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MICRODOSIMETRIC CONCEPTS RELEVANT TO HZE-PARTICLES

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ABSTRACT

The biological effectiveness of HZE-particles is determined by the extreme microscopic concentrations of energy transfer in the vicinity of the particle tracks. The concept of linear energy transfer fails to describe this situation adequately. The more rigorous microdosimetric concepts are presented. A simplified treatment, based on the radial distribution of energy around the track core, is then considered.

Keywords: *Microdosimetry, radiobiology of heavy ions, linear energy transfer*

1. GENERAL CONSIDERATIONS

All ionizing radiations produce biological effects by the same mechanisms, namely by electronic collisions and the resulting excitations and ionizations in the irradiated tissue. Furthermore the yields of the primary radiation products are substantially the same for the various types of ionizing radiations.

There are nevertheless great differences in the relative biological effectiveness of ionizing radiations. These differences are due to the different spatial distribution of the primary radiation products within the irradiated organism. One deals here with two distinct aspects. The first is the *macroscopic*, the second the *microscopic* non-uniformity of energy deposition. HZE-particles differ greatly from conventional radiations in both aspects. It is therefore important to examine, in how far established concepts and quantities of radiation biophysics are applicable to space radiations.

The microscopic pattern of energy deposition in the cell is the essential factor which determines the biological effectiveness of an ionizing radiation. It is the object of this article. In a simplified treatment, such as is used in radiation protection, it is often sufficient to apply the concept of *linear energy transfer* (LET) which describes the average rate of energy transfer along the track of a charged particle. The description in terms of LET is, however, only an approximation. For a quantitative analysis of radiobiological phenomena one needs more rigorous concepts. These are provided by the new speciality which has become known as *microdosimetry*. In the first part of this article the essential quantities and functions of microdosimetry are defined. LET and its limitations are then considered, and criteria are given which permit a decision whether a particular situation requires microdosimetric treatment, or whether the LET concept can be applied. A detailed discussion of one of the most important microdosimetric characteristics of HZE-particle, the radial distribution of dose around the track, is then given.

Macroscopic distribution of imparted energy is a more conventional problem of radiation physics. This problem will here not be dealt with, however it is appropriate to mention its basic aspects.

From the knowledge of ranges and stopping powers it is, in principle, straightforward to compute the penetration of charged particles into an irradiated object. In the case of HZE-particles the problem is compounded by the break-up of the ionizing heavy particles and the atomic nuclei of the irradiated substance. Many of the relevant cross-sections are as yet poorly known, and further work in this field is urgently required.

A related problem is linked to the question, how one can, with a minimum of relevant parameters, describe radiation quality in the case of HZE-particles. This is the problem of the build-up of the radiation field in an extended target such as the human body. A local measurement with a small detector in an otherwise receptor-free radiation field may yield values of absorbed dose, of LET, or of dose equivalent which are not representative for the exposure of an individual who might

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occupy the location. In fact the measurement may even fail to yield uniquely defined values. An attempt has therefore recently been made to introduce a new quantity, the *dose equivalent index*, which provides a meaningful parameter for radiation protection even under otherwise unspecified conditions and for unconventional radiations such as HZE-particles. These matters are treated in two recent reports of the International Commission of Radiation Units and Measurements (Refs.1, 2).

2. CONCEPTS AND QUANTITIES OF MICRODOSIMETRY

Absorbed dose is a statistical concept; it is defined in terms of the expectation value of energy imparted to an element of matter divided by its mass. The random nature of energy deposition plays, however, a considerable role if the mass element is small, if the dose is low, and if the radiation is densily ionizing. The energy actually imparted to the mass element may then differ widely from the statistical expectation value, and absorbed dose is not a relevant quantity. One has therefore introduced a new quantity, *specific energy*, z, which is the random variable corresponding to the non-stochastic quantity absorbed dose (Refs.1,3,4). The specific energy is defined as the ratio of energy imparted, ε, to the volume element and the mass, m, of the volume element:

$$z = \frac{\varepsilon}{m} \qquad (1)$$

The absorbed dose is the average of z, or, in a more rigorous formulation, it is the limit of the mean value $\bar{z}$ of specific energy as the size of the reference volume is reduced to zero:

$$D = \lim_{m \to o} \bar{z} \qquad (2)$$

Both D and z are measured in rad or, in accordance with the International System of Units, in gray (1 Gy = 1 J/kg = 100 rad). Nevertheless one must strictly discriminate between the two quantities D and z whenever one deals with cellular or subcellular structures.

One may note that the limit value in Eq(2) will not exist if one considers a vanishing mass element in free space. This problem and its implications are discussed in ICRU-report 25 (Ref.2). In the present context it will be sufficient to consider a mass element in a uniform medium. One may also assume that the radiation field is uniform throughout the mass element.

Under a specified irradiation condition and for a given microscopic reference volume one can never predict the value of z. One can, however, state a probability distribution of the values of specific energy. Usually one considers spherical volume elements. The distribution of z depends on the size of the volume, on the type of the radiation and on the absorbed dose, D. The distribution is designated by f(z;D). According to the usual definition of a probability density f(z;D) dz is the probability that the specific energy is between z and z+dz.

It is in most cases unnecessary to deal with the functions f(z;D). Instead it is sufficient to consider the distribution of increments z which are produced in individual events of energy deposition. The term *energy deposition event* (or simply *event*) denotes energy transfer to the reference volume due to a primary charged particle and/or its secondaries (Ref.1). The single event distribution is designated by $f_1(z)$, where $f_1(z)dz$ is the probability that a specific energy between z and z+dz is produced in an event.

The distributions $f_1(z)$ can be experimentally determined by means of tissue-equivalent spherical proportional counters, the socalled Rossi counters (Ref.4,5). They can also be computed. For two reasons knowledge of the single event spectra is usually sufficient. First, it is possible to base the quantitative analysis of cellular effects of ionizing radiation mainly on the spectra $f_1(z)$ (Ref.6). Secondly it is always possible to compute the dose-dependent spectra f(z;D) from $f_1(z)$. Since the energy is imparted to a volume in events which are statistically independent, the distribution f(z;D) is the solution of the *compound Poisson* process:

$$f(z;D) = \sum_{\nu=1}^{\infty} e^{-n} \frac{n^{\nu}}{\nu!} f_{\nu}(z) \qquad (3)$$

where $f_{\nu}(z)$ is the ν-fold convolution of $f_1(z)$ and n is the expected number of events (Ref.7).

Eq(3) can be solved by numerical integration, it can also be solved with the help of the fast Fourier transform algorithm.

The relation between $f_1(z)$ and f(z;D) is here considered because it is an important part of the conceptual frame work of microdosimetry. For HZE-particles, however, much more even than for conventional radiations, the functions $f_1(z)$ contain the essential information, while f(z;D) need hardly be invoked. The reason is, that one deals typically with low doses, low dose rates, and with densily ionizing particles. It is then unlikely that the nucleus of a cell is traversed by more than one HZE-particle. The situation is therefore sufficiently characterized by a description of the energy deposition in individual events.

While only few cells are traversed by HZE-particles those few cells experience large values of specific energy z. Fig.1 illustrates this. The mean number of events per unit absorbed dose is here given as a function of the diameter of the site. On a second abscissa scale the inverse quantity, the mean specific energy per event, is given. The relations are given for particles with an LET of 10 keV/µm, 100 keV/µm, and 1000 keV/µm. Even for a large site such as the entire nucleus of the cell (d $\approx$8 µm) the mean number of events per rad is much less than 1 and the event sizes are correspondingly large. One deals therefore at small doses exclusively with single event processes.

One must note that Fig.1 is based on an approximation in terms of the LET-concept, i.e. the particle tracks are idealized as infinite lines with no radial extension and with continuous rate L of energy transfer. This approximation is sufficient for a crude assessment of event frequencies and mean event sizes. As will be seen in the following paragraph, it is insufficient for a realistic treatment of the cellular effects of HZE-particles.

3. INAPPLICABILITY OF THE LET-CONCEPT

The LET-concept has a certain range of applicability, but it can also lead to erroneous statements concerning the energy deposition in microscopic regions. There are three factors which limit the validity of the LET-concept. The first factor is the finite range of the particles which may lead to incomplete traversals of the cell, or at least to a change of the LET of the particle while it is traversing the cell. This factor is usually not important since in most cases of interest the ranges of HZE-particles are larger than the dimensions of the cell (see Fig.2).

The second factor is the energy transport by δ-rays, i.e. by secondary electrons, away from the track core. The spectrum of δ-rays produced by a HZE-particle depends only on its velocity. Accordingly the effective radius r_p of the penumbra of the track can be given as a function of the energy per nucleon, E_n. The following formula has been proposed (Ref.9):

$$r_p/\mu m = 0.768\ E_n/MeV - 1.925\sqrt{E_n/MeV} - 1.257 \quad (4)$$

For particles with high charge the stopping power is so large that overlap of the penumbra of the track with the nucleus of the cell will rarely fail to lead to energy deposition in the nucleus. The effective cross-section of the cell nucleus is then $\pi(r_n+r_p)^2$ where r_n is the radius of the nucleus and r_p is the radius of the penumbra of the particle track. If r_p is ten times smaller than r_n the geometrical cross-section of the nucleus of the cell is increased by 20%. One might take this as the limit of the applicability of the concept of LET, and state that the radial extension of the track must be taken into account if $r_p > 0.1 r_n$. For a radius of 4 μm of the cell nucleus this leads to a critical value r_p = 0.4 μm, and according to Eq(4) to a critical energy of 4 MeV/nucleon.

This means that the LET-concept is generally not applicable to particles of high energy and high atomic number. The radial extension of the track must always be taken into account. This applies *a fortiori* to cellular structures which are smaller than the nucleus.

In Fig.3 the LET of different heavy ions is given as a function of the energy per nucleon of the particles. The solid parts of the curves correspond to that narrow range of the particle energies where the LET-concept is applicable to the nucleus of the cell. On the left part of the curves the LET-concept is inapplicable because the range of the particles is too small (<10 μm); on the right side it is inapplicable because of the radial extension of the tracks. For smaller sites the applicability of LET will be restricted to even smaller energies of the heavy particles.

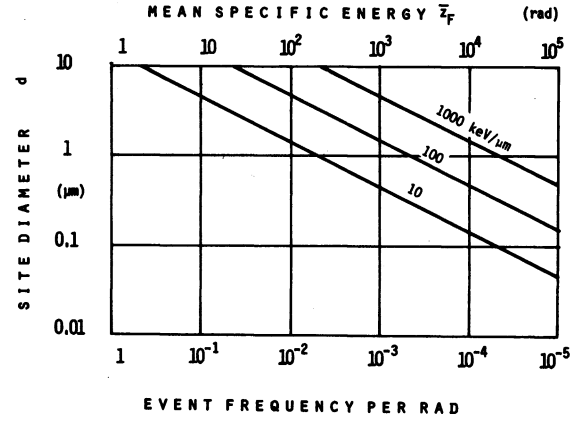

Figure 1. Event frequency and mean specific energy $\bar{z}_F$ produced by particles of different LET in spherical tissue regions of various diameters d

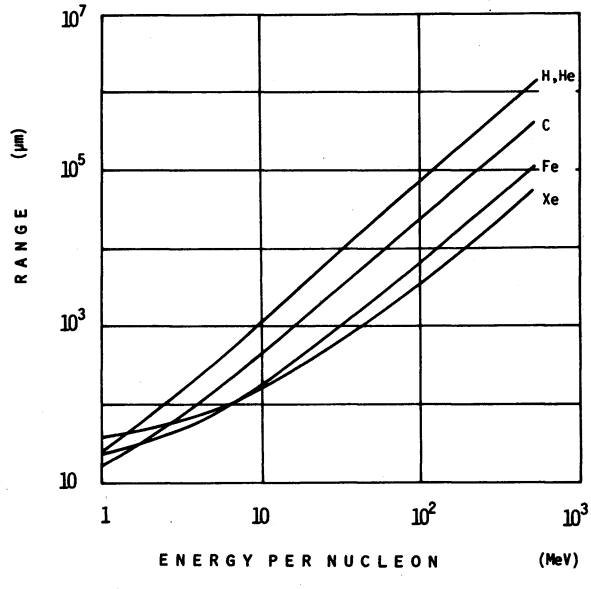

Figure 2. Ranges of heavy ions in water as a function of energy per nucleon (data from Ref.8)

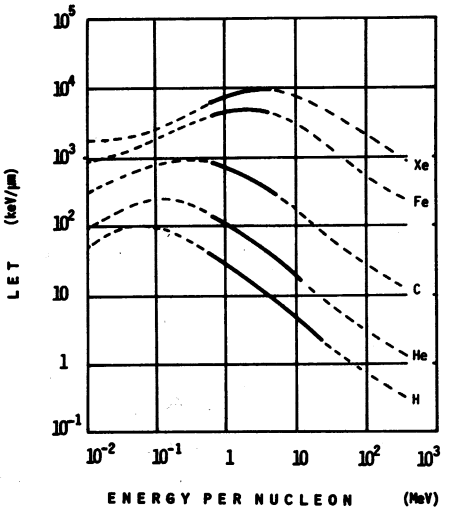

Figure 3. Stopping power of heavy ions in water as a function of energy per nucleon (data from Ref.8).

The solid line segments indicate those energy ranges where the LET-concept describes correctly the energy transfer to the nucleus of a mammalian cell.

The partial overlap of the penumbra of the track with the nucleus of the cell which occurs at 4 MeV/nucleon in 20% of all events, leads to relatively small energy depositions. For low values of Z, i.e. for particles with moderate LET, this means that these events are not very significant. For particles with low Z the validity of the LET concept extends therefore, as indicated in Fig.3, to somewhat higher energies (see also Ref.10). For high values of Z, however, it is in fact the *indirect events* which are of greatest concern for radiation protection. The reason is that most of the direct traversals of the primary particle through the nucleus of the cell, will lead to inactivation of the cell (Ref.11,12). Genetic effects and carcinogenesis, as the critical somatic effect, must therefore be predominantly due to the indirect events in which the particle merely injects δ-rays into the nucleus of the cell. These indirect events are therefore a central topic in considerations of radiation protection in space. The following section will deal with this subject.

4. CONSIDERATION OF THE RADIAL PROFILE OF THE PARTICLE TRACK

According to the socalled equi-partition law a charged particle loses equal amounts of energy in *glancing (soft) collisions* with small energy transfers, and in *knock-on (hard) collisions* with larger energy transfers. The energy lost in soft collisions forms the very narrow track *core*. The energy lost in hard collisions forms the extended *penumbra* of the track.

The energy losses in hard collisions can have values between the mean excitation potential I (= 65eV for water) and $4(m/M)E_n = 0.0022\ E_n$; where E_n is the energy per nucleon of the heavy particle, m is the electron mass, and M is the mass of a nucleon. In the relativistic case a slightly modified formula applies (Ref.13). The cross-section for an energy loss E in a hard collision is inversely proportional to E^2:

$$\sigma(E) \sim 1/E^2 \quad \text{for } E < E_{max} = 0.0022\ E_n \qquad (5)$$

Accordingly the fraction of energy lost in hard collisions with energy loss exceeding E is:

$$\Delta(E) = 0.5 \int_E^{E_{max}} E \frac{1}{E^2}\, dE \Big/ \int_I^{E_{max}} E \frac{1}{E^2}\, dE$$

$$= 0.5\ \frac{\ln(E_{max}/E)}{\ln(E_{max}/I)} \qquad (6)$$

This useful formula permits for any HZE-particle a ready assessment of the fraction of energy going into delta-rays of a specified range of energies. One can express the relation in the simple statement that equal logarithmic intervals of energy contribute equally to the stopping power.

From the differential collision cross-sections one can, in principle, calculate the average radial energy distribution around the track core. Such calculations have been performed; the results must be considered as somewhat tentative since they have not been experimentally checked except for particles with energy of only a few MeV (Ref. 14). Chatterjee and Schäfer (Ref.9) give a formula for the absorbed dose D produced at a point in water at a distance r from the trajectory of a HZE-particle. If one normalizes to the stopping power L one can write the formula in the following form:

$$\frac{D/\text{rad}}{L/\text{keV}/\mu\text{m}} = 2.55 \begin{cases} \dfrac{1+b}{(r_c/\mu\text{m})^2} & r < r_c \\ \dfrac{b}{(r/\mu\text{m})^2} & r > r_c \end{cases} \qquad (7)$$

where r_c and r_p are the radii of the core and the penumbra of the track. The coefficient b is equal to:

$$b = 0.5 \,/\, (\ln(r_p/r_c) + 0.5) \qquad (8)$$

The parameter r_p is approximated by Eq(4), and r_c is set equal to:

$$r_c/\mu\text{m} = 0.0116\ \beta \qquad (9)$$

where β is the particle speed divided by the speed of light.

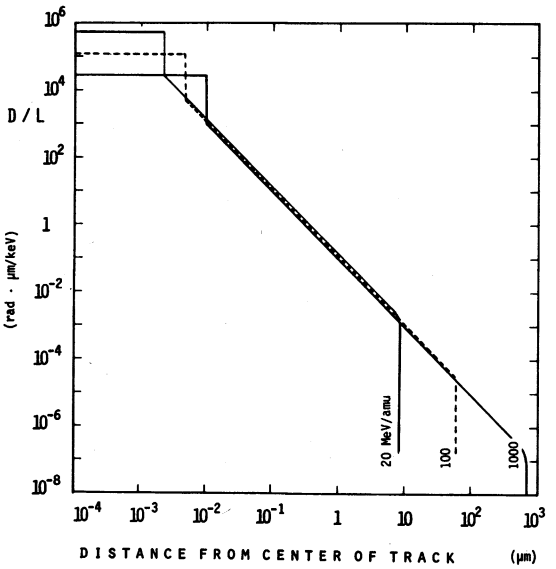

Figure 4. Absorbed dose divided by the total collision stopping power of a particle as a function of the distance r from the trajectory.

Curves are given for particles of 20 MeV, 100 MeV, and 1000 MeV per nucleon in tissue

Fig.4 represents the resulting curves for particles of 20 MeV, 100 MeV, and 1000 MeV per nucleon. Multiplying the ordinate values by the LET of the particle one obtains the absorbed dose at various distances from the trajectory.

One may note that it is correct to speak in this context of an absorbed dose. The absorbed dose is defined in terms of an expectation value, and it is therefore, as stated earlier, not equal to the energy density actually produced in a mass element at the point in question.

One will also note that the description of the track core is a rough simplification. This is, however, irrelevant to radiobiological applications, where direct energy transfer or diffusion of radiation induced free radicals always extends over distances larger than the radius of the track core. The main point is, in the present context, the radial extension of the penumbra.One notes from Fig.4 that the absorbed dose in the penumbra is proportional to L with only a slight dependence on the velocity of the particle.

As a rough approximation one may use the relation:

$$D = 0.13\ L/r^2 \qquad (10)$$

if the units rad, keV, and μm are used. For low particle energies (∿20 MeV/nucleon) the doses are according to Eqs(7) and (8) about 15% higher, for high energies (∿1000 MeV/nucleon) they are about 15% lower. In view of the approximate nature of the equations one may disregard these factors.

This simple rule permits important conclusions. In particular it implies that the doses are very high in the immediate vicinity of the track core while they decrease rapidly at larger distances. Table I gives typical examples. One finds that even in the case of a very heavy particle such as a Xe-nucleus the dose at a distance of 10 μm is low; the effective penumbra even of very high atomic number particles is therefore more narrow than the dimension of a mammalian cell.

Fig.5 represents the fraction of energy which is transported beyond a specified distance r from the trajectory. These relations result from an integration over the curves in Fig.4. The fractions are generally low if one considers distances larger than the diameter of a cell nucleus. Furthermore the biological effectiveness is relatively low since this energy is imparted to the nucleus of the cell by isolated delta-rays reaching the outer fringes of the penumbra where the dose is low.

These considerations support the following conclusions. For particles of LET less than roughly

Particle	Energy per nucleon (MeV)	LET (keV/μm)	Distance from trajectory 1μm	10μm	100μm
Fe	20	1900	280	-	-
	100	580	74	0.7	-
	1000	170	20	0.2	0.002
Xe	20	6000	888	-	-
	100	2100	270	2.7	-
	1000	550	61	0.6	0.006

Table I Absorbed doses in rad at different distances from the trajectory of energetic Iron and Xenon ions

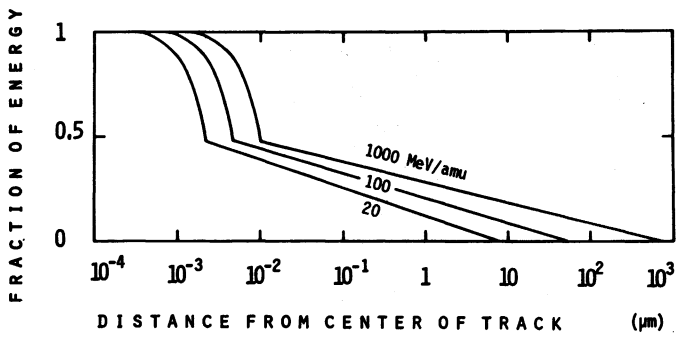

Figure 5. Fraction of energy imparted at distances larger then r from the trajectory for particles of 20 MeV, 100 MeV, and 1000 MeV per nucleon in tissue

100 keV/μm direct traversals of the cell nucleus are the cause of cytogenetic effects and of cell transformations. For particles of higher LET direct traversals of the nucleus are less important because they will in most cases lead to inactivation of the cell. Cellular inactivation is however not usually the critical problem of radiation protection. Most important are, for particles of very high LET, those events where the particle traverses the cytoplasm in close vicinity to the nucleus of the cell, so that indirect events occur and a considerable number of δ-rays is injected into the nucleus. Particles which do not enter the cell have only a slight probability to produce damage in its nucleus.

5. CONCLUSIONS

It has been concluded that the concept of LET is not, except as a very rough approximation, applicable to HZE-particles. A quantitative assessment of the cellular effects of these particles requires explicit microdosimetric treatment. Essential aspects of the microdosimetry can be understood in terms of the distribution of dose around the trajectory.

It will nevertheless be necessary to develop the microdosimetry of HZE-particles further in order to include additional factors.

The radial distribution of absorbed dose specifies merely the *expected* energy density in an infinitesimal mass element. The dose varies rapidly with distance from the track core. If the dimension of the biological target is comparable to its distance from the trajectory, the expected energy density must therefore be obtained by an integration over the dose profile. This leads then, if one considers all possible positions of the object, to functions which are analogous to the explicit microdosimetric distributions $f_1(z)$. The resulting functions are, however, subject to the important limitation that they describe expectation values rather than actual energy imparted to the site. One might say that one deals with an *amorphons track model* which treats the particle track as an average phenomenon without δ-ray structure. A more realistic description will have to account for energy loss straggling of the primary particle and for the resulting statistics of the traversal of the site by δ-rays.

A rigorous microdosimetric treatment will require the use of the explicit distributions $f_1(z)$ or of similar concepts which account for the actual fluctuations of energy transfer to the cellular or subcellular structures. Little work of this type has yet been performed for HZE-particles. It is, however, likely that the availability of the new generation of heavy ion accelerators will change the situation.

Another factor which will require more detailed treatment is the spatial correlation of spallation products. In the preceding section it has been concluded that the effective lateral extension of the track of HZE-particles is more narrow than cellular dimensions even for extreme values of Z. Cellular damage at larger lateral distances from the trajectory of the primary particle can however be caused by spallation products. Experimental microdosimetric studies of clusters of spallation fragments will accordingly be important. Quite generally experimental microdosimetric studies will be required whenever one deals with mixed high energy radiation fields of unknown composition.

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