LOW DOSE

The application of the linear extrapolation to low dose finds favor in regulatory bodies because of its simplicity. It is based on the widespread application of the linear-quadratic two parameter fitting formula to radiobiological data. This mathematical form has no theoretical base, nor is it falsifiable, for it makes few, if any, predictions. Indeed, experimental studies of Hill and Skarsgard (1999) found many deviations from the LQ model, particularly in the dose-survival response of human tumour cells

A significant aspect of this extrapolation is its assertion that single electron transits through cell nuclei results in cell killing. The importance assigned to this assertion is indicated by the following comments of Goodhead (1992).

"Most of the current biophysical models, based largely on 1-track/2-track mechanisms, make the clear prediction that a single track can produce virtually all detrimental stochastic effects of interest. Indeed they imply that single tracks, acting alone, produce the dominant effect even up to much higher doses of hundreds of mGy. Further they are almost all now in agreement that these single-track effects arise from initial local physical damage over dimensions ~1-50 nm. ... But one model in particular, disagrees fundamentally that a single low LET track has the ability to cause cellular changes. The amorphous track model of Katz and co-workers has probably been more successful than any other model in parameterizing, fitting and predicting cell survival curves for a wide variety of radiations, especially heavy ions."

We know of no experimental confirmation of the statement above that all single track effects arise from initial local physical damage over dimensions ~1 to 50 nm. Surely this is not the case for cell killing, which has never been correlated with single electron transits through any part of a cell. In our assignment of radiosensitivity parameters to cell killing and chromosome aberration of Chinese Hamster cells from beams of heavy ions from He to O (Katz and Huang, 1980), we have found that the parameters for these two sets of data are remarkably similar. We take this to imply that chromosome aberration is the agency for cell killing from high LET radiation. This is consistent with the Katz speculation that cell killing by heavy ions is analogous to beans in a bean bag, the beans being chromosomes and the bag being the cell nucleus.

The Katz model (Butts and Katz, 1967, Katz et al. 1972, Katz and Waligorski, 1994) has also had wide application to non-biological systems, and may well be the only predictive model in radiobiology, and in other applications as well. Recall its many innovations in radiobiology; the clarification of the concept of cross-section (Katz, 1990), the attribution of all high LET effects to delta rays, the structure of particle tracks, the observation that z^2/β^2 is a superior basis for examination of heavy ion effects than LET, the prediction of "Darmstadt Hooks" and their attribution to "thindown" (Katz, 1986) as for tracks in nuclear emulsion, the prediction of single particle effects from microbeam experiments (Katz and Cucinotta, 2000), and others. This issue is not alone a question of models. Experimental findings disputing the assertions of Goodhead are cited by Katz and Waligorski (1994). Cole et al. (1980) have found that some 500 electrons pass into the nucleus of a CHO cell, on average, for inactivation. Warters et al. (1977) found that some 500 tritium β decays in the nucleus of a CHO cell are required for observable killing. Yet the conceptual and mathematical complexity of the Katz model retards its acceptance by national and international regulatory bodies.

Our journal correspondence regarding the substitution of Fluence for Dose in regard to low dose extrapolations has not gained a sympathetic hearing (Katz and Waligorski, 1992), (Katz and Cucinotta, 1995). The objections, by Sinclair and Bond, largely centered on the inability of fluence considerations to derive RBE values. But RBE's are based on dose, a concept of questionable value at such low fluence that the amorphous character of dose is violated.

LOW FLUENCE

For many years the extrapolation to low dose has been controversial. At issue has been the choice of appropriate models for radiobiological and epidemiological data, and the question of a low dose threshold.

There is an implicit approximation that both cells and dose are amorphous, arbitrarily subdivisible, like butter, reasonable at high fluence, but surely questionable at low fluence. Indeed, radiation is particulate, due to a "rain" of charged particles. When only a few particles "rain" on 100 square microns of tissue, the effect cannot be imagined as uniformly distributed.

Imagine that an irradiated area is subdivided into $1 \times 1 \mu\text{m}$ square pixels. At a fluence of n particles per pixel, the probability that a pixel experiences no hits is $\exp(-n)$. At $n=1$ this probability is 0.37, that is 37% of the irradiated area is spared. This is proposed as the low fluence threshold for extrapolation of observational data from high to low fluence. At $n=20$ every pixel in a square centimeter is hit a least once. For relativistic electrons whose LET is $0.2 \text{ keV}/\mu\text{m}$ in water, as for 5 MeV electrons, these fluences translate to doses of 0.032 Gy and 0.64 Gy respectively.

For relativistic electrons the fluence at a dose of 1 Gy is 31.25 per square micron. At this dose the amorphous approximation is reasonable. But it is unacceptable at a milligray.

To simplify further calculations, we find the dose at a threshold fluence of 1 per square micron at an LET of $1 \text{ keV}/\mu$ to be 0.16 Gy.

A recent paper, M Scholz et al. (2001), illustrates the number of hits, about 11, within the perimeter of a cell nucleus whose cross sectional area is 470 square microns, at a fluence of 2 million particles per square centimeter. Our calculation yields 9.3 hits to the nucleus, as an approximation to observation, confirming the utility of our subdivision. In this case it seems absurd to approximate dose and biological structure as amorphous.

For conceptual simplification we may use 2 digit random number generators to identify the location of hits in a 10×10 square matrix, whose axes are numbered from 0 to 9. Such an arrangement where the distribution of the location of 25 trials is displayed in a paper titled Randomness (Katz, 1969). This represents a fluence of 25 particles in 100 square microns.

A change in the basis of extrapolation from dose to fluence cleanses all earlier controversies. A low fluence threshold cannot be denied.

What remains is the choice of its level and the choice of LET values for the assignment of practical dose thresholds for different radiations.

DISCUSSION

The principal objection of Goodhead and others to Katz theory rests with its use of a multi-target model for the inactivation of cells by low LET radiation. This is an important aspect of the theory of RBE for

biological cells. Without it the theory will not accomplish its goal: to fit families of survival curves obtained with particles of different LET with a single set of 4 parameters when bombarding the same family of cells. This cannot be accomplished with a linear-quadratic model. From these parameters and knowledge of the charged particle-energy spectrum in a radiation field the theory has made it possible to compute, indeed, to predict, the response of cells to other high LET radiation fields, including neutrons, pions, and mixed radiations as in the spread Bragg Peak and neutrons admixed with gamma rays, and even to predict the outcome of single particle transits through single nuclei. The multi-target model implies a threshold in conflict with the conventional wisdom.

Since the linear-no threshold is a strongly held belief, as are other points made by Goodhead, it is unlikely that it will be replaced by Katz theory however well it is documented.

To circumvent these beliefs we approach the low dose problem via fluence and geometry rather than through a revised biological model. Here we demonstrate that an extrapolation from high to low fluence encounters an obstacle at such low fluence that the customary approximation that both dose and biological matter are amorphous, without structure, is invalid, thus implying the validity of a low fluence threshold. Thus we emphasize that both dose and RBE are undefined below the low fluence threshold. It may be appropriate to consider including a low fluence threshold proviso in a redefinition of dose.

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