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His$^+$ Reversions Caused in *Salmonella typhimurium* by Different Types of Ionizing Radiation

H. ROOS, W.-H. THOMAS, M. FITZEK, AND A. M. KELLERER

Institut für Medizinische Strahlenkunde der Universität Würzburg, Versbacher Straße 5, D-8700 Würzburg, Federal Republic of Germany

ROOS, H., THOMAS, W.-H., FITZEK, M., AND KELLERER, A. M. *His*$^+$ Reversions Caused in *Salmonella typhimurium* by Different Types of Ionizing Radiation. *Radiat. Res.* **116**, 292–304 (1988).

The yield of *his*$^+$ reversions in the Ames *Salmonella* tester strain TA2638 has been determined for ^{60}Co γ rays, 140 kV X rays, 5.4 keV characteristic X rays, 2.2 MeV protons, 3.1 MeV α particles, and 18 MeV/U Fe ions. Inactivation studies were performed with the same radiations. For both mutation and inactivation, the maximum effectiveness per unit absorbed dose was obtained for the characteristic X rays, which have a dose averaged linear energy transfer (LET) of roughly 10 keV/μm. The ratio of the effectiveness of this radiation to γ rays was 2 for inactivation and about 1.4 for the *his*$^+$ reversion. For both end points the effectiveness decreases substantially at high LET, i.e., for the α particles and the Fe ions. The composition of the bottom and the top agar was the one recommended by Maron and Ames [*Mutat. Res.* **113**, 173–215 (1983)] for application in chemical mutagenicity tests. The experiments with the less penetrating radiations differed from the usual protocol by utilization of a technique of plating the bacteria on the surface of the top agar. As in an earlier study [Roos *et al.*, *Radiat. Res.* **104**, 102–108 (1985)] greatly enhanced yields of mutations, relative to the spontaneous reversion rate, were obtained in these experiments by performing the irradiations 6 h after plating, which differs from the conventional procedure to irradiate the bacteria shortly after plating.

INTRODUCTION

The *Salmonella* mutagenicity test (*1*) is the most widely used short term test for chemical mutagens, and it is therefore desirable to examine its response to different types of ionizing radiation. Several investigations have been performed in the past. Of special importance are the studies of Isildar and Bakale, who have made a broad investigation of the effects of sparsely ionizing radiations on six of the most common tester strains (*2, 3*), and the work of Imray and McPhee, which includes an assessment of the influence of plasmids (*4*). In the earlier investigations the test appeared to be relatively insensitive to ionizing radiation. However, this apparent lack of sensitivity resulted because brief exposures were applied shortly after plating. While this was in seeming analogy to the work with chemical mutagens, it did not account for the difference between the short duration of the irradiation and the continued presence of chemical mutagens. The mutation frequencies were greatly enhanced relative to the spontaneous rates when a modified procedure was introduced (*5*) where the exposures were performed at a later phase during incubation (6 h after plating). With this new method a doubling dose of only 1.3 Gy of ^{60}Co γ rays was found for the strain

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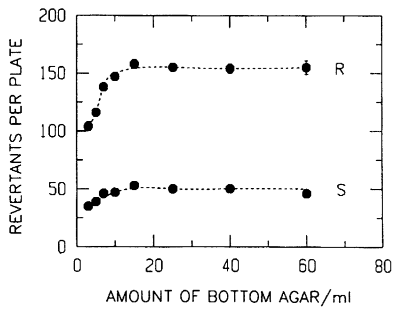

FIG. 1. Number of spontaneous revertants (S) and number of revertants (R) after exposure to 9.5 Gy of ^{60}Co γ rays versus the amount of bottom agar. Exposures were performed immediately after plating. A plateau at about three times higher frequency of the induced reversions was obtained for exposure with preincubation.

TA2638, and other strains showed similarly reduced doubling doses. Inactivation corrections, which were essential with the conventional method, are of less influence with the new technique.

The aim of the present study, with the improved experimental procedure, was the determination of the relative effectiveness of various ionizing radiations. There is still insufficient understanding of the different results obtained for radiation-induced mutagens in mammalian cells and in prokaryotes. In mammalian cells one finds, both for inactivation and for mutational tests such as the hypoxanthine-guanine phosphoribosyl transferase test, increased efficiencies for densely ionizing radiations with a maximum near linear energy transfer (LET) of 100 keV/μm (*6*). In their work with *E. coli* Munson and co-workers (*7, 8*) have found increased efficiencies of inactivation for radiations of intermediate LET. They infer from their experiments a peak at an LET of about 20 keV/μm, and they find a steep decrease in efficiency at higher LET. A corresponding peak was not seen in mutagenicity studies performed by these authors; they found that mutations to prototrophy of three auxotrophic strains of *E. coli* are induced with an effectiveness which decreases steadily with increasing LET. In view of these findings it seemed desirable to perform analogous studies for the *Salmonella* mutagenicity test with radiations that cover a broad range of LET. We have chosen ^{60}Co γ rays, 140 kV X rays (9-mm aluminum filter), 5.4 keV Cr-$K\alpha$ characteristic X rays, protons of 2.2 MeV, α particles of 3.1 MeV, and, for very high LET, Fe ions of 18 MeV/U.

MATERIALS AND METHODS

I. Bacterial Strain

The tester strain TA2638 (*his*G428, rfa, pKM101) was provided by Dr. B. N. Ames, Department of Biochemistry, University of California, Berkeley.

Among a variety of tester strains, we have found particularly high mutation yields with ionizing radiations not only in TA2638 but also in TA102. The former was selected for the present studies because of its special stability and its low spontaneous reversion rate. We have also found it advantageous to use a strain which, unlike TA102, contains no plasmid carrying the *his*⁻ site; the number of plasmids per cell is difficult to control and can be a potential source of instability in the experimental results. The genetic stability of the strain TA2638 was routinely tested for crystal-violet sensitivity (rfa mutation), uv sensitivity (uvrB

TABLE I

Half-Value Layers of the Photon Radiations and Ranges of the Charged Particles in Agar; Dose Averaged Restricted LET (100 eV Cutoff) and Dose Averaged Unrestricted LET

photons	half-value layer	$\bar{L}_{100,D}$	$\bar{L}_{\infty,D}$
γ rays (^{60}Co)	1080 mm	5.53 keV/μm	0.40 keV/μm
X rays (140kV)	380 "	8.31 "	4.29 "
X rays (5.4keV)	0.23 "	11.3 "	9.66 "
charged particles	range		
Fe ions (18MeV/u)	0.480 "	469 "	1690 "
protons (2.2MeV)	0.090 "	12.3 "	15.2 "
α particles (3.1MeV)	0.017 "	47.9 "	132 "

mutation), and ampicillin resistance (pKM101). In a series of investigations in our laboratory, extended over about 4 years, strain TA2638 has exhibited remarkable stability in the frequency of spontaneous and radiation-induced revertants and also in inactivation yields after exposure to ionizing radiation.

II. Preparation of Samples

The recommendations of Maron and Ames (9) have been followed with the minor modification of using a bottom-agar layer consisting of 25 ml glucose-agar medium instead of 30 ml. That this modification is of negligible influence in our experiments with ionizing radiation can be judged from the data in Fig. 1.

All chemicals were of analytical grade; water was deionized and quartz distilled. Oxoid and Difco media were used. Cultures of bacteria were started with 0.4 ml bacterial suspension from frozen permanent stocks, and plating was performed toward the end of the exponential phase (8 h). Further details have been given in the preceding publication (5).

Among the six different radiations which were employed (see Table I), two were sufficiently penetrating to permit the normal method of sample preparation in which 0.1 ml bacterial suspension (containing about $5 \cdot 10^8$ bacteria) is mixed with 2 ml top agar and poured onto minimal glucose agar plates (diameter 85 mm). This results in a 0.3-mm top-agar layer which contains the bacteria. The number of plated bacteria is fairly uncritical in the reversion experiments with our modified technique, because the number of revertants per plate is, over a certain range, nearly independent of this parameter (5).

For the less penetrating radiations (5.4 keV characteristic X rays, 2.2 MeV protons, 3.2 MeV α particles, and 18 MeV/U Fe ions) the technique of sample preparation had to be modified. This critical aspect of the experiments must be considered in some detail.

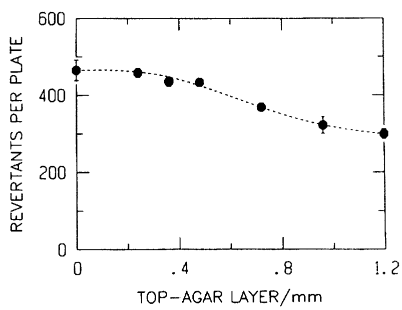

FIG. 2. Number of radiation-induced revertants per plate (revertants minus spontaneous revertants) versus thickness of the top-agar layer. The samples were exposed to 9.5 Gy of ^{60}Co γ radiation.

TABLE II

Comparison of the Surface Plating Technique and the Standard Technique

observation	number of experiments	surface-plating techn. / standard technique
plating eff.	10	1.01 ± 0.01
revertants	11	1.03 ± 0.01
spont.rev.	7	1.10 ± 0.02
inactivation	20	1.03 ± 0.04

Note. The irradiations were performed by ^{60}Co γ rays. In the mutation experiments the absorbed dose was 8 Gy; different doses between 7 and 50 Gy were applied in the inactivation experiments. The errors given are standard errors.

Reduction of the amount of top agar would be one possibility to concentrate the bacteria on the surface (see Fig. 2). For zero top-agar thickness the standard supplements of 0.1 μM D-biotin and 0.1 μM L-histidine were mixed with the bacterial suspension, and the resulting volume of 0.3 ml was then spread directly on the bottom-agar surface. The suspension liquid enters the bottom agar, but the bacteria remain on its surface so that the radiation needs to penetrate only the bacteria (long and short diameter about 2 and 1 μm).

In an alternative method, the 0.1 ml of bacterial suspension was spread on the surface of the solidified top agar (containing the supplement of biotin and histidine) with a Drigalski spatule. This method has been chosen for the experiments because it departs less from the standard procedure. The standard method, where the bacteria are distributed within the top-agar layer, and the surface-plating technique, where they are spread on the surface of the top agar, were compared for plating efficiency, number of spontaneous revertants, number of radiation-induced revertants, and inactivation of the bacteria by ionizing radiation (see Table II). A certain difference was seen for the frequencies of spontaneous revertants which were increased from 50 to about 55 per plate. This difference, however, is not directly relevant to the subsequent comparison of the effectiveness of different radiations which is evaluated in terms of the slope of the dose dependence.

III. Methods of Irradiation and Dosimetry

All exposures were performed at room temperature. The dose rate of photons and α particles was adjusted to 0.2 Gy/min in the mutation experiments. For technical reasons, the dose rate at the accelerators had to be higher; it was adjusted to 10 Gy/min for both the proton and the Fe ion exposures.

In the photon and α particle exposures the samples were kept out of the incubator for the same time (approximately 1 h) regardless of dose. All exposures less than 10 Gy were split into two fractions with an interval chosen so that the total duration and therefore the time outside the incubator was always 50 min. The split-dose irradiations were compared with equal single doses applied either at the beginning or at the end of the 50 min period. There were no systematic differences, and one can therefore conclude that variation of the total exposure time from 10 to 50 min is of little importance.

With regard to the accelerator experiments one must still ask whether there is a time factor at the substantially higher dose rates and the short exposure times of one or a few minutes. Additional experiments were therefore performed (at the GSF, Munich) with a dose rate of 2 Gy/min ^{60}Co γ radiation; the results are consistent with those obtained at 0.2 Gy/min (see Fig. 3). One concludes that differences observed between photon and charged particle irradiations are not a matter of different dose rates.

In the inactivation experiments substantially higher doses were required, and this necessitated a substantially prolonged exposure time of 2 h for the highest dose, 25 Gy of α rays. For the Co γ exposures and the soft X-ray exposures it was possible to keep the exposure times at 1 h by varying the exposure distances.

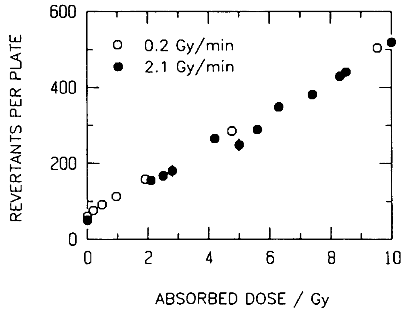

FIG. 3. Revertants per plate versus absorbed dose. The irradiations were performed with ^{60}Co γ rays, and different dose rates were compared.

Additional experiments (at the GSF, Munich) with Co γ rays at 25 Gy/min again did not indicate the presence of a time factor (Fig. 4). For the inactivation experiments, too, one must therefore conclude that the comparison to the accelerator experiments (10 Gy/min) is unaffected by differences in dose rate.

The γ exposures were performed with a ^{60}Co therapy unit. Exceptions were the additional high-dose rate experiments which utilized two calibrated ^{60}Co sources at the GSF, Munich.

The 140 kV X rays were produced by a 150 kV tube with beryllium window (Philips, MÖD 152 BE) operated at 140 kV and were filtered by 9 mm aluminum. Characteristic X rays were generated by a tube with Cr anode and beryllium window (Siemens, AG CR 61). The tube was operated at 10 kV to produce 5.4 keV Cr-$K\alpha$ characteristic X rays. The radiation was filtered by a 20-μm Cr foil to reduce the bremsstrahlung (see (*10*)).

Photon dosimetry was performed with a calibrated therapy-dosimetry system (Dosimentor system; Dr. Pychlau GmbH, Freiburg) with suitable ionization chambers. An ionization chamber of type M 23342 was used for the dosimetry of soft X rays. A calibration factor for this chamber is usually provided for low energy photons of 8.4 keV. The calibration factor for photons of 5.4 keV is 2% in excess of the value for 8.4 keV; it was kindly provided by Dr. P. Pychlau, GmbH, Freiburg (personal communication). The chambers are calibrated for measuring exposure; conversion to absorbed dose utilized the appropriate mass–energy absorption coefficients for tissue (^{60}Co γ rays: 37.2 Gy/(C/kg); 140 kV X rays: 34.9 Gy/(C/kg); 5.4 keV characteristic X rays: 35.7 Gy/(C/kg)). 3 MeV protons were delivered by the 3 MV van de Graaff generator of the GSF. A device to achieve homogenous irradiations of 85 mm petri dishes was constructed for this experiment (Fig. 5). The proton beam left the accelerator through a 4-μm titanium exit foil. This foil was supported by a beam defining slit (22 mm × 0.5 mm). The sample was exposed to the beam on a

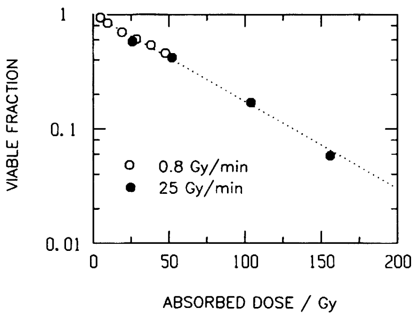

FIG. 4. Viable fraction of bacteria versus absorbed dose. The irradiations were performed with ^{60}Co γ rays, and different dose rates were compared.

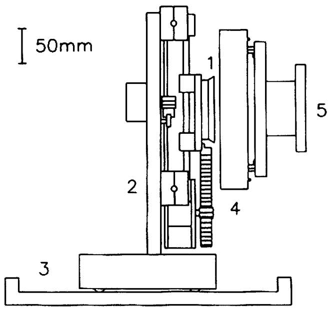

FIG. 5. Diagram of the device for proton irradiations. 1, sample; 2, scanning device (retractable from the ionization chamber for changing the sample by means of the guide way, 3); 4, ionization chamber; 5, adaptor to beam-guide tube with exit window (not visible).

computer controlled device for two-dimensional scanning. For the smallest doses a single scan was performed, for the higher doses several scans. The proton-beam current was monitored with a thin-window transmission ionization chamber located between exit window and sample. This monitor was calibrated by comparison with the proton fluence determined from etched particle tracks in Cr39 plastics. Traversal of the Ti-exit window and of the monitor ionization chamber reduced the proton energy from 3 MeV to 2.2 MeV (for details see (*11*)). Absorbed dose was calculated from the measured particle fluence with the LET value 15.0 keV/μm recommended by ICRU report 36 (*12*).

The construction of the α irradiator is indicated in Fig. 6 (for details see (*13*)). Alpha particles emerging from the ^{241}Am source (activity 0.37 GBq, energy of α particles 5.53 MeV, diameter of active area 85 mm) are collimated to an angle less than 12° from the normal. The collimator removes α particles which leave the source obliquely; this avoids a sharp decrease of absorbed dose with depth in the irradiated sample. To reduce energy loss, source and collimator are mounted in a container which is flushed with helium under normal pressure. In comparison to air, this reduces energy losses by a factor of more than 6. The exit foil can be thin (2.5 μm Mylar) since it supports no pressure differences. Petri dishes are exposed to the α rays in inverted position; the distance between exit window and top agar is 1 mm. The collimator is wobbled in circular motion; this reduces the maximal difference of the fluence on the exit window from 4% for a fixed position of the collimator to less than 1%. Both values apply for a homogenous source. To improve homogeneity the source is rotated. Measured over a spot of 6 mm^2 area there are maximum differences of intensity on the surface of the source of about 20%. With rotating source the corresponding maximum differences on the surface are less than 3%. The energy distribution of α-particle fluence after traversal of the exit window (see Fig. 7) was measured with a semiconductor detector. The most probable α-particle

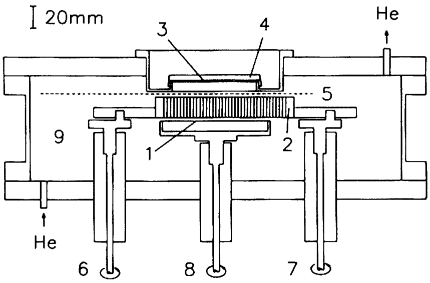

FIG. 6. Simplified view of the α-irradiation device. 1, source; 2, moving collimator; 3, exit window; 4, sample; 5, shutter; 6, 7, synchronously rotating axes supporting the collimator; 8, rotating axis supporting the source–turn table; 9, helium container.

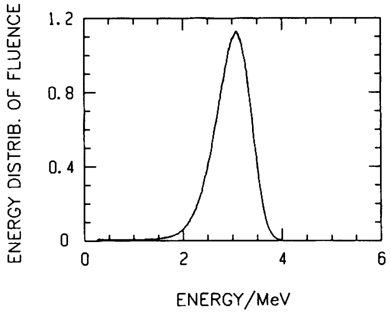

FIG. 7. Measured energy distribution of α-particle fluence after traversal of the exit window.

energy is 3.1 MeV. From the data of Fig. 7 the sum distribution of remaining ranges (Fig. 8) and the depth distribution of dose in tissue (Fig. 9) was calculated with LET data from ICRU report 36.

Irradiations with 18 MeV/U Fe ions were performed at the linear accelerator UNILAC of the GSI (Darmstadt). The samples were irradiated in an exposure facility with an automatic sample changer constructed by the GSI (*14*). The beam was defocused and the samples were wobbled to achieve homogenous irradiations. An integrated part of the exposure facility is a secondary electron emission chamber monitoring the Fe-ion beam current. This monitor was calibrated by comparison with the particle fluence determined from track counts on etched glass samples. Absorbed dose was calculated from the measured particle fluence with LET data of Ziegler (*15*).

RESULTS

The experimental results on bacterial survival and on the frequency of revertants per plate are represented in Figs. 10 and 11. In the inactivation studies the individual points are mean values for at least six plates; some points have been derived from larger numbers of plates. In most experiments data points have been obtained from repeated experiments. In the work with Fe ions at the GSI such repetitions were not possible, and all points are the result of one experiment obtained with the same bacterial culture. The data for the protons are based on two separate experiments which indicated no systematic deviations. Standard errors were derived from counts on the plates exposed to the same dose in an experiment; where they are not visible in the

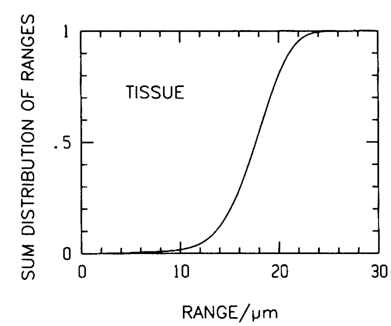

FIG. 8. Sum distribution of remaining ranges in tissue for direct exposition of the samples at the exit window.

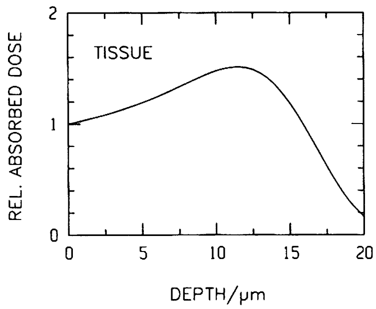

FIG. 9. Relative absorbed dose versus depth in tissue.

diagrams they are smaller than the symbols. The standard errors do not account for errors between different dose points, due for example to inaccuracies in the dilution series, nor do they account for fluctuations between experiments. The overall influ-

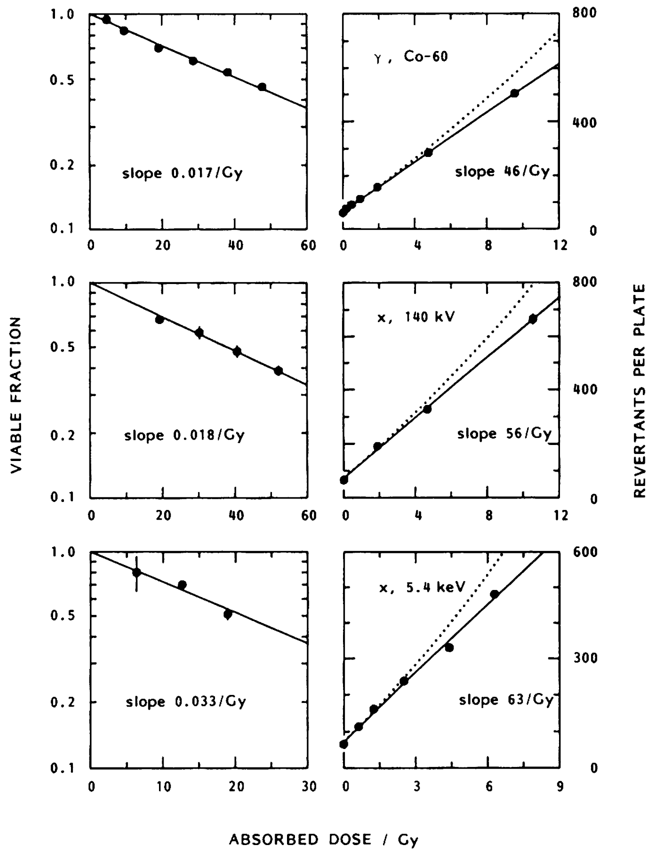

FIG. 10. Viable fraction of irradiated bacteria (left panels) and number of revertants per plate (right panels) versus absorbed dose. Samples exposed to ^{60}Co γ rays, 140 kV X rays filtered by 9 mm Al, and 5.4 keV Cr-$K\alpha$ characteristic X rays. Dotted lines represent the data with inactivation correction.

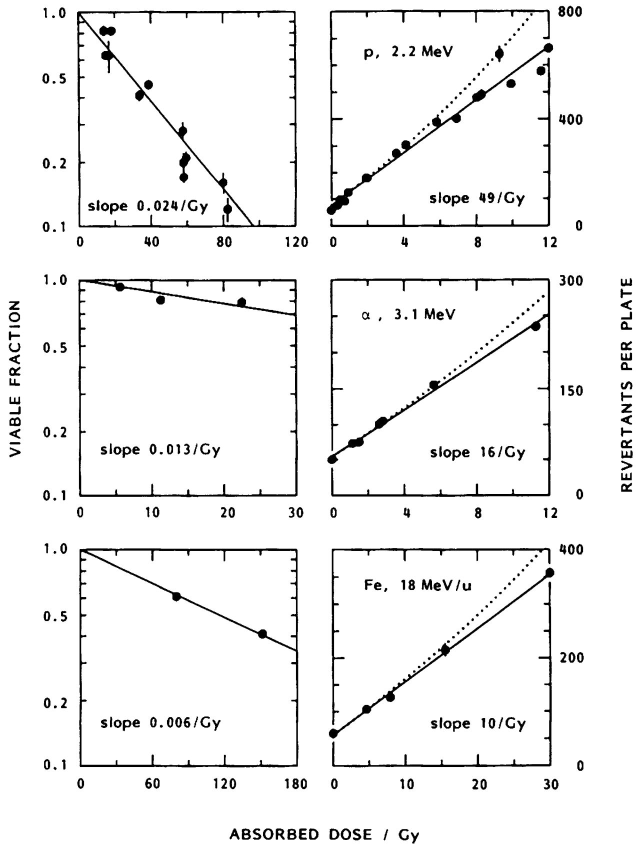

FIG. 11. Viable fraction of irradiated bacteria (left panels) and number of revertants per plate (right panels) versus absorbed dose. Samples exposed to 2.2 MeV protons, 3.1 MeV α particles, and Fe ions of 18 MeV per nucleon. Dotted lines represent the data with inactivation correction.

ence of such errors can be judged from the spread of the points in individual dose–effect relations. The solid lines are least-squares fits to the observations, with equal weights for all points.

All survival curves are consistent with exponential relations. Even for the γ rays and the higher energy X rays there is no indication of a shoulder. With decreasing photon energy slopes are increasing. Because of the marked differences of effectiveness, different dose scales had to be used. Figure 12 serves to facilitate the comparison. The highest effectiveness for inactivation is found with 5.4 keV X rays (slope: 0.033/Gy), the lowest effectiveness with 18 MeV/U Fe ions (slope: 0.006/Gy). The numbers of revertants per plate were consistent with linear dependences on absorbed dose. Inactivation corrections were of minor influence (see dotted lines in Figs. 10 and 11), since the largest inactivated fraction corresponding to any of the points in the mutation studies was only 0.25. The mutagenicity, too, increases with decreasing photon energy; the comparison is facilitated by Fig. 13. As in the inactivation experiments,

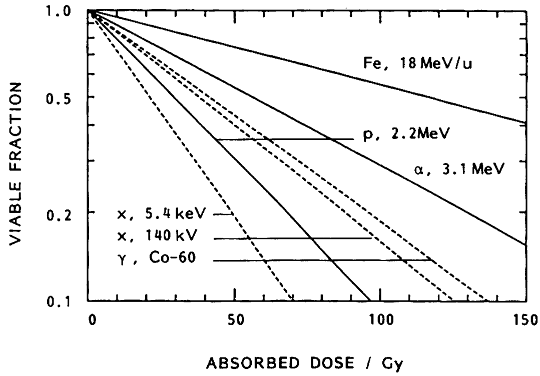

FIG. 12. Exponential functions of dose fitted to the observed viable fractions of irradiated bacteria for the six different radiations (see Figs. 10 and 11).

the soft X rays were most effective (doubling dose: 2.3 Gy), whereas the Fe ions were far less effective (doubling dose: 11.4 Gy).

DISCUSSION

The delayed exposure method was used for the *Salmonella* mutagenicity test to perform experiments with tester strain TA2638 (*his*G428, rfa, pKM101) exposed to six different types of ionizing radiation. The modified method results in substantially enhanced yields of mutations, reducing the relative contribution of the spontaneous revertants and making inactivation corrections less necessary. The radiations which were employed covered a wide range of LET from sparsely ionizing γ rays to heavy ions of 1700 keV/μm. The results show a pronounced peak of inactivation for the 5.4 keV characteristic X rays. These have a dose average LET of approximately 10

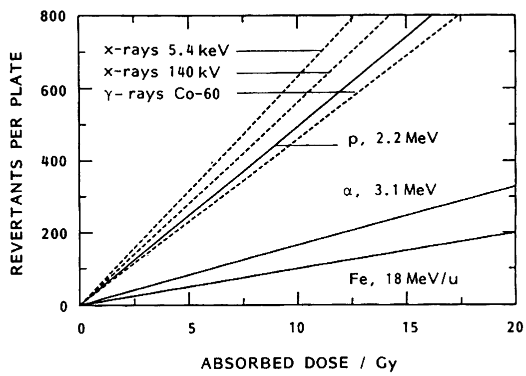

FIG. 13. Linear regressions in dose of the observed numbers of revertants per plate for the six different radiations (see Figs. 10 and 11).

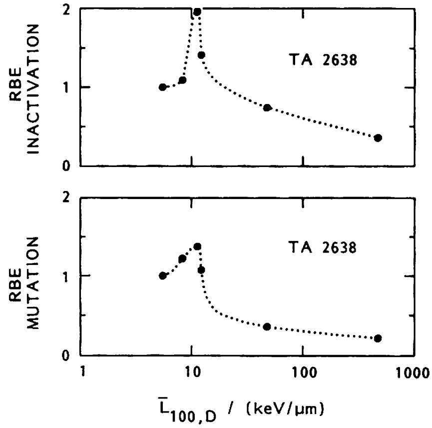

FIG. 14. RBE for inactivation (upper panel) and mutation (lower panel) of the bacteria by the different radiations. The dose average restricted LET (100 eV cutoff) is chosen as reference parameter (from left: ^{60}Co γ rays, 140 kV X rays, 5.4 keV X rays, protons, α particles, Fe ions). The dotted lines are inserted for better readability of the diagrams; they have no mathematical significance.

keV/μm, largely independent of the cutoff that is employed. A similar but less pronounced peak is seen for the mutations.

The occurrence of a peak for inactivation at moderate values of LET is in substantial agreement with the earlier findings of Munson and colleagues (*7, 8*) for inactivation of *E. coli* by different types of ionizing radiation. These authors have not reported a similar peak for mutations to prototrophy in *E. coli* B/r. However, their results and the related data of Munson and Bridges (*16*) on bacterial phage T4 need not necessar-

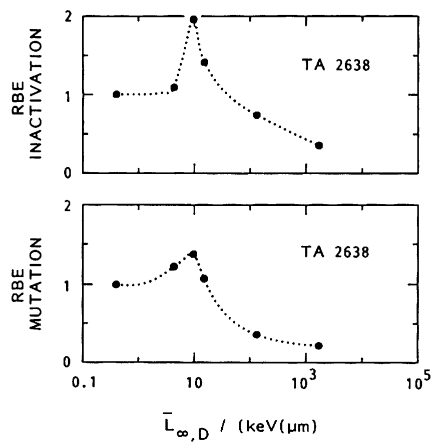

FIG. 15. RBE for inactivation (upper panel) and mutation (lower panel) of the bacteria by the different radiations. The dose average unrestricted LET is chosen as reference parameter (from left: ^{60}Co γ rays, 140 kV X rays, 5.4 keV X rays, protons, α particles, Fe ions). The dotted lines are inserted for better readability of the diagrams; they have no mathematical significance.

ily be inconsistent with a peak of RBE for mutations near LET = 10 keV/μm, as we see it in the present experiments. From our study one would infer that RBE values for inactivation and mutation in bacteria are largely parallel.

Various authors have developed models to link energy concentrations in cellular and subcellular structures to the effectiveness of different types of ionizing radiations in causing mutations and cell inactivation (see e.g. (*17*)). Such models utilize either the concept of LET or microdosimetric quantities. The microdosimetric quantities depend on the assumed target structure and size, and it would be highly tentative to relate the present observations to specific parameters. The LET concept, on the other hand, is a simplification but it has the advantage of being less closely linked to assumptions on the structure of the relevant targets. It is therefore of some interest to correlate the observed data with restricted and unrestricted LET and its mean values. Such a correlation, although largely empirical, can bring out essential features of the results.

On the basis of present radiobiological understanding it has been variously suggested that the effectiveness of different types of ionizing radiation is linked to DNA damage produced by energy concentrations on the nanometer scale. Short of a microdosimetric treatment, such energy concentrations need to be linked to restricted LET rather than total LET which includes the long-range δ rays. Blohm and Harder (*18*) have held that the dose mean LET with a cutoff of 100 eV is the appropriate quantity. In the two panels of Fig. 14 the RBE for inactivation and mutation is plotted versus the dose average of restricted LET (Δ = 100 eV). The averages of LET for the different radiations are based on work of Harder and Blohm (*19*); they are derived by averaging the contributions of the heavy particles and those of the δ rays that exceed the cutoff energy. The inclusion of the δ rays is essential for the protons; without this contribution they would be assigned LET values which are substantially too low. The sharp peaks in Fig. 14 are striking and may suggest that $\bar{L}_{100,D}$ is not the suitable parameter. The soft X rays have very nearly the same mean values of restricted LET as the protons, but their effectiveness with regard to both mutation and inactivation is substantially larger. This may imply that the effect is determined not only by energy concentrations over distances of one or a few nanometers but also by energy concentrations over a larger scale. The spatial distribution of DNA and the volume of the bacterium of about 1.6 μm^3 are not inconsistent with this possibility. In view of these considerations an alternative diagram in terms of the mean values, $\bar{L}_{\infty,D}$, of unrestricted LET, is added in Fig. 15. With this reference parameter the peaks are still pronounced, but the comparison of the soft X rays and the protons appears less incoherent.

Possible influence of variations in dose rate has been investigated with γ rays. In this part of the experiment it has been found that variations in exposure time between fractions of a minute to more than an hour lead to no observed changes in inactivation probability or mutation frequency in strain TA2638. This is in line with the observed exponential relation for survival and the linear dose dependence for histidine reversions in this strain.

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