January 1997

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[Published in :]

Microdosimetry

An Interdisciplinary Approach

Edited by

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Medical Research Council, Radiation & Genome Stability Unit, Harwell, UK

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European Commission, Directorate General for Science, Research & Development, Radiation Protection Research, Brussels, Belgium

THE ROYAL SOCIETY OF CHEMISTRY
Information Services

[1997]

RADIAL DOSE MODEL OF SSB, DSB, DELETIONS AND COMPARISONS TO MONTE-CARLO TRACK STRUCTURE SIMULATIONS

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1 INTRODUCTION

The initial lesions formed in DNA by ionizing radiation include base damage, single strand breaks (SSB), double strand breaks (DSB), DNA cross links, and deletions[1]. Deletions occur through energy deposition and perhaps more importantly through recombination repair[2] of DSB's. Several mechanisms for the formation of DSB's and deletions related to energy deposition can be considered. Track simulation codes have indicated the importance of clusters of ionizations in small volumes similar to the size of a nucleosome. These clusters have been related to several types of damage to DNA, including DSB and deletions resulting from multiple DSB's formed by single electron tracks[3–5]. The deletion size expected from clusters can be estimated at 2–100 bp as constrained by the wrapping of DNA about histones in the nucleosome and expected cluster regions of <5 nm. A second mechanism for deletion results from the higher order structure of DNA. Single ion tracks passing through cells will intersect several segments of DNA and deletions of kbp size as related to chromatin structure are expected and have recently been measured[6]. In heavy ion irradiation, the high densities of ionizations leads to the overlap of electron tracks suggesting an alternative mechanism for the formation of DSB's or deletions. For electron or photon irradiation, the contribution of electron overlap in causing DNA damage has been estimated to be small[4] at doses below 10^6 Gy. The radial distribution of dose from secondary electrons exceeds 10^6 Gy near an ions path and the lateral region of such energy deposition may extend to distances >100 nm for large ion charge suggesting an electron overlap contribution for formation of DSB's or deletions.

The radial dose model of track structure[7] considers the acute dose response of a biological system for energetic photons or electrons and the radial dose profile of ions to evaluate action cross sections for the same endpoint. This approach has been quite successful in fitting experimental data for inactivation and mutation by protons and heavy ions[7,8]. In this paper we discuss calculations of strand break and deletion formation using the radial dose model of track structure. The radial dose model is limited to the prediction of average quantities based on measurements for energetic photons or electrons. Such measurements exist for yields of SSB and DSB, and for limited information on the size distribution of large DNA fragments. Good predictions of SSB and DSB cross sections for SV-40 virus in EO buffer were found by Katz and Wesley[9] using this approach. The measurement of deletions as caused by energy deposition has proven difficult, therefore excluding the mapping procedure used in the radial dose model to make prediction of deletions from ions. In order to make estimates of deletion cross sections, we consider the results of Monte-Carlo track simulations for energetic electrons[3–5] to estimate the probability of ionization clusters including 2 DSB's within a small volume of the size of a nucleosome. In contrast to the radial dose approach, track simulations make detailed considerations of energy depositions in

DNA such as the stochastics of ionization events and the dependence on the secondary electron spectrum. Comparisons are made to measurements of RBE's for SSB and DSB, and to track simulation results for ions.

2 CROSS SECTIONS FOR DNA DAMAGE

The induction of SSB's is observed to increase linearly with dose for all radiation types. The cross section for ions is then modelled as a one-hit process as given by

$$\sigma_{SSB} = 2\pi \int t\, dt\, (1 - \exp(-D(t)/D_{SSB})) \quad (1)$$

where t is the impact parameter of the ion, D(t) is the radial dose of the ion, and D_{SSB} the D_{37} dose for the induction of SSB by X-rays[10]. The induction of DSB is also observed to increase linearly with dose for all radiation types. Because of the large ionization density at small t, we consider 2 mechanisms for the production of DSB by ions. In the first, clusters of ionizations from single electron tracks in a volume similar to a nucleosome lead directly to DSB's. The second mechanism considers the role of overlapping electron tracks near to the path of an ion by folding the probability function for SSB's using an inter-separation of up to 10 bp for the two SSB's. The cross section for DSB production is then written as

$$\sigma_{DSB} = \sigma_{DSB\text{–clusters}} + \sigma_{DSB\text{–overlap}} \quad (2)$$

where

$$\sigma_{DSB\text{–cluster}} = 2\pi \int t\, dt\, (1 - \exp(-D(t)/D_{DSB})) \quad (2a)$$

$$\sigma_{DSB\text{–overlap}} = 2\pi \int t\, dt\, (1 - \exp(-D(t)/D_{DSB}))\, (1/V) \int dr\, (1 - \exp(-D(t-r)/D_{SSB}) \quad (2b)$$

The cross sections for production of several breaks in the sugar-phosphate backbone of DNA could be defined if the related D_{37} dose were known. In order to investigate these effects in the radial dose model we consider the results of track simulations for electrons.

In the track simulation approach[3–5], the yield of DNA breaks is evaluated by relating the total energy deposited in DNA segments to the number of breaks of various types. A volume model of DNA is used which considers the volume of sugar-phosphate moieties and their rotation about histones. SSB formation is assumed to occur if energy deposition in the sugar-phosphate volume above a threshold value (~17.5 eV) occurs. Higher-order damage as determined by the occurrence of one or more SSB's on the same or opposite strands in various combinations are also scored. More recent calculations consider the early chemistry of water radicals[5]. The track simulation approach by considering the stochastics of ionization and excitation events is also able to consider the frequency distribution of breaks along DNA. Details of the model are given in ref. 3–5.

We assume that cross sections for these various types of damage have two contributions from clusters of ionizations in small volumes and from electron overlap in the ion's track. Cross sections for 2 DSB's within 10bp (denoted DSB^{++}) are found in a similar fashion to that of eq. (2) with D_{37} doses based on yields of SSB, DSB, and DSB^{++} for electrons from the track simulation model, scaled to D_{37} measurements[10] for SSB as shown in Table 1.

Table 1. *D_{37} Values for Strand Break Induction by Energetic Electrons*

D_{SSB}, Gy	D_{DSB}, Gy	D_{DSB++}, Gy
5	75	2200

3 RESULTS AND DISCUSSION

Comparisons for yields of strand breaks are shown in Figure 1. The radial dose model predicts lower yields for induction of SSB's as compared to the track simulation results with the differences greater for LET values corresponding to energies below 1 MeV/u. For DSB, contributions from the one-track mechanism from clusters in the radial dose model contributes about 1/2 of the yield at high energies, but is overcome by the electron overlap terms at low energies where the density of the track increases. The RBE in the radial dose model is general less than 1 when a one-hit mechanism is assumed which results from wastage of energy or over-kill effect. Both models predict a drop in break induction for energies below about 0.5 MeV/u, however in the radial dose model this drop is more rapid. In this region the maximum range of the secondary electrons falls below 10 nm and the effects of scaling all electrons to X-rays may become less appropriate[4]. Also, in the radial dose approach contributions from excitations of DNA are not considered. In the track simulation, excitations and ionizations are considered on equal footing in evaluating energy deposition. In Figure 2 we show comparisons to experiments[10–11] for RBE's for SSB in mammalian cells. There is some under-estimation of the RBE for He, while good agreement is found for the higher charged ions. The large decrease in RBE at high LET's for Ne, Ar, and U is reproduced by the model and occurs due to the decreasing range of the secondary electrons. In Figure 3 RBE's for DSB and small deletions in the models and experiments[10–13] are compared. The contribution from electron overlap in the radial dose model leads to RBE's above unity for lower charges in agreement with experiments. For higher charge ions, the RBE approaches unity at low LET and below unity at higher values. For the predictions of RBE's for small deletions, the radial dose model predicts RBE's greater than unity for all charges as electron contributions becomes dominate over the one track mechanism. For higher-order damage such as several DSB's or large deletions higher RBE's would be expected than found here for small deletions (DSB^{++}).

The radial dose model predicts a dominant role for electron overlap for ions, especially as the severity of damage increases, corresponding to larger volumes of energy deposition. The differences between the track models considered for low energy H and He results from the use of a stochastic approach in the track simulation model, including its treatment of short-ranged electrons and the description of excitations by ions. It is expected that continued analysis of the models and new measurements will be required to understand the role of each of these factors.

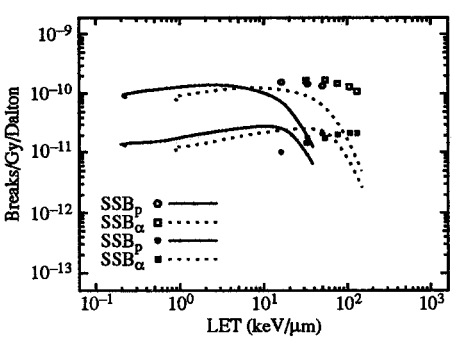

Figure 1. *Calculations of yields for strand breaks. Lines are radial dose and symbols track simulation model.*

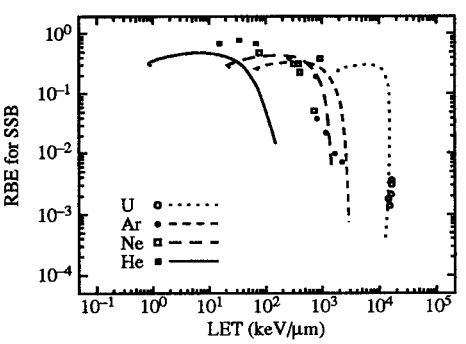

Figure 2. *Comparisons of RBE's for SSB's in model radial dose model to experiments.*

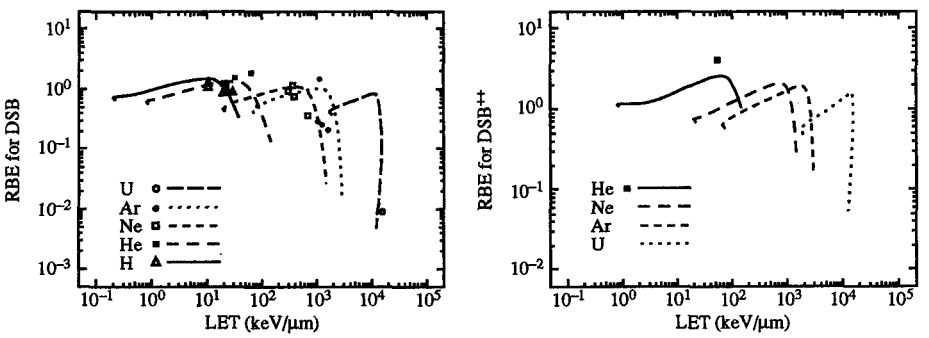

Figure 3. *Comparison of RBE's for DSB and DSB^{++} small deletions in radial dose model to experiments and result of the track simulation model for small deletions for He.*

4 ACKNOWLEDGEMENTS

This work was partially supported by NASA and EC Contract F14P-CT95-0011.

5 REFERENCES

1. D. T. Goodhead, *Int. J. Radiat. Biol.*, 1989, **56**, 623.
2. E. C. Friedberg, G.C. Walker, and W. Siede, DNA Repair and Mutagenesis, ASM Press, Washington D.C., 1995.
3. D. E. Charlton, H. Nikjoo, and J. L. Humm, *Int. J. Radiat. Biol.*, 1899, **56**, 1.
4. D. T. Goodhead and H. Nikjoo, *Int. J. Radiat. Biol.*, 1989, **55**, 513.
5. H. Nikjoo, et al., *Int. J. Radiat. Biol.*, 1994, **66**, 453.
6. B. Rydberg, *Radiat. Res.*, 1996, **145**, 200.
7. R. Katz, et al., *Radiat. Res.*, 1994, **140**, 402.
8. R. Katz and S. Wesely, *Radiat. Environ. Biophys.*, 1991, **30**, 81.
9. F. A. Cucinotta, et al., *Int. J. Radiat. Biol.*, 1996, **69**, 593.
10. J. Heilmann, H. Rink, G. Taucher-Scholz, and G. Kraft, *Radiat. Res.*, 1993, **135**, 46.
11. G. Kampf and K. Eichorn, *Studia Biophys.*, 1983, **1**, 17.
12. M. Belli, et al., *Int. J. Radiat. Biol.*, 1994, **65**, 529.
13. T. J. Jenner, et al., *Int. J. Radiat. Biol.*, 1992, **61**, 631.