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Effects of track structure and cell inactivation on the calculation of heavy ion mutation rates in mammalian cells

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Abstract. It has long been suggested that inactivation severely effects the probability of mutation by heavy ions in mammalian cells. Heavy ions have observed cross sections of inactivation that approach and sometimes exceed the geometric size of the cell nucleus in mammalian cells. In the track structure model of Katz the inactivation cross section is found by summing an inactivation probability over all impact parameters from the ion to the sensitive sites within the cell nucleus. The inactivation probability is evaluated using the dose–response of the system to γ-rays and the radial dose of the ions and may be equal to unity at small impact parameters for some ions. We show how the effects of inactivation may be taken into account in the evaluation of the mutation cross sections from heavy ions in the track structure model through correlation of sites for gene mutation and cell inactivation. The model is fit to available data for HPRT mutations in Chinese hamster cells and good agreement is found. The resulting calculations qualitatively show that mutation cross sections for heavy ions display minima at velocities where inactivation cross sections display maxima. Also, calculations show the high probability of mutation by relativistic heavy ions due to the radial extension of ions track from δ-rays in agreement with the microlesion concept. The effects of inactivation on mutations rates make it very unlikely that a single parameter such as LET or Z^{*2}/β^2 can be used to specify radiation quality for heavy ion bombardment.

1. Introduction

The level of biological injury to be expected from galactic cosmic rays (GCR) during prolonged manned spaceflight is difficult to estimate because of the lack of human data from exposures to high charge and energy (HZE) particles. Experimental studies for estimating the risk from long-term GCR exposures include track segment irradiations with HZE particles in which animals or cell cultures are used. The most useful end points for such studies with animals are cancer induction and mortality. Cellular studies using cytotoxicity as an end point are useful for providing estimates of relative biological effectiveness (RBE), whereas the stochastic end points of mutagenesis or neoplastic transformation provide RBEs for more important end points and additional information on the late effects that may be useful in extrapolations of the level of risk for man and on the underlying mechanisms of damage from HZE particles.

An experimental assay has been developed for studies of mutations at the hypoxanthine guanine phosphoribosyl transferase (HPRT) locus in mammalian cell cultures. The HPRT gene is located on the *X* chromosome, and the mutation of this gene is related to DNA damage. The HPRT locus is a well-studied system for considering the expression of large deletions or rearrangements (Cox and Masson 1979, NCRP 1990). This assay system has been used by several groups with a variety of light and heavy ion types in several cell lines (Cox and Masson 1979, Thacker *et al.* 1979, Kronenberg and Little 1989, Kranert *et al.* 1990). One of the shortcomings of this assay system is that the chromosome involved is necessary for cell replication, which results in the loss of potential mutants. Human–hamster hybrid systems are being used to obtain higher mutation rates in other studies (NCRP 1990). Also, measurements (Kronenberg and Little 1990) of mutations to trifluorothymidine resistance locus indicate slow-growth mutants that are not typical of the HPRT mutants, an indication that some variability exists in mutations at specific genetic loci in human cells.

In describing mutagenesis from heavy ions, the question arises of whether there will be any mutations observed at all if single tracks of heavy ions kill the cell due to the large energy they deposit in the cell nucleus. Goodhead *et al.* (1980) and

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Kranert *et al.* (1990) discussed this problem, noting that for heavy ions the inactivation cross section is generally smaller than the nuclear area for mammalian cells and that track structure effects should be considered in order to understand the role of inactivation of heavy ion mutagenesis. Studies by Lett *et al.* (1989) with repair deficient LS1784 S/S cells show that inactivation cross sections may exceed the geometric cross section in some cases. In this paper we use the track structure model of Katz *et al.* (1971, 1985) in order to evaluate the mutation cross section for ion bombardment of Chinese hamster fibroblasts (V79). We show that the mutation cross section for ions throughout the periodic table can be described by the track model when inactivation effects are accounted for in the model. In effect, we will have a qualitative model of what has long been suggested (Grahn 1973, Todd 1983, Kiefer 1993) of heavy ion mutagenesis, including the concept of a microlesion where mutated cells surround a core of inactivated ones.

The action cross section was first described by Butts and Katz (1967) using the spatial distribution of energy about an ion to map the response of low linear energy transfer (LET) irradiations such as γ-rays or electrons to that of an ion. An inactivation probability as a function of impact parameter or radial distance about the ion can be described in this manner using the ions' radial dose and the γ-ray response function. For a finite target size, the radial dose is averaged over the target volume assumed to be a short cylinder of radius a_0. Several experiments have now been performed (Facius *et al.* 1983, Weissbrod *et al.* 1992) to measure the inactivation probability $P(t)$ for ion bombardment of *Bacillus subtilis* spores. These measurements appear to indicate that the probability is not unity for small impact parameters for uranium bombardments seeming to contradict the predictions of the track structure model. Recently, calculations for the inactivation probability of spores (Cucinotta *et al.* 1995) have shown that if the sensitive targets in the spores are allowed to be displaced from the center of the spore volume, a good representation of these measurements is provided by the track model and a unit probability for small impact parameters is not ruled out. Recent measurements of the DNA content in yeast cells by Kost and Kiefer (1993) also support the assertion that the impact parameters in the inactivation measurements are likely to be displaced from the sensitive site(s) for inactivation.

The experimental data for the dose–response for mutations from γ-rays in mammalian cells is severely limited. Data below doses of 0·5 Gy are difficult to obtain due to poor statistics. Data above doses 10 Gy are also difficult to obtain due to the high inactivation rates leading to poor recovery of mutants. The track structure model relies on extrapolating effects of low LET irradiations at high dose-rate to that of ions using the low-LET dose–response. The extrapolation becomes difficult due to the limited range of data for the dose–response. The track model employs a multitarget or multihit model for the functional form of the dose–response. Wilson *et al.* (1993) have developed a linear repair/misrepair kinetics model for multiple lesion formation appropriate for the case of mutation in competition with inactivation. We consider both the multitarget and linear kinetics model for the low LET dose–response model in this paper.

Our accounting of inactivation effects on heavy ion mutation cross sections relies on the assumption that the sensitive sites for inactivation may be displaced from that of mutation. We average the displacement distance over the nuclear volume for the V79 cells; this leads to a good representation of the existing measurements of mutation cross sections in V79 cells. Parameters for cell inactivation are fixed in the model from inactivation data. The resulting model shows, in agreement with the data, that the mutation cross section for very heavy ions plotted as a function of ion energy is a minimum when the inactivation cross section is a maximum. Also, we show that the effects of inactivation on mutations from light ions is small. In the remainder of this paper we first describe the calculation of the mutation cross section in the track model when inactivation is considered. The model is then fit to the existing data for V79 cell HPRT mutations and the mutation probability as a function of ion charge and energy, is discussed.

2. Inactivation and mutation cross sections in track model

In order to introduce the effects of survival probability on the evaluation of mutation cross sections in the track model we first review the evaluation of the inactivation cross section (Butts and Katz 1967, Katz *et al.* 1971). The dose–response of the system to low LET irradiations

for the endpoint of inactivation (loss of colony-forming ability) is assumed to be known and represented by the probability function $P_I(D)$, where D is the absorbed dose in Gy. Track structure is understood by finding the spatial distribution of local dose about the path of an ion, as deposited in the sensitive volume elements of the cell. For calculations, the average radial dose as a function of the radial distance t is a short cylinder of radius a_{0_I} is used to denote $\bar{D}_I(t)$. The inactivation cross section of a single putative target is found by integrating the probability for inactivation evaluated with the average radial dose in a_{0_I} over all radial distance, as (Katz *et al.* 1971)

$$\sigma_I = \int_0^{T_{max}} 2\pi t \, P_I(\bar{D}_I(t)) \, dt, \tag{1}$$

where T_{max} is the maximum range of the δ-rays, often denoted the penumbra radius, which is a function of ion velocity β.

In implementing equation 1 for describing survival curves a multitarget model for low LET dose–response is often assumed where

$$P_I(D) = \left[1 - e^{-D/D_{0_I}}\right]^m, \tag{2}$$

where m is the target number and D_{0_I} is the low LET characteristic dose, at which there is an average of one hit per target. The surviving fraction of cells after low LET irradiation at D is $N/N_0 = 1 - P_I(D)$. The use of a multitarget model to fit the high dose-rate, low LET dose–response is convenience in the calculations, and it can be shown (Cucinotta *et al.* 1995a) that other parametric models will work equally as well in predicting action cross sections for ions using equation 1.

The inactivation cross section evaluated from equation 1 plotted as a function of an ion's velocity is observed to reach a plateau at a about $1\text{-}1{\cdot}4\,\pi a_{0_I}^2$ marking the transition from the grain count regime to the track-width regime (Katz *et al.* 1971). The sensitive targets for the case of $m > 1$ are contained in some volume represented by the cross sectional area σ_{0_I} which may be less than the total cross sectional area of the cell nucleus. The cross sections calculated by equation 1 are then multiplied by the ratio $\sigma_{0_I}/1{\cdot}4\pi_{0_I}^2$ when $m > 1$. a_{0_I} and σ_{0_I} are determined by fitting the model equations to the experimental data set using track segment irradiations. In the track model, the surviving fraction after irradiation with track segment ion bombardments is separated into intratrack and intertrack effects as

$$\frac{N}{N_0} = \pi_i \times \pi_\gamma, \tag{3}$$

where the intratrack or ion-kill contribution is given by

$$\pi_i = e^{-\sigma_i F}, \tag{4}$$

where F is the ion's fluence and the intertrack or γ-kill probability is

$$\pi_\gamma = 1 - P_I(D_\gamma), \tag{5}$$

where D_γ is the γ-kill dose given by

$$D_\gamma = \left(1 - \frac{\sigma_I}{\sigma_{0_I}}\right) F, \tag{6}$$

with $D_\gamma = 0$ for $\sigma_I > \sigma_{0_I}$.

At sufficiently large fluence, the survival curves resulting from equation 1 to 6 display an exponential tail and the extrapolated cross section can be found as (Katz *et al.* 1971)

$$\sigma_{ext} = \sigma_I + \left(1 - \frac{\sigma_I}{\sigma_{0_I}}\right) \frac{LET}{D_{0_I}}. \tag{7}$$

The extrapolated cross section is also termed the final slope 'cross section' and is identical to σ_I (the initial slope cross section) only when $\sigma_I > \sigma_{0_I}$.

In order to evaluate the mutation cross section in the track model the probability of survival of the cell must be considered in order for the mutation phenotype to be expressed. Unlike the target(s) for inactivation, the target(s) for gene

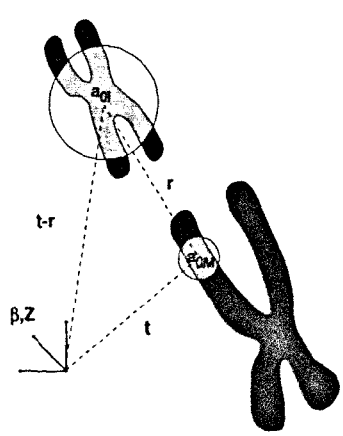

Figure 1. Schematic diagram of correlation of lesion sites for mutation and inactivation relative to path of ion of velocity β and charge Z at impact parameter t from mutated gene with r displacement of two sites. In calculations, r is averaged over nuclear volume.

mutation are well localized. For the HPRT mutation assay these are on the X chromosome. We will assume that the targets for inactivation are located randomly in the cell nucleus (i.e. not chromosome specific). In Figure 1 we depict the sites for mutation and interactivation relative to the ion's path.

The cross section for mutation is evaluated by considering the dose–response probability per surviving cell for low LET induction of the mutation, denoted P_M, multiplied by the dose–response probability that the cell survives. The product of the mutation frequency per survivor, P_M, times the survival probability, $1 - P_I$, represents the number of mutants observed. Track structure is introduced by correlating the location of these events within the cell nucleus. The cross section for production of observable mutants is then

$$\sigma_M = \int_0^{T_{max}} 2\pi t \, dt \, P_M(\bar{D}_M(t)) \frac{1}{V_N} \times \int d\vec{r}(1 - P_I(\bar{D}_I(\vec{t} - \vec{r}))) \qquad (8)$$

where V_N is the volume of the cell nucleus and the radial dose at the gene, $\bar{D}_M$, is averaged over the mutation site of radius a_{0_M}. The success of equation 8, as shown in calculations below, is to correlate the spatial distributions of lesions for these endpoints. In calculations, V_N is restricted to account for the finite size of a_{0_I} such that the displacement keeps the inactivation sites inside the nuclear volume. We expect the displacement distance then to be localized within about 3 μm from the mutation site. For calculations, both a spherical and cylindrical geometry for the volume integral in equation 8 were considered with similar results found and therefore a spherical volume is assumed in the results discussed below. Many factors, such as the finite chromosome number, chromosome geometry, temporal position, etc., preclude any ab-initio correlation of the mutation and inactivation lesion sites. Its actual value for calculations is described below.

3. Calculations of cross sections

For calculations of cross sections the radial dose from secondary electrons based on the model of Kobetich and Katz (1968) is used. We have updated some of the physical inputs in this calculation (Cucinotta *et al.* 1995b), including the use of the secondary electron spectrum from proton impact in water from Rudd (1989), a revised angular distribution ansatz, and the electron range-energy and stopping power formula from Tabata *et al.* (1972). Also, we have included a contribution for excitations to the radial dose model using the ansatz of Brandt and Ritchie (1974), normalized such that the summed contributions from excitations and δ-rays (from modified Kobetich and Katz model) conserves the LET for each ion where

$$LET = 2\pi \int_0^{T_{max}} t \, dt [D_\delta(t) + D_{exc}(t)]. \qquad (9)$$

We have not considered the effects of nuclear stopping power which should become important at low energies (< 1 MeV/u).

For survival, the X-ray response parameters as well as the geometric parameters have been fitted by Katz *et al.* (1994) as listed in Table 1. For HPRT mutations the X-ray response in V79 cells has been measured by Kranert *et al.* (1989) for doses of 1–10 Gy. The multitarget model can be applied directly to the mutation frequency as shown by

Table 1. Cellular response parameters for V-79 cells

Endpoint	m	D_0(Gy)	$\sigma_0(\mu m^2)$	a_0(nm)
Inactivation	3	1·82	42·8	820
HPRT mutations	2	950	$6{\cdot}5 \times 10^{-3}$	50

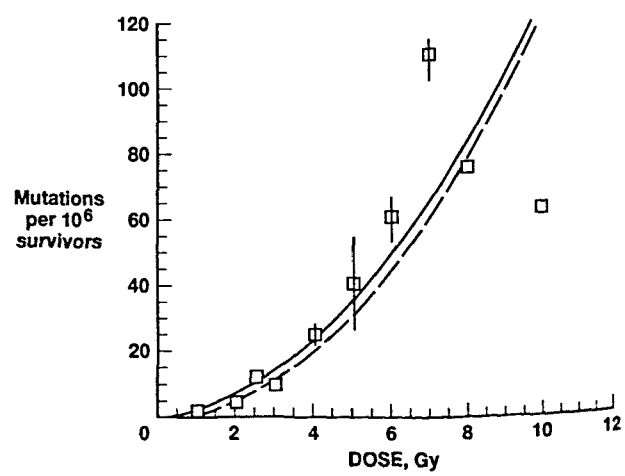

Figure 2. X-ray dose–response for the number of mutations per 10^6 surviving cells for HPRT mutations in V79 cells. Data are from Kranert *et al.* (1990). The solid line is fit of multitarget model to data with parameters listed in Table 1 and the dashed line is fit of linear repair kinetics model of Wilson *et al.* (1993).

the solid line in Figure 2 with the resulting parameters $m = 2$, $D_{0_M} = 950$ Gy. Wilson *et al.* (1993) formulated a linear kinetics model of repair/misrepair to treat multiple lesion types such as mutation and inactivation and which also considers dose-rate effects. The fit of this model to the X-ray data is shown by the dash line in Figure 2. For our purpose of treating track structure effects on evaluating mutation cross sections, the use of the multitarget model or linear kinetics model for mutations gave similar fits to the data. The multitarget model is used in the figures shown. As described by Wilson *et al.* (1993), the parameters used by Katz *et al* (1994) can be used in a linear kinetics model when inteter m values are assumed.

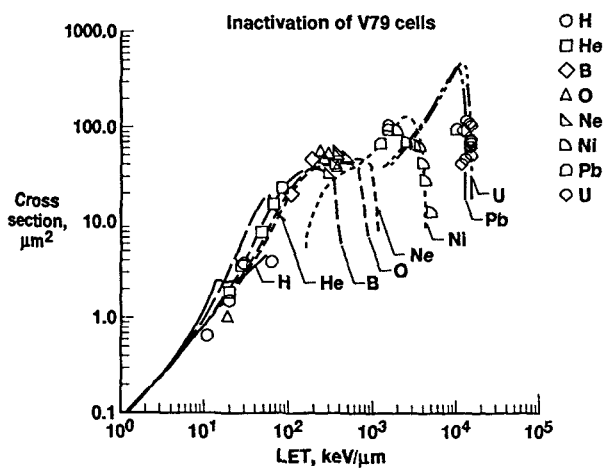

Figure 3. Calculations and experimental values of inactivation cross sections (final slope) for V79 cells plotted versus LET. Data are from Thacker *et al.* (1979), Kranert, *et al.* (1990), Belli *et al.* (1993), and Kiefer *et al.* (1994).

We have considered only integer m values in our fits, although non-integers would perhaps provide a superior fit. The drop-off in mutation frequency at higher doses of X-rays in Figure 2 is a common feature of such data. The lack of X-ray data at larger doses (> 10 Gy) leaves some uncertainty in the mapping to ion effects using equation 8.

Calculations of inactivation cross sections are compared with experimental data as a function of LET in Figure 3. Shown are the final slope or extrapolated cross sections for several charges. Cellular response parameters for inactivation (Katz *et al.* 1994) are listed in Table 1. The maximum value of the inactivation cross section versus LET for each specific ion occurs in the energy range of about 5–30 MeV/u. The decrease in the inactivation cross section is called thindown and occurs when $T_{max} < a_{0_I}$. The nuclear area for V79 cells will vary with cell type, strain, growth conditions, etc., and has been reported as $130\,\mu m^2$ by Goodhead *et al.* (1980) corresponding to the experiments of Thacker *et al.* (1979), roughly three times the value of $\sigma_{0_I} = 42{\cdot}8\,\mu m^2$. We note that for a small range of energies and for very large charges, the model inactivation cross sections exceed the reported geometric area of $130\,\mu m^2$.

In the evaluation of mutation cross sections using equation 8 the upper limit on $|\vec{r}|$ should be on the order of 1–$3\,\mu m$ in view of the measured nuclear area for V79 cells and the fitted values of σ_{0_I} and a_{0_I}. We have treated the maximum r, denoted r_{max}, as a fitting parameter estimated as $r_{max} = 1{\cdot}75\,\mu m$ from calculations. We first show plots of σ_M for uranium and oxygen ions versus energy in Figure 4 for several fixed values of r. For small r, virtually no mutations are seen for heavy

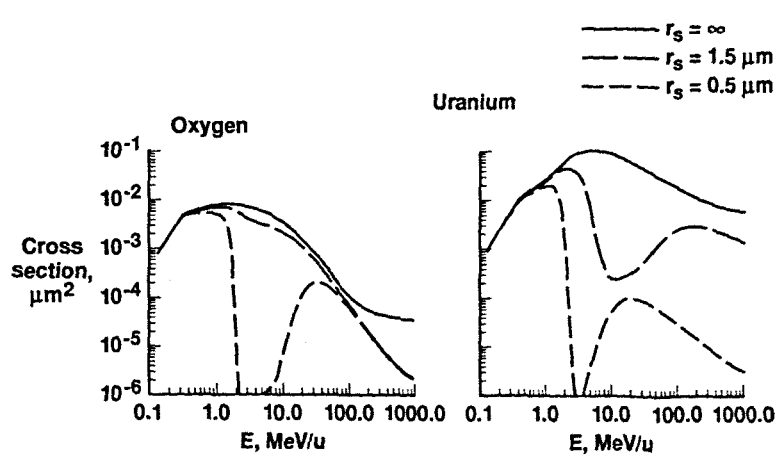

Figure 4. (a) Calculations of mutation cross sections versus energy for oxygen ions at various fixed separation distances from mutation lesion site to inactivation lesion site. (b) Same as for (a) for uranium ions.

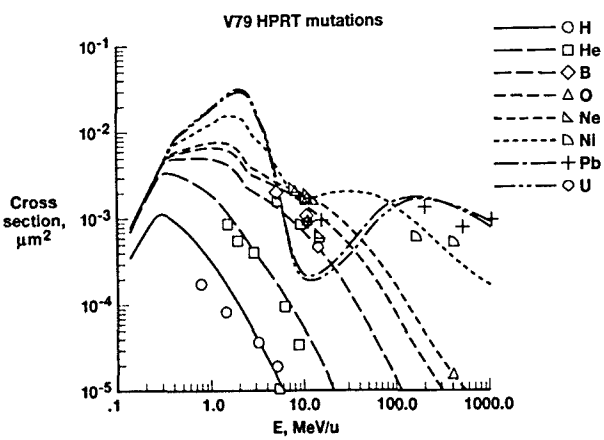

Figure 5. Calculations and experimental values of mutation cross sections plotted versus energy for HPRT mutations in V79 cells. Data are from Thacker *et al.* (1979), Kranert *et al.* (1990), Belli *et al.* (1993), and Kiefer *et al.* (1994), and is initial slope data when available.

ions of modest energies where the highest rates of inactivation occur. At low energies (< 1 MeV) the mutation cross sections increases where thindown in the inactivation cross sections occur. A second maximum in the inactivation cross section in yeast and bacteria has been observed at low energies (Schneider *et al.* 1990) which is not accounted for by the δ-ray model and would most likely reduce the mutation cross sections in the energy region from 0·1 to 1·0 MeV/u over the calculations shown here if the same effect is presented for the inactivation of V79 cells.

In Figure 5 we show the model calculations and experimental values for V79 mutation cross sections versus ion energy for several ion types. The data shown for heavy ions with $Z > 8$ are from Kranert *et al.* (1990) and Kiefer *et al.* (1994). The data shown for He and B are the initial slope cross sections from Thacker *et al.* (1979) and the data for protons from Belli *et al.* (1993). Different strains of V79 cells are used by the authors noted. Cellular response parameters for mutation are listed in Table 2. The value of a_{0_M} most strongly affects the fit for light charged ions and is somewhat sensitive to the angular distribution of secondary electrons assumed in calculations. The a_{0_M} obtained by fits, as noted by Goodhead (1989), corresponds to a large portion of the HPRT gene. The agreement between calculations and experiment is good. Heavy ions are seen to display minima in their mutation capability due to inactivation effects. This minima occurs for kinetic energies from a few to about 30 MeV/u. The overestimation of the model inactivation cross section for uranium in this energy regime affects the mutation cross sections too severely; however, the trends are correct. A statistical test of our fits has not been made at this time. We note that the usefulness of a statistical test of the model may be limited since the measurements discussed are from several laboratories (Thacker *et al.* 1979, Kranert *et al.* 1990, Belli *et al.* 1993). Relativistic heavy ions thus become more effective due to the large radial extent of their tracks from δ-rays. The spreading of the ions track at high energies reduces the effects of inactivation, thus increasing the likelihood of mutation. Note also that ions of moderate charge become more efficient than higher charge ions in the moderate energies region from about 5 to 50 MeV/u. Light ions are only mildly effected by inactivation effects.

In Figure 6 we show the mutation cross sections plotted versus LET. A 'hook' structure distinct from the 'hooks' seen in inactivation cross sections due to thindown effects is observed. A sharp rise in σ_M is seen for a narrow band of LETs as correlated with the thindown of σ_I for the same LET band. A complicated structure of σ_M predicted by the model prohibits the use of a single quantity such as LET or Z^{*2}/β^2 for defining radiation quality as noted by Kranert *et al.* (1990).

Table 2. Photon initial slopes and geometric parameters for several cell lines

Cell type	Initial slope for HPRT mutations, (10^7cGy^{-1})	Geometric area (μm)	Radius (μm)	Reference
V79	0·35	130	6·4	Thacker *et al.* (1979) Goodhead *et al.* (1980)
Human lymphoblasts	0·6	87	5·3	Kronenberg (1994)
Human skin fibroblasts	2·3	220	8·4	Tsuboi *et al.* (1992)

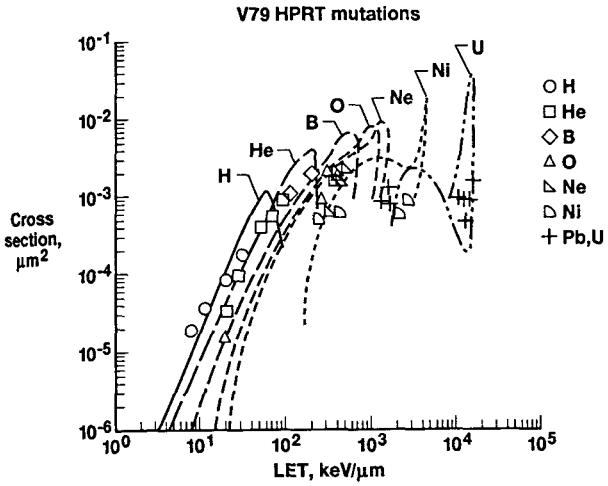

Figure 6. Same as for Figure 5 plotted versus LET.

4. Discussion and conclusions

Cross sections for HPRT mutations have also been reported for human fibroblast cells (Cox and Masson 1979, Tsuboi *et al.* 1992) and for human B-lymphoblastoid cells (Kronenberg *et al.* 1989, 1994). The fibroblasts' and lymphoblasts' response to heavy ions has been noted to be quite different by Kronenberg (1994) as seen, e.g., in the large differences in cross sections for relativistic iron nuclei of similar energies where the cross sections in fibroblasts are about a factor of 15 larger in the human fibroblasts. The present models suggest that these differences are inherent in the γ-ray response of individual cell types without regard to any specific expression pathways for heavy ions. In Table 2 we list reported initial slope estimates and cross sectional areas for several cell lines in which HPRT mutations have been measured. We note that the low LET response is different, being larger for the human fibroblasts and similar for the V79 and lymphoblasts. This is also true of the measured cross sectional area with the human fibroblast nuclear area almost twice as large as that of the V79 and lymphoblasts. If the multi-target model or linear kinetics model is fit to the human skin fibroblast data (Tsuboi *et al.* 1992) with $m = 2$, D_{0_M} of around 650 Gy is found, which compares with the 950 Gy found for V79 cells. In contrast with the human lung fibroblast system (Cox and Masson 1979), the human fibroblasts used by Tsuboi *et al.* (1992) do express curvature in the γ-ray dose–response for both inactivation and mutation. The linear kinetics model fits both sets of fibroblast lines by introducing a finite misrepair term for the lung fibroblasts. In the cross section formula of equation 8, the values of V_N are also expected to be increased for the larger nucleus of the human fibroblast cells. It is difficult to determine if an increase in the cell volume will reduce the role of inactivation on the mutation rate. We expect that the differences in low LET response to be sufficient to explain the differences in mutation rates between cell lines without the introduction of any new mechanisms for ions. The recent measurements of Kiefer *et al.* (1994) using 400 MeV/u Nickel support this premise where the mutation cross section in V79 cells in $5{\cdot}0 \times 10^{-4}\,\mu m^2$ in comparison with 600 MeV/u iron nuclei in lymphoblasts and fibroblast with mutation cross sections of $3{\cdot}7 \times 10^{-4}$ and $56{\cdot}5 \times 10^{-4}\,\mu m^2$ respectively.

The track structure model uses a model fit to experimental measurements for high dose-rate response to low LET radiations, the radial dose distribution about the path of a heavy ion, and a few geometric parameters to predict the effects of the identical system to an arbitrary ion. In the past this procedure has been shown to be quite successful for describing inactivation cross sections in many biological samples. Herein we have shown that a similar procedure can be applied to predict mutation rates when the effects of inactivation are included by spatially correlating lesion sites. The continued success of the track model in fitting biological data with ion beams suggests that a fundamental approach to biological damage from energetic photons would provide much of the understanding needed for ion beams as well. The action cross sections for mutation plotted versus LET will have a distinct structure due to the effect of inactivation, especially for heavy ions. The use of a single parameter such as LET or Z^{*2}/β^2 to represent radiation quality is thus even less accurate for mutations than inactivation.

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