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INTERPRETATION OF MUTATION INDUCTION BY ACCELERATED VERY HEAVY IONS IN BACTERIA

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INTRODUCTION

Interpretation of biological effects of ionizing radiation is quite a difficult problem (see e.g. 1). The most popular theories relevant to the interpretation of experimental data are track structure theory (2-6) and microdosimetry (7-9). Particular models are, however, not generally accepted (see e.g. 10,11). In order to select appropriate radiation field descriptors, detailed calculations of energy depositions and their clusterization have been performed (12-14). The results showed correlation between the induction frequency of some types of clusters and cell inactivation by ionizing radiation. However, available experimental data on mutation induction have not been quantitatively interpreted. This study shows that the field descriptors appropriate for some biological effects at some range of particle parameters could be quite simple quantities. In order to construct such field descriptors appropriate experimental data are needed. We used mutation induction in bacteria as a model system for this purpose.

EXPERIMENTAL RESULTS

Our experimental results on mutation induction by ionizing radiation in bacterial cells have been published without quantitative interpretation of the relative biological effectiveness and its dependence on particle parameters (15-19). Using *lacZ*$^+ \rightarrow$ *lacZ*$^-$ mutations in *Escherichia coli HfrH* we have shown that the mutagenic effectiveness increases with LET_∞ up to some maximum value at about 20 keV/μm (15). In the range of very heavy ions (Z>10) we have shown that the induction of *his* revertants in *Bacillus subtilis* decreases with decreasing particle energy in the range up to 10 MeV/u (17). Our experimental data on mutation induction in wild-type bacteria obtained at different radiobiological heavy-ion facilities are summarized in Fig.1. Forward mutations *lacI*$^+ \rightarrow$ *lacI*$^-$ were detected in *Escherichia coli* strain Y_{mel} on X-gal plates (18, 19); vegetative cells of *Salmonella typhimurium*, strain *TA102* were used to detect *his*$^- \rightarrow$ *his*$^+$ reversions (18, 16). Forward mutagenesis in *lacZ* gene was investigated using *Escherichia coli* cells on tetrazolium plates (15). Reversions in *Bacillus subtilis* spores *his*$^- \rightarrow$ *his*$^+$ were investigated after irradiation of the cells in a dry state using selective plates (17).

Bacteria in thin layers were exposed to heavy ions from U-120 heavy-ion accelerator (20), Institute of Nuclear Physics (INP), Řež at Prague. Irradiation with

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neon and iron ions was performed at BEVALAC (21), Lawrence Berkeley Laboratory (LBL), Berkeley, California; irradiation with low energy high Z ions at UNILAC (22), Gesellschaft für Schwerionenforschung (GSI), Darmstadt, FRG. Induction of *lacZ* mutations was measured at a U-200 cyclotron (23), Joint Institute for Nuclear Research, Russia.

The efficiency of mutation induction was determined from the equation $m(D) = \alpha_{\gamma,m} \times D$ for γ-rays or $m(F) = \sigma_{i,m} \times F$ for heavy ions; where m is the mutation frequency, $\alpha_{\gamma,m}$ is the mutation induction constant, and $\sigma_{i,m}$ is the mutation induction cross-section; D is the radiation dose and F is the particle fluence. The initial slopes of the dose or fluence dependences, $m(D)$ or $m(F)$, respectively were estimated for different types of ionizing radiation by means of standard statistical methods (least square fit). Therefore theoretical analysis presented in this paper will be related to low doses of γ-rays and low fluences of heavy ions. Owing to the fact that different bacterial strains and conditions of irradiation were used, the ratio $\sigma_{i,m}/\alpha_{\gamma m}$ was taken for comparison and plotted in Fig.1. The significance of this quantity (MPE) is similar to relative biological effectiveness (RBE). MPE is however derived from more fundamental quantities; it will be called mutagenic effectiveness per particle (*MPE*).

The results show that there is no common dependence of the particle mutagenic effectiveness of heavy ions on LET_∞. Therefore the energy of ions must be taken into consideration. The rationale of our approach is based on the consideration of mutation induction, which is related to some critical amount of deposited energy. The probability of the occurrence of the effect will be high for a certain amount of energy and it will decrease for both lower and higher quantities of energy. This means that not in all cases - depending on Z and E of the particle - the energy deposited in the centre of ion path (the "track-core") will contribute to the effect. The energy deposited in the sensitive volume of bacteria (approx. $0.1\mu m^3$) by the "track-core" depends mainly on LET_∞ of the particle; for LET_∞=100 keV/μm the specific energy is about 50-100 Gy. Above this value of LET_∞ the probability of cell inactivation by one particle passing through a bacterial cell will increase substantially. Therefore, mutation induction will be related mainly to indirect hits and the fraction of energy deposited in indirect hits could be quite a good radiation field descriptor related to mutation induction in bacteria.

THEORETICAL RESULTS

The fraction of energy deposited in indirect hits, f_δ, can be calculated from different track-structure models (3-6). Some of them are based on the model of "core and penumbra" as developed by Chatterjee (3) and Kudryshov (5), on classical collision dynamics (6) or on Monte Carlo simulations of energy deposition (4, 9). The following method of calculation has been used.

The sphere with given radius (r) was randomly placed into the track described by particular model and the energy inside, w, was estimated by its value in random element in three-dimensional space. If the impact parameter, ρ, was greater (smaller) then the radius of the sphere, r, the energy was added to indirect, w_{ind}, (direct, w_{dir}) hits. The probability of hit increases with impact parameter (owing to radial symmetry) and therefore the energy contributions were multiplied by ρ. The fraction of energy deposited in indirect hits: $\frac{\Sigma w_{ind}}{\Sigma w_{dir}+\Sigma w_{ind}}$ is plotted as a dependence on particle specific energy E_n in Fig. 2 for different models: Kudryshov, 1973, Chatterjee and Magee, 1973, Katz, 1988, Kiefer and Straaten, 1986.

Owing to the divergency of the local dose at $\rho=0$ ($D \to \infty$) in the case of the model of Katz, 1988 the results of MC-calculations are not reliable. We have therefore introduced an artificial track core much smaller as compared with our biological object by integration of the core area. The energy deposited inside the core area was assumed to be homogeneously distributed in it. We have calculated the dependence of f_δ on the radius of the artificial track core (r_{core}) and established that the results do not depend on r_{core} if $r_{core} < 0.01$ μm.

The shapes of the functions $f_\delta(E_n)$ are similar for different track structure models (Fig. 2), the absolute values are however somewhat different. The results of calculations depend on the density of energy, e.i. local dose, deposited in the outer parts of the track and on the range of δ-electrons. The models of Chatterjee and Magee, 1973 and Kudryashov, 1973 give relatively smaller local doses in outer parts of the track as compared with the other mentioned models. The energy is concentrated more in the track core (about 50%) at very small volumes. Also the ranges of the δ-electrons in the two models are smaller as compared with the models of Katz, 1988 or Kiefer and Straaten, 1986.

Using the $f_\delta(E_n)$ function we can define two quantities: the fraction of LET deposited in indirect hits, $LET_\delta = LET_\infty \times f_\delta$, and the complementary fraction of

energy deposited in direct hits: $LET_{\Delta} = LET_{\infty} \times (1-f_{\delta})$. These quantities could be used to describe the biological effects of radiation (in similar way as *LET* or E_n).

If the cells are killed by the passage of the "track core", the only contribution to mutation induction can come from indirect hits and the mutation frequency will depend on the density of the energy deposited from δ-rays. The mutagenic effectiveness of heavy ions can be thus predicted on the assumption that the δ-electrons are as efficient in mutation induction as γ-rays if the dose deposited from δ-rays is the same. Starting from the equation for the radiation dose of accelerated heavy particles, *D* [Gy], using the particle fluence, *F* [p/μm2]:

$$D = 0.16 \times LET_{\infty} \times F \qquad (1)$$

we can substitute the *LET* [keV/μm] *by* its fraction corresponding to indirect hits, $f_{\delta} \times LET_{\infty}$, and the dose will be then the dose related to mutation induction:

$$D_m = 0.16 \times f_{\delta} \times LET_{\infty} \times F. \qquad (2)$$

The mutation induction frequency will be $\alpha_{\gamma,m} \times D_m$. Using the definition of the mutation induction cross-section and the definition of *MPE* we can come to the equation:

$$MPE = 0.16 \times LET_{\infty} \times f_{\delta}. \qquad (3)$$

Mutagenic effectiveness per particle (*MPE*) of heavy ions with linear energy transfer in the range of LET_{∞}>100keV/μm is shown as a function of $0.16 \times f_{\delta} \times LET_{\infty}$ in Fig. 3. Experimental data are taken from Fig.1 for LET_{∞} >100 keV/μm. Theoretical dependence is in agreement with Eq.3 represented by a straight line (Fig. 3). This regimen of the induction of mutations by heavy ions is called "δ-ray mutagenesis". The agreement between experimental and theoretical data is better for the models of Kudryshev, 1973 and Kiefer and Straaten, 1986 as compared with the other two models (Fig. 3a,d). Survival of direct hits at $LET_{\infty} \approx 100 keV/\mu m$ can lead to increased *MPE*. Experimental data as well as theoretical curves are plotted in dependence on LET_{∞} and on particle energy E_n in Fig. 4 a,b.

Mutagenic effectiveness of heavy ions at the range of particle parameters near to LET_{max}=20 keV/μm is higher as compared with the effectiveness of γ-radiation (14, 17). It means that the mutagenic effectiveness of the track core is higher as compared with γ-radiation (or δ-electrons) owing to higher concentration of energy

deposited at nanometer sites. Therefore the fraction of particle energy deposited by indirect hits might not be significant for the induction of mutations if the cells survive direct hits. We tested this hypothesis using "restricted *LET*", $LET_{\Delta}=LET_{\infty}\times(1-f_{\delta})$.

Fig.5 shows that the quantity LET_{Δ} could be reasonably good parameter to which the mutagenic effectiveness of light ions (D, He) or ions with a very high energy could be related (with LET_{∞} near to 20 keV/μm). This regimen of the induction of mutations by heavy ions is called "track-core mutagenesis". All the data follow a common curve, regardless of the atomic number. The curve increases substantially in the range of $LET_{\infty}\leq 20 keV/\mu m$. The nonlinear shape of this dependence means that not only energy absorbed in the sensitive volume is an important characteristic. Some values of LET_{Δ} (at about 20 keV/μm) are more effective due to appropriate spatial distribution of the deposited energy. Greater density of energy deposition leads to lethal events, the lower one is not effective in the induction of corresponding mutagenic lesions. If the dimension of the target (DNA) of about 3 nm is considered, the amount of deposited energy in it will be 60 eV. This energy represents the optimum for the induction of mutagenic lesions. The growth of the *MPE* for the "track-core mutagenesis" is restricted at higher *LET* (owing to the lethal effects). On the other hand, the cross-sections of the "δ-ray mutagenesis" increase proportionally to LET_{δ} (theoretically without limit).

Table 1. Mutagenic effectiveness per particle (*MPE*) calculated for different types of ionizing radiation.

Ion	E_n [MeV/u]	*LET* [keV/μm]	Strain	*MPE* [Gy.μm^2]	S.D. [Gy.μm^2]
D	5.0	8.0	E.coli	1.08	0.14
	5.0	8.0	S.typhimurium	1.15	0.27
He	0.9	115	E.coli	2.4	1.8
	1,7	72	E.coli	14,4	1,9
	2,5	54	E.coli	13,8	2,1
	3.4	44	E.coli	12.3	2.4
	3.4	44	S.typhimurium	11.3	3.0
	6.0	28	E.coli	12.3	1.1
	6.0	28	S.typhimurium	11.8	2.2
	8,0	22	E.coli	8,1	0,7
C	7,0	220	E.coli	5,6	2,1
Ne	1.5	1400	B.subtilis	0	
	3.3	900	B.subtilis	0	
	5.7	650	B.subtilis	9.0	1.2
	5.9	630	B.subtilis	9.6	1.3
	10.2	430	B.subtilis	21.6	2.7
	14.4	330	B.subtilis	19.2	1.9
	18.6	280	B.subtilis	40.7	4.6
	425	30	S.typhimurium	9,5	2,8
	600	26	E.coli	3,0	0,4
	600	26	S.typhimurium	4,2	0,5
Fe	400	210	E.coli	28.6	3.1
	400	210	S.typhimurium	32,8	4,3
Ni	0,9	5000	B.subtilis	0	
	3,4	3700	B.subtilis	40.7	4.6
Kr	10,0	3930	E.coli	145	24
	10,0	3930	S.typhimurium	208	63
	10,8	3200	B.subtilis	69.5	9.0
	17,7	2500	B.subtilis	59.8	7.2
Xe	2,1	8700	B.subtilis	26.3	4.8
	2,8	8300	B.subtilis	44.3	9.0
	4,2	7600	B.subtilis	59.9	7.7
	6,9	6700	B.subtilis	101	10
	9,5	6000	B.subtilis	142	13
	11,8	5500	B.subtilis	121	14
	16,8	5000	B.subtilis	139	33
U	2,6	15400	B.subtilis	62.9	6.8
	7,7	13700	B.subtilis	176	28
	10,7	12600	B.subtilis	281	38
	11,9	12200	B.subtilis	259	35

Mean values and standard deviations are estimated using SigmaPlot, Curve Fit option.

DISCUSSION

Bacteria are used as a model system in many different investigations. The understanding of mechanisms related to some phenomenon in bacteria is usually of great importance for other living systems. Based on our experimental data we have shown that the cross-sections for mutation induction, σ_m, by ionizing radiation in bacteria in the range of very heavy ions can be undersood at quantitative level.

The fraction of particle energy deposited in indirect hits in bacteria, f_δ, is of great importance for our interpretation. The values of f_δ have been calculated by means of Monte-Carlo simulation using different track structure models (3-6). The calculations performed with different models yield very similar $f_\delta(E_n)$ dependences over specific particle energy, E_n, in the range of 1-1000 MeV/u. Long range of the δ-electrons in the model of Katz, 1986 leads to the higher absolute values of f_δ . The models of Kudryshev, 1973 and Chatterjee and Magee, 1973 assume that about 50% of energy is deposited inside small dimesions along the path of heavy ion (up to several nanometers). The best description of our experimental data has been achieved using the models of Kudryshev, 1973 and Kiefer and Straaten, 1986 (Fig.3a,d). The model of Kudryshev, 1973 is based on the assumption that the track core has constant radius (1 nm) and about 50% of energy is deposited in it. The range of δ-rays is equal to $p = 0.04 \times E_n^{1.75} [\mu m]$, where the energy is given in MeV/u. The local dose outside the track core D_δ [Gy] is proportional to the the following expression

$$D_\delta \approx \frac{Z_{ef}^2}{E_n^{1.06}} \times \frac{1}{\rho^2}, \qquad (4)$$

where Z_{ef} is the effective charge of the particle and ρ is the distance from the path of the ion (in μm). The total energy deposited outside the track-core is proportional to LET_∞ in a broad range of values of particle specific energy. The model of Kiefer and Straaten, 1986 has similar characteristics. The range of δ-rays is given by the equation: $p = 0.0616 \times E_n^{1.7}$ and the local dose

$$D_\delta = 0.000125 \times \frac{Z_{ef}^2}{\beta^2} \times \frac{1}{\rho^2}, \qquad (5)$$

where ρ is given in μm and the dose in Gy. The local dose calculated according to the model of Kiefer and Straaten is lower as compared with the model of Kudryshev, however, the range of δ-rays is longer. For higher particle kinetic energy the local dose at given impact parameter tends to constant limit value.

The dependence of the fraction f_δ on the particle specific energy and on the radius of the sensitive cell structure has been described using an empirical function

$$f_\delta = A\times(1 - exp(-p/B))\times log(p + exp(-p/C))/\ log(D\times E_n) \qquad (6)$$

where $p = 0.06\times E_n^{\,1.7}/r$.

The function has been basically obtained using the range of δ-rays from the model of Kiefer and Straaten, 1986 (the range in the other models can be both longer or shorter). The fraction f_δ has been calculated as the fraction of energy deposited in the track of heavy particle with the specific energy E_n in the space outside from the cylinder with the radius r.

The parameters A,B,C, and D have been determined using SigmaPlot, Curve Fit option as the best fit to the data obtained from the Monte-Carlo calculations. The dependence of f_δ on the radius of the sensitive cell structure, r. has been tested for the model of Kudryshev, 1973. The results for three different radii are shown in Fig. 6.

Two different ranges of LET_∞ can be distinguished. In the range of high LET_∞ (>approx. 100 keV/μm) *MPE* (σ_m) increases with increasing specific particle energy if LET_∞ is kept approximately constant. In the range of low LET_∞ (< approx. 100 keV/μm), *MPE* (σ_m) decreases with increasing E_n. The results show that in the two ranges of LET_∞ two different modes of particle mutagenic action can be found. "δ-ray mutagenesis" is related to those particles whose track-core energy is high enough to kill the cell (LET_∞ >approx.100 keV/μm). "Track-core mutagenesis" is observed in lighter ions or ions with high energy if direct hit of the sensitive cell structure by the particle is not a lethal event. The effectiveness of the "δ-ray mutagenesis" is proportional to $LET_\delta = LET_\infty \times f_\delta$, where f_δ is the fraction of particle energy deposited by δ-electrons in indirect hits in the bacteria. "Track-core mutagenesis" increases with *LET* restricted to the sensitive volume (LET_Δ) but is not proportional to it. The quantities LET_δ and LET_Δ are relevant biophysical characteristics of ionizing radiation for mutation induction in bacteria for ranges of particle parameters mentioned above.

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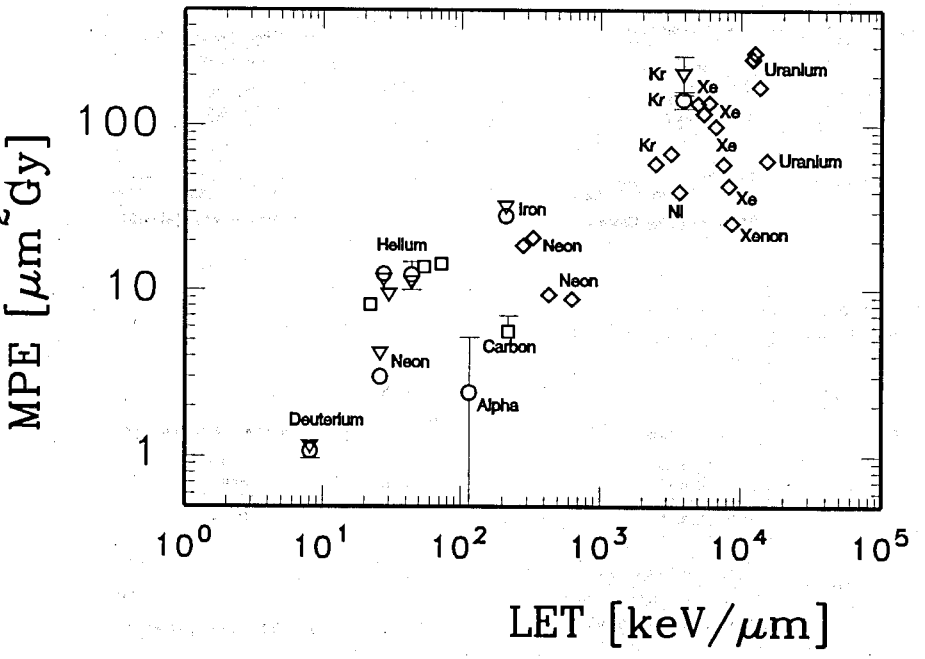

Fig.1. Mutagenic effectiveness per particle (*MPE*) (mutation induction cross-section, σ_m, related to mutation induction constant of γ-radiation, $\alpha_{\gamma m}$) is shown for *Escherichia coli* Y_{mel}, *lacI*$^+$ →*lacI*$^-$ forward mutations (circles), *Salmonella typhimurium his*$^-$→*his*$^+$ reversions (triangles), *Escherichia coli HfrH lacZ*$^+$→*lacZ*$^-$ mutations (squares), and *Bacillus subtilis his*$^-$→*his*$^+$reversions (diamonds).

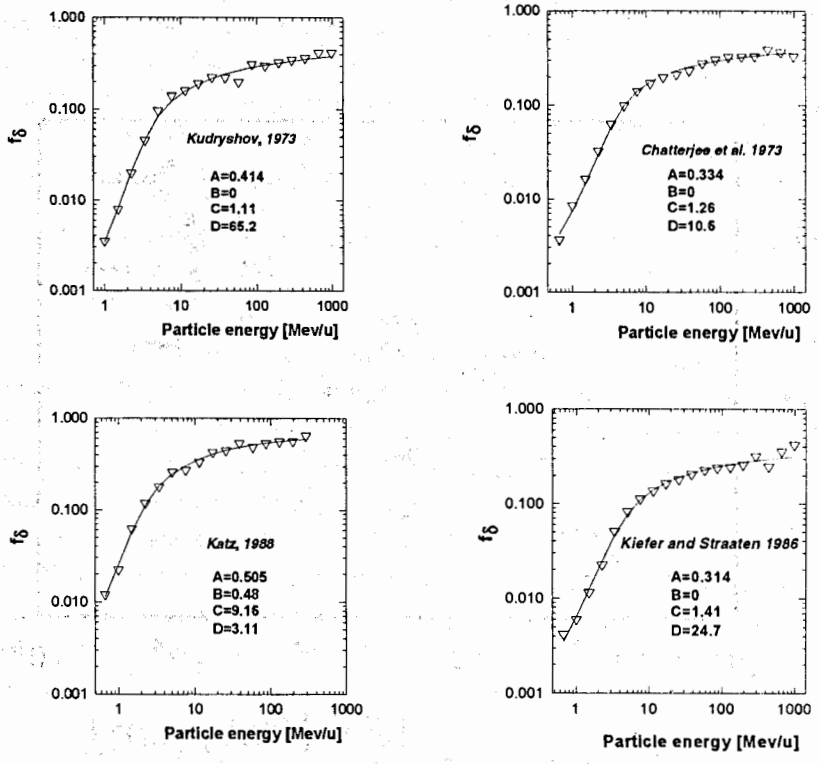

Fig.2. Results of the Monte Carlo calculations of the fraction of energy deposited by heavy ions in indirect hits in spherical objects with dimesions of bacteria (r=0.3 μm).

The fraction of energy deposited in indirect hits is plotted as a dependence on particle specific energy, E_n, for different track-structure models: Kudryshov (5), Chatterjee and Magee (3), Katz (4), and Kiefer and Straaton (6). The best fit of the semiempirical function $f_\delta = A\times(1 - exp(-p/B))\times log(p + exp(-p/C))/\ log(D\times E_n)$ where $p = 0.06\times E_n^{\,1.7}/r$ (according to the model of Kiefer and Straaten, 1986) to the points obtained from the MC calculations is shown by the solid lines.

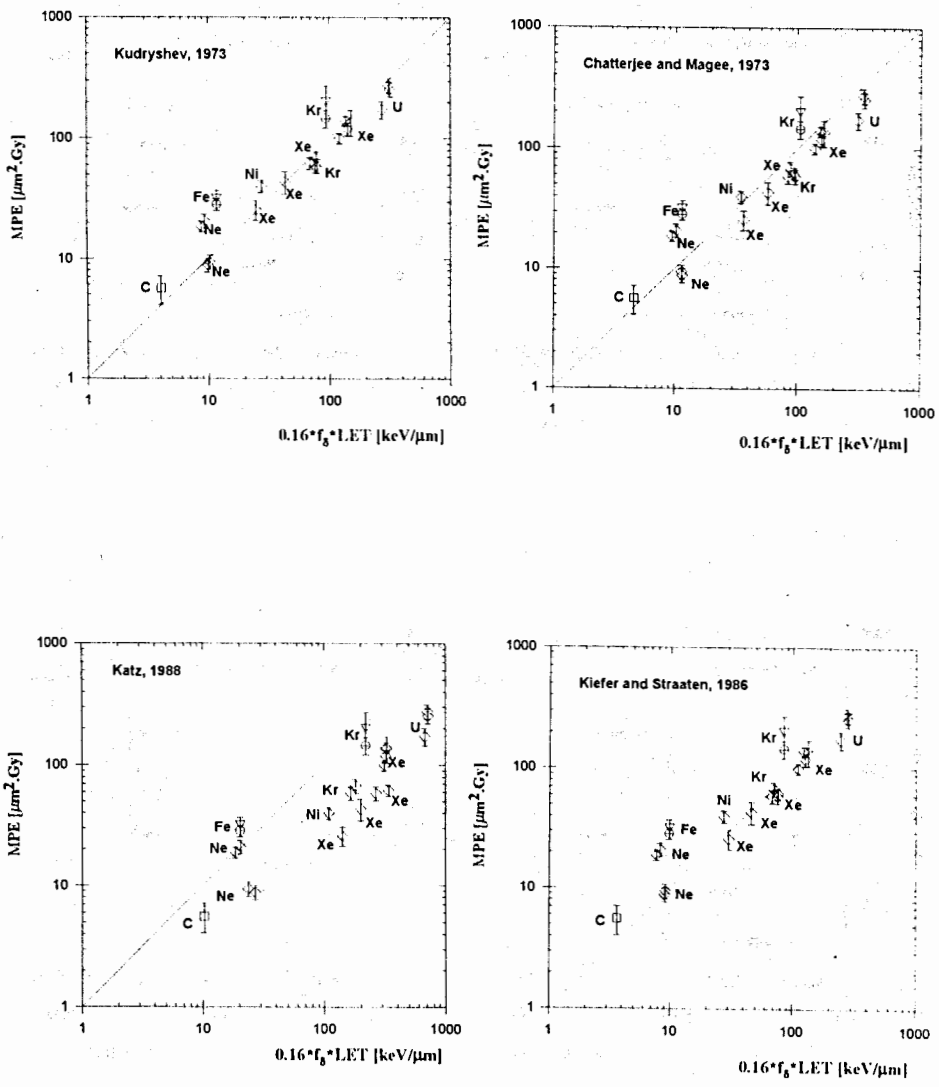

Fig.3. The comparison of different track structure models tested against experimental data. Mutagenic effectiveness per particle (*MPE*) of heavy ions with linear energy transfer in the range of LET_∞>100keV/μm is shown as a function of the quantity $0.16 \times f_\delta \times LET_\infty$. Theoretical dependence (the line) is calculated with the assumption that the δ-electrons are as efficient in mutation induction as γ-rays (Eq.3). Survival of direct hits at $LET_\infty \approx 100 keV/\mu m$ could lead to increased *MPE*. Experimental data are taken from Fig.1.

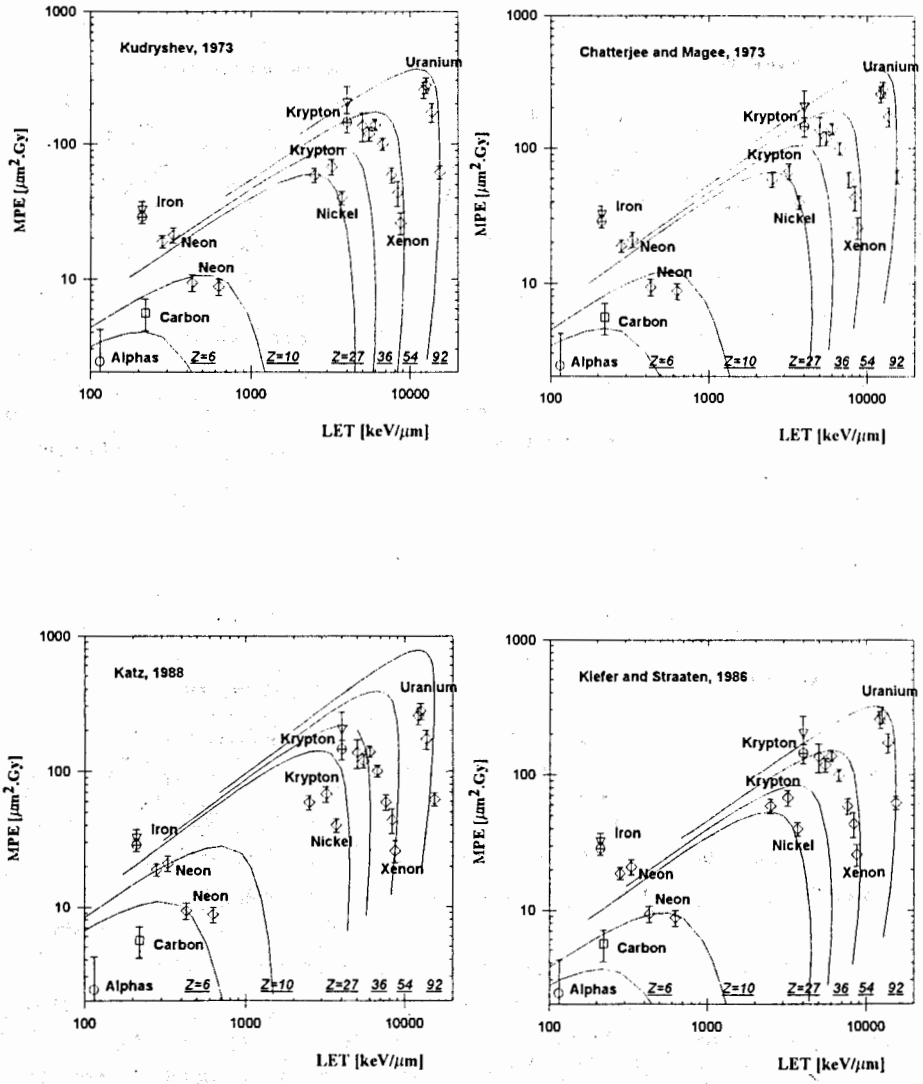
Kudryshev, 1973
Chatterjee and Magee, 1973
Katz, 1988
Kiefer and Straaten, 1986
MPE [μm².Gy]
LET [keV/μm]
1000
100
10
100
1000
10000
Uranium
Krypton
Xenon
Nickel
Iron
Neon
Carbon
Alphas
Z=6
Z=10
Z=27
36
54
92

Figure 4a

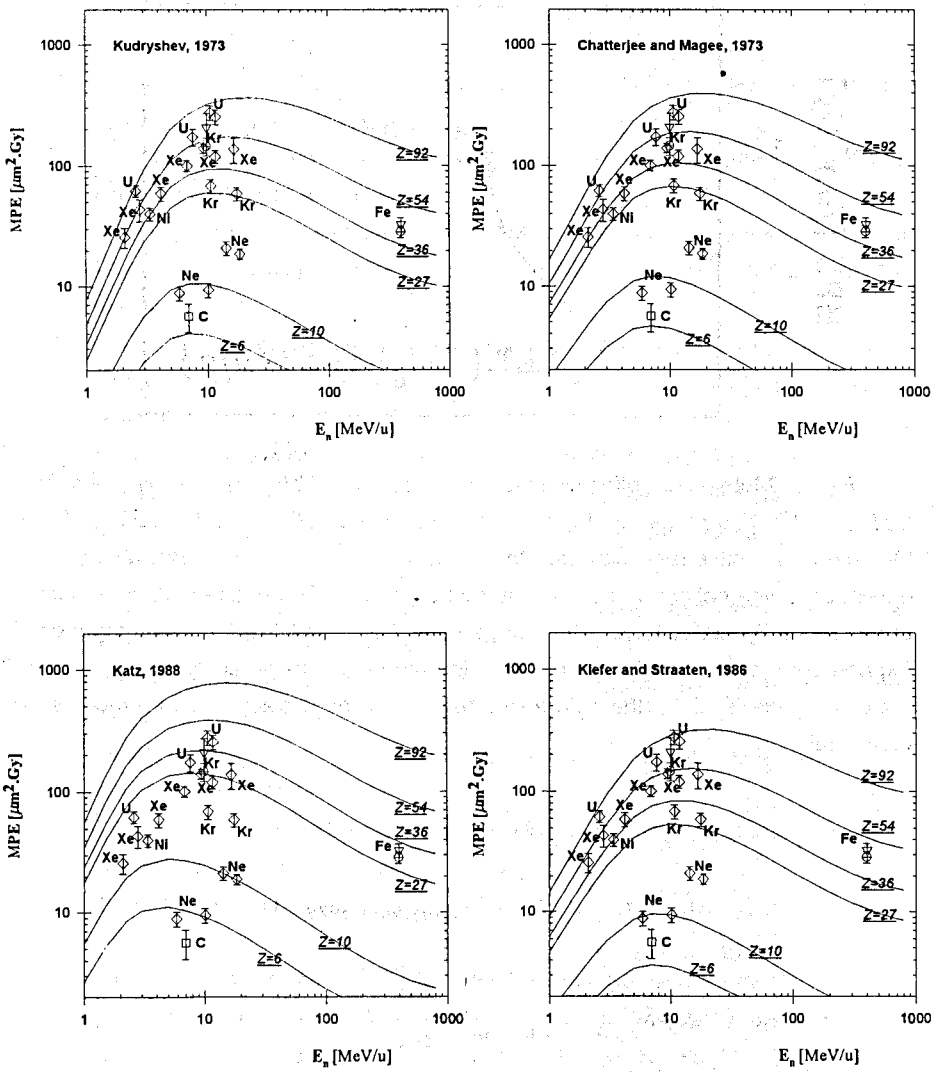

Fig.4. The dependence of *MPE* on particle parameters: LET_∞ (a) and particle specific energy E_n (b). Experimental data are taken from Fig.1; theoretical lines are calculated according to the model of Kudryshev, 1973.

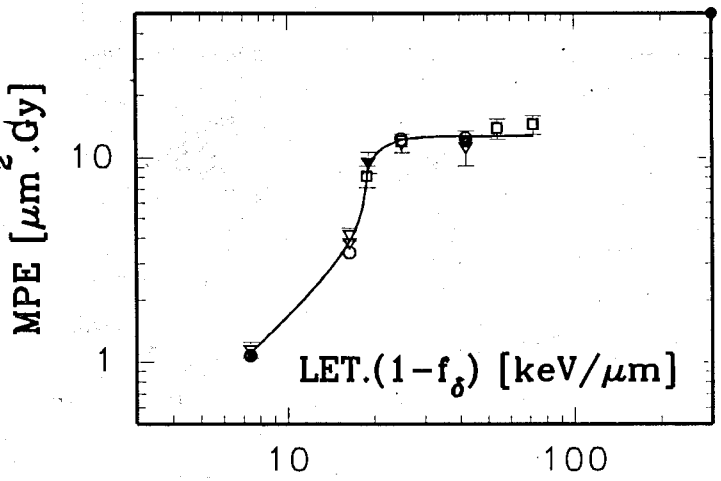

Fig.5. Mutagenic effectiveness per particle (*MPE*) of heavy ions with LET_∞<100 *keV/μm* as a function of "restricted *LET*" ($LET_\Delta = LET_\infty \times (1-f_\delta)$). Mutagenic effectiveness can be described within experimental deviations as a nonlinear mathematical function of the restricted *LET*. The regimen of the induction of mutations by heavy ions in this range of *LET* is called "track-core mutagenesis". Experimental data are taken from Fig.1, the model of Chatterjee has been used for the calculation of LET_Δ (the differences between various track structure models are very small).

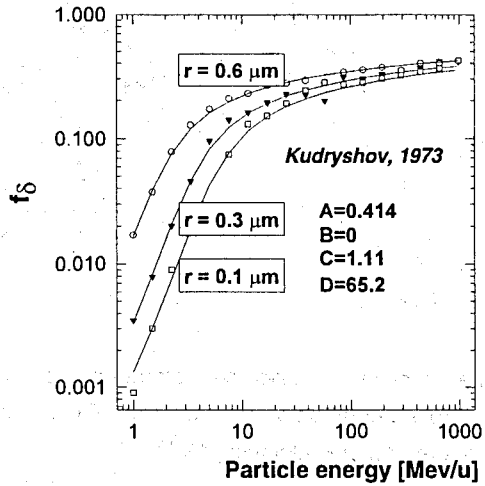

Fig. 6. The dependence of the fraction of energy deposited in indirect hits on the radius of the sensitive volume, r, of the cell. MC calculations are shown together with the lines calculated according to the semiempirical function (see Fig. 2).

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Козубек С. и др. E19-94-164
Интерпретация результатов по индукции
мутаций у бактерий тяжелыми ионами

Предложена простая модель для расчета эффективности индукции мутаций ионизирующими излучениями у бактерий. Проведены оценки радиационных полей для частиц различных энергий и для различных размеров чувствительных структур. При расчетах были использованы четыре модели структуры трека. Полученные расчетные данные были сопоставлены с экспериментальными результатами по индукции мутаций у бактерий. Рассмотрены две модели мутагенного действия частицы. Экспериментальные данные хорошо согласуются с теоретическими результатами, если используется соответствующая модель структуры трека. Очень хорошее согласие получено при использовании моделей структуры трека, разработанных Kudryashev, 1973, и Chatterjee and Magee, 1973.

Работа выполнена в Лаборатории ядерных проблем ОИЯИ.

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Kozubek S. et al. E19-94-164
Interpretation of Mutation Induction
by Accelerated Very Heavy Ions in Bacteria

We propose a simple approach for the calculation of the efficiency of mutation induction in bacteria. The approach is based on the calculation of the fraction of energy deposited by accelerated particles in indirect hits, e.i. in events in which the particle does not pass through the cell, however, the cell is hit by δ-electrons. This descriptor of the radiation field has been evaluated for different values of the particle energy and different radii of sensitive structure. Four models of the track structure have been used for calculations. The results have been compared with experimental data on mutation induction in bacteria. Two different modes of particle mutagenic action can be distinguished. Available experimental data agrees reasonably well with the results of the presented theory if appropriate track structure is taken. Very good results have been obtained with the track structure models of Kudryashev, 1973 and Chatterjee and Magee, 1973.

The investigation has been performed at the Laboratory of Nuclear Problems, JINR.

Communication of the Joint Institute for Nuclear Research. Dubna, 1994