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Response parameters that describe the production of recessive lethal mutations in *C. elegans* from ionizing radiation are obtained with the Katz track structure model. The authors used models of the space radiation environment and radiation transport to predict and discuss mutation rates for *C. elegans* on the IML-1 experiment aboard STS-42.

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## Summary

The Katz track structure model has been applied to describe recessive lethal mutagenesis in the nematode *Caenorhabditis elegans* after exposure to heavy ions. Based on models of the cosmic-ray environment and heavy-ion transport, mutation rates for the International Microgravity Laboratory 1 (IML-1) experiment on the Space Transportation System 42 (STS-42) are predicted and the results are discussed.

## Introduction

The nematode *Caenorhabditis elegans* (*C. elegans*) is being studied (refs. 1 to 3) as a model radiobiological system that can provide information on mutagenesis after exposure to galactic cosmic radiation (GCR). *C. elegans* is particularly well suited for study because this nematode has a relatively small, fixed number of cells with only six pairs of chromosomes; many of its genes have been identified and mapped. Nelson (refs. 2 and 3) has reviewed several properties of *C. elegans* that favor its use in understanding the biological effects of heavy charged particles, especially for genetic processes, and its mutagenesis rates have been measured for several heavy-ion beams (ref. 3). The International Microgravity Laboratory 1 (IML-1) mission on the Space Transportation System 42 (STS-42) carried an experimental package containing *C. elegans* to study the effects of microgravity and tested ground-based understanding of GCR effects in space conditions if significant exposures occurred. The STS-42 mission duration of about 7 days in an orbit of 57° by 163 n.mi. exposed the *C. elegans* package to a complicated mixture of particles that vary in composition with the amount and type of shielding surrounding the package. Major concerns were anomalous effects on radiation response from microgravity or physiological stress from spaceflight.

Several considerations could affect our extrapolations from ground-based to flight experiments: fluxes one or two orders of magnitude below those achieved using accelerators, protracted exposure, and the broad charge and velocity spectrum of the GCR. The track structure model of Katz et al. (refs. 4 to 9) utilizes a charge- and velocity-dependent fit to radiobiology experiments and is the only model that can predict cellular endpoint response for the complete GCR spectrum. Biological response at low fluence is described by an action cross section representing the probability that a single ion leads to the endpoint in question. Laboratory measurements at high dose for photons and with a few ions allow for a parametric determination of the cross section in terms of ion charge and velocity that can be applied to the GCR spectrum. Compared with other radiobiological models, the zero initial slope for X rays assumed by the Katz track structure model for multitarget endpoints leads to the maximum prediction for GCR effectiveness.

In this report, we consider experimental data for ion (ref. 3) and photon (refs. 3 to 10) production of recessive lethal mutations in *C. elegans* for response parameters to describe this endpoint in the Katz track structure model. This is the first application of the track structure model to an animal system. We then consider the GCR and trapped particle spectrum that is expected for IML-1 and predict the expected mutation rates by using models of the cosmic-ray environment, accurate transport codes, and shielding models.

## Track Structure Model

The track structure model of Katz et al. (ref. 4) attributes biological damage from energetic ions to the secondary electrons (delta rays) produced along the ion path. The deleterious effects of energetic ions are correlated with those of gamma rays by the assumption that the response in sensitive sites near the ion path is part of a larger system irradiated with gamma rays at the same dose. The response from ion effects is then determined by knowledge of the gamma-ray response and the delta-ray dose surrounding the ion path. For a multitarget response with target number $m$, the inactivation of cells by gamma rays is assumed to follow a Poisson distribution reflecting the random accumulation of sublethal damage with a radiosensitivity parameter $D_0$.

When ions inactivate the cells, two modes are identified: "ion kill," which corresponds to intratrack effects, and "gamma kill," which corresponds to intertrack effects. Here, the ion-kill mode is unique to ions corresponding to single-particle inactivation of cells described by the cross section $\sigma$. The action cross section for a sensitive site is determined as

$$\sigma = \int_0^\infty 2\pi t \; dt \left[1 - \exp\left(-\overline{D}/D_0\right)\right]^m \qquad (1)$$

where $\overline{D}$ is the average dose at the sensitive site from the ion delta rays. The cell damage is divided by Katz et al. (ref. 4) into a grain-count regime, where inactivation occurs randomly along the path of the particle, and into a track-width regime, where many inactivations occur and are said to be distributed like a "hairy rope." In the grain-count regime, $\sigma$ may be parameterized as

$$\sigma = \sigma_0 \left[1 - \exp\left(-Z^{*2}/\kappa\beta^2\right)\right]^m \qquad (2)$$

where $\sigma_0$ is the plateau value of the cross section, $\beta$ is the ion velocity, the effective charge number is given by

$$Z^* = Z\left[1 - \exp\left(-125\beta/Z^{2/3}\right)\right] \tag{3}$$

and $\kappa$ is a parameter related to the radius of the sensitive site $a_0$ by

$$D_0 \frac{a_0^2}{\kappa} \approx 2 \times 10^{-11} \text{ Gy/cm} \tag{4}$$

The transition from the grain-count to the track-width regime (refs. 4 and 5) occurs at a value of $Z^{*2}/(\kappa\beta^2)$ on the order of 4. At lower values of $Z^{*2}$ we are in the grain-count regime and, at higher values, the track-width regime.

In the grain-count regime, the fraction of the cells damaged in the ion-kill mode is $P = \sigma/\sigma_0$, where $\sigma$ is the single-particle-inactivation cross section and $P$ is the probability of damage. In the track-width regime, where $\sigma > \sigma_0$, it is assumed that $P = 1$. In the track model a fraction of the ion dose $(1 - P)$ is assumed to add cumulatively to the ions from other particles to inactivate cells in the gamma-kill mode. The surviving fraction of a cellular population $N_0$, whose response parameters are $m$, $D_0$, and $\kappa$ or $a_0$ after irradiation by a fluence of particles $F$, is then written as

$$\frac{N}{N_0} = \Pi_i \Pi_\gamma \tag{5}$$

where

$$\Pi_i = \exp(-\sigma F) \tag{6}$$

is the ion-kill survival probability and

$$\Pi_\gamma = 1 - \left[1 - \exp(-D_\gamma/D_0)\right]^m \tag{7}$$

is the gamma-kill survival probability. The gamma-kill dose fraction is

$$D_\gamma = (1 - P)D \tag{8}$$

where $D$ is the absorbed dose. The fraction of mutations produced by ions is evaluated as

$$M = 1 - \Pi_i \Pi_\gamma \tag{9}$$

when mutation response parameters are applied. The track structure model is applied next to estimate *C. elegans* mutation rates after exposure to charged particles.

## Response Parameters

Testing procedures for several types of mutations in *C. elegans* have been developed (refs. 3 and 10) over the last decade. Now, mutation response parameters for recessive lethal mutations are being considered through fits to the data of Nelson et al. (ref. 3) based on results of ion beam experiments in the Lawrence Berkeley Laboratory Bevelac 0-degree Beam Spectrometer. The response to gamma rays has also been measured (refs. 3 and 10) from about 5 to 30 Gy. A linear fit to the gamma-ray data could be used; however, we obtain a good representation by using equation (7) with $m = 2$ and $D_0 = 68$ Gy. Figure 1 shows that the fit is consistent with the ion data. The plateau value of the action cross section for recessive lethal mutations is near 0.2 $\mu$m$^2$ from the data presented in reference 3. We do not consider track-width effects too cumbersome for use in GCR transport codes at this time. We used the parameterization of equation (2) with $\sigma_0 = 0.25$ $\mu$m$^2$ and $\kappa = 700$ to compare the track model prediction with measured mutation rates. Our findings are shown in figures 2 to 4. The quality of the fit is quite good for the overall data set, as shown on a linear scale with all data reproduced to within a factor of 2 or better. In figure 4, we included target fragment effects extracted from reference 9 for the low linear energy transfer (LET) ions. At high fluence levels, target fragments have minimal effect, but will dominate the effect of low LET ions at lower fluences (ref. 9). Several other ions considered in reference 3 were closer to the Bragg peak than the plateau region and were not considered because fragmentation and other effects complicate the comparisons. Table I is a summary of the response parameters for *C. elegans* mutations. In figure 5, the resulting action cross section versus

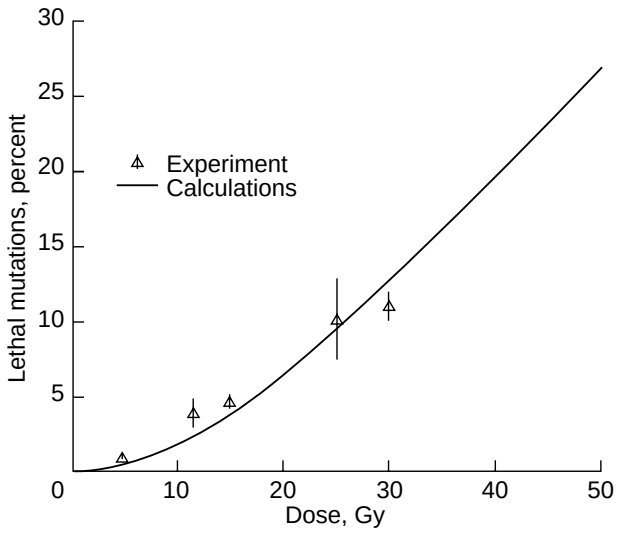


Figure 1. Percentage of mutations in *C. elegans* versus gamma-ray dose. Data from references 3 and 10.

Table I. Response Parameters for Recessive Lethal Mutations

| | $m$ | $D_0$, Gy | $\sigma_0$, cm$^2$ | $\kappa$ |
|---|---|---|---|---|
| *Caenorhabditis elegans* | 2 | 68 | $2.5 \times 10^{-9}$ | 700 |

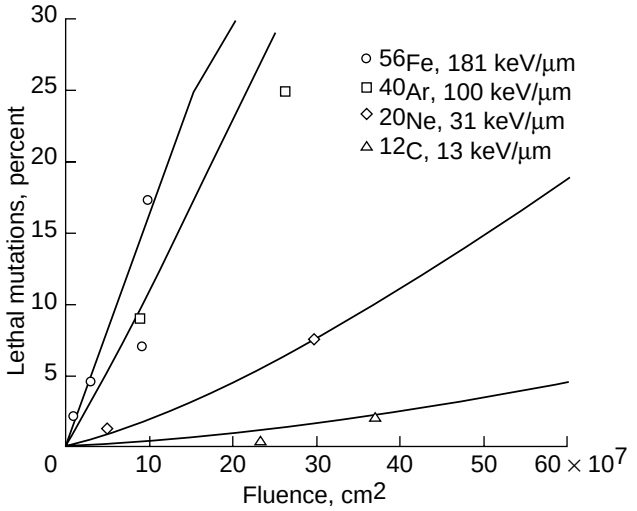


Figure 2. Percentage of mutations in *C. elegans* versus ion fluence for several ions. Data from Nelson et al. (ref. 3).

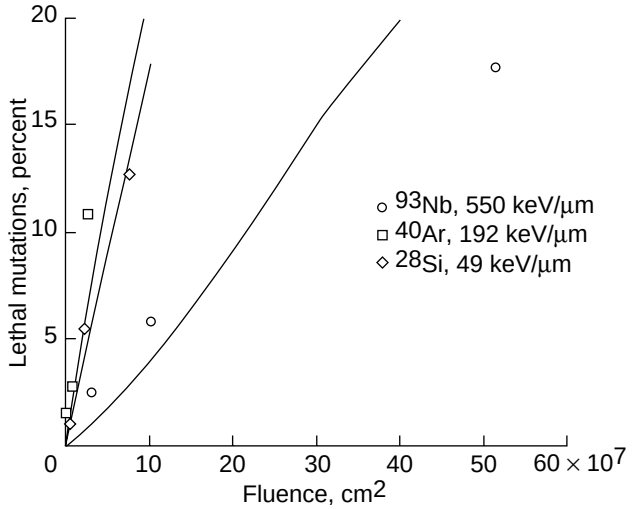


Figure 3. Percentage of mutations in *C. elegans* versus ion fluence for several ions. Data from Nelson et al. (ref. 3).

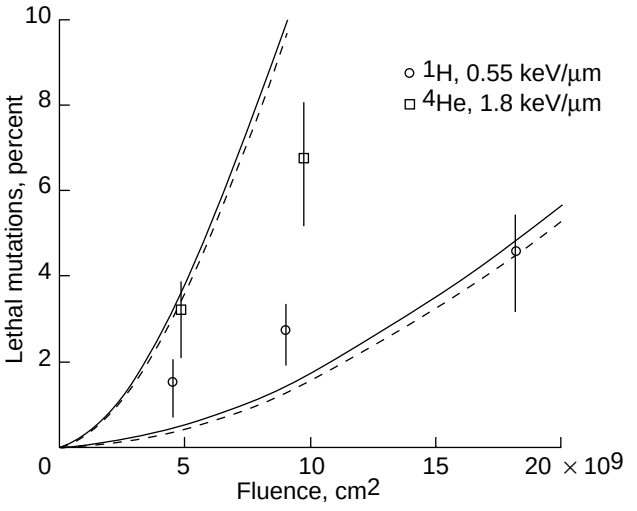


Figure 4. Percentage of mutations in *C. elegans* versus ion fluence for ions with low LET. Data from Nelson et al. (ref. 3). Solid line includes target fragmentation effects.

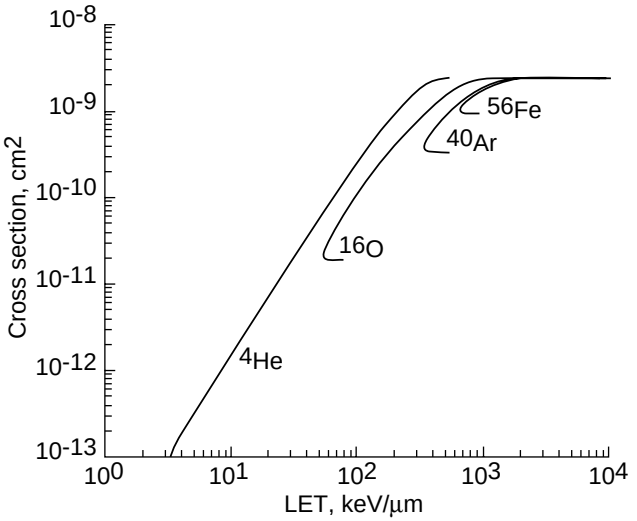


Figure 5. Action cross section versus LET for several ions.

LET is shown for several ions. The cross sections extend from the stopping region to energies above 100 GeV/nucleon. The radial dose distribution of delta rays used in the track structure model does not reflect relativistic effects that may be important at the highest energies. In reference 11, Fermi has

suggested that relativistic effects may cancel such that a nonrelativistic calculation is accurate. The plateau in the cross section at the highest LET for each ion could be corrected for track width and thin-down effects by using equation (1). The cross section obtained there indicates a target size much smaller than that typical of cellular inactivation, approaching the target sizes in cell transformation and mutation studies (refs. 12 and 13).

## Discussion

Solar maximum was achieved in 1990 and the next solar minimum is expected in about 1996; that solar minimum should approach the high fluxes of 1977. Because accurate solar modulation models are not available for transport codes, we present predictions based on 1990 and 1977 galactic cosmic radiation (GCR) spectra and actual measurements (ref. 14). The scaling assumed for the less abundant elements is taken from the Naval Research Laboratory model (ref. 15). Recent measurements (ref. 16) on the Space Transportation System 40 (STS-40) indicated that transport code predictions with the 1990 spectrum were about half those of the measurements. Several factors could lead to this disagreement: solar modulation of the GCR spectrum, the magnetic cutoffs used in the predictions, meson production (which is not included in the transport codes), and the nuclear fragmentation parameters used for heavy-ion transport. Predictions using solar minimum and maximum spectra are expected to bound the actual fluxes on STS-42. In figure 6, we show the unattenuated GCR spectrum for an orbit of 57° by 163 n.mi. for the solar minimum and maximum.

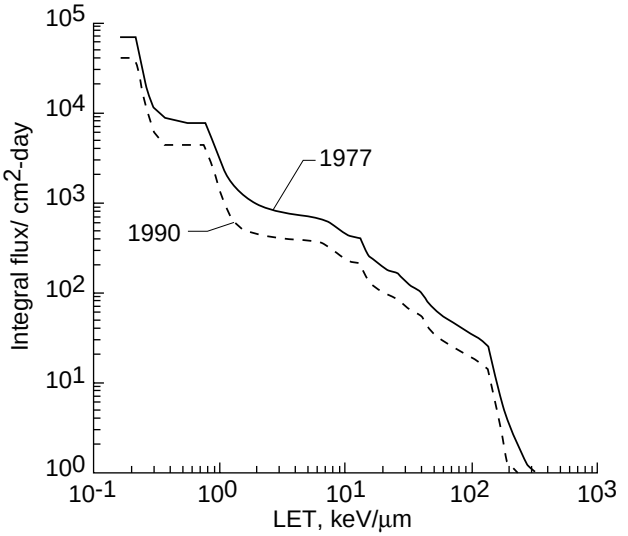


Figure 6. Unattenuated integral flux spectrum versus LET for solar minimum and maximum in an orbit of 57° by 163 n.mi.

The International Microgravity Laboratory 1 (IML-1) experiment was placed inside the Spacelab for its early 1992 mission. Therefore, we are particularly interested in assessing the fractions of mutagenesis in space behind the STS-42 shielding. Figure 7 shows the expected energy spectrum of trapped protons based on the Goddard Space Flight Center energy-space-particle model AP-8. The plot reflects our finding that very few high-energy protons had sufficient range to penetrate the STS-42 shielding.

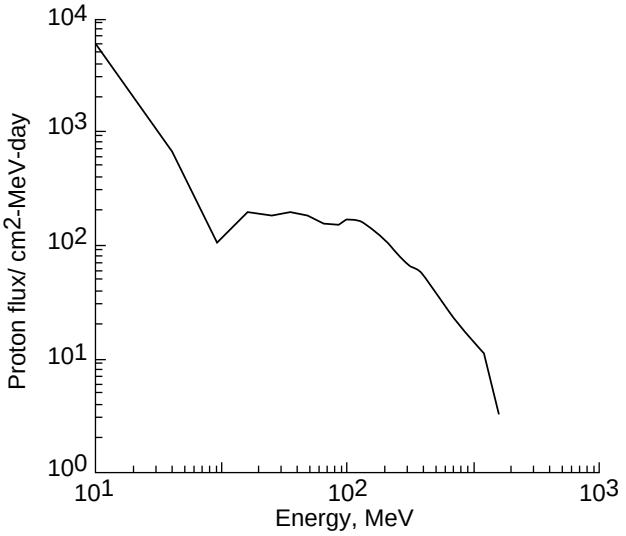


Figure 7. Trapped proton energy spectrum for STS-42.

The corresponding shielding distribution is shown in figure 8. Also shown is the distribution for dosimeter location 2, which was in the least shielded location on STS-42. For the Spacelab, a significant fraction of the solid angle is above 20 g/cm$^2$ aluminum, and we expect that many heavy ions were fragmented with the large buildup of proton and neutron secondaries near *Caenorhabditis elegans (C. elegans)*. The action cross section is plotted against range in figure 9 to illustrate how beam attenuation with shielding affects the biological damage expected for various ions. The low and medium charged ions should be drastically affected; the high $Z$ particles with significant range should be only slightly changed in cross section; however, the use of equation (2) in the track-width regime will lead to an underestimate of cross section. The attenuated linear energy transfer (LET) values for the solar maximum and minimum spectra are shown in figures 10 and 11, respectively.

The Langley Research Center cosmic-ray transport code (ref. 17) was used to predict the resulting

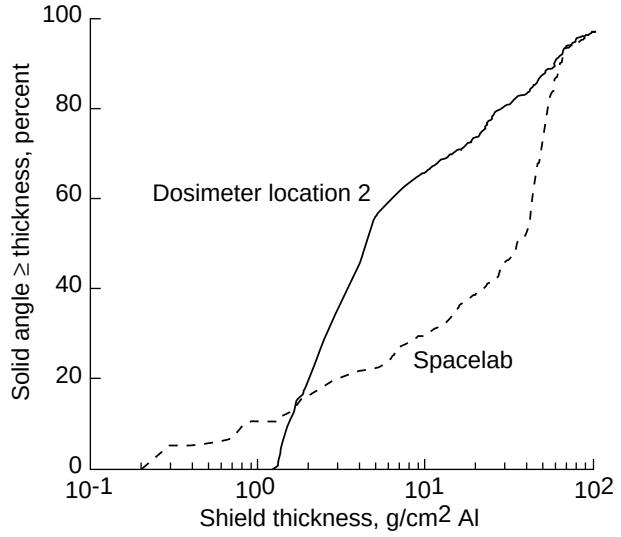


Figure 8. Shielding distribution for Spacelab and dosimeter location 2.

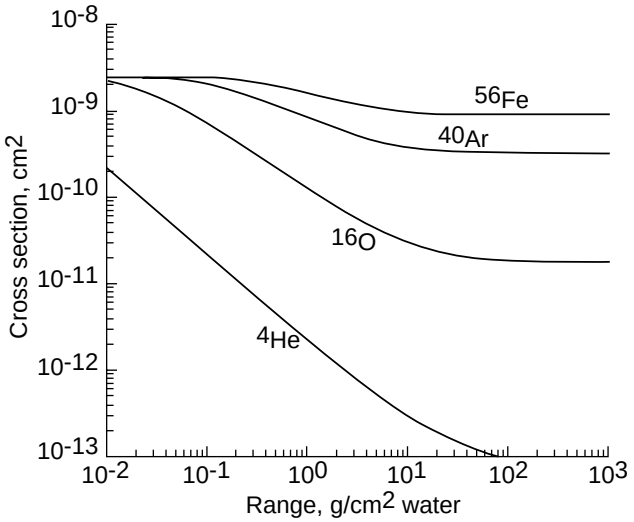


Figure 9. Action cross section versus range for several ions.

mutation rates (ref. 7) for the solar maximum and minimum spectra. Mutation rates were obtained as a function of aluminum shield thickness and were averaged over the shield distributions in figure 8 and over the predictions in table II. It is clear from the table II predictions that few mutations are expected in even a large *C. elegans* population because of the short exposure period. Also shown in table II are predicted values for relative biological effectiveness (RBE) with energetic photons the reference radiation. The high values indicate that our reference photon radiation did not produce indicative numbers of mutations at low doses compared with the low exposure. The exposure could be improved, however, if we optimize the exposure geometry (if possible within Spacelab constraints) and greatly increase the exposure period. The substantial Spacelab shielding promotes a trapped proton-induced mutation rate of less than $10^{-7}$ for the mission that is much smaller than the GCR contribution.

Part of the *C. elegans* population was stored at 2°C in Spacelab so that researchers could identify tracks through the surrounding plastic track detector (CR-39). The temperature differential may have altered repair mechanisms in that population; these mechanisms can be interpreted by a repair model that incorporates the track structure model discussed in reference 18.

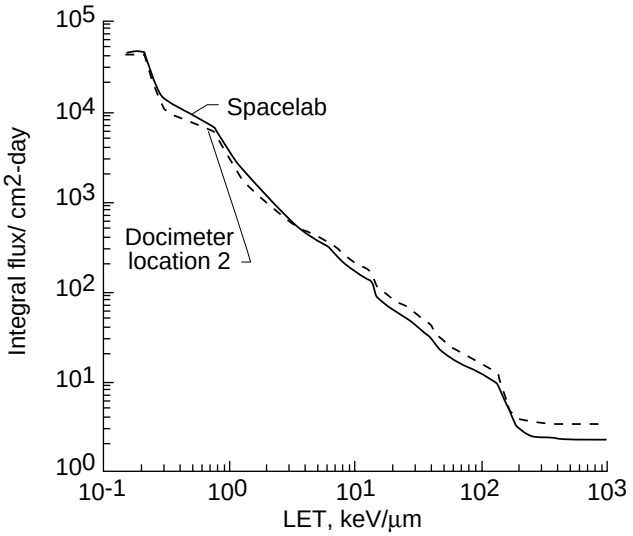


Figure 10. Solar maximum integral flux spectrum versus LET at Spacelab and dosimeter location 2.

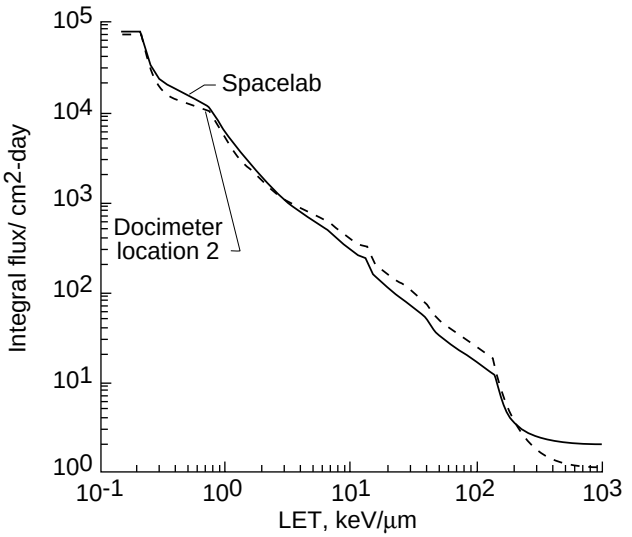


Figure 11. Solar minimum integral flux spectrum versus LET at Spacelab and dosimeter location 2.

Table II. Mutation Rates, RBE Values, and Dose Predictions for STS-42

| Location | Dose, mrad | | Mutation factor | | RBE | |
|---|---|---|---|---|---|---|
| | Min | Max | Min | Max | Min | Max |
| Spacelab | 57 | 34 | $0.77 \times 10^{-6}$ | $0.47 \times 10^{-6}$ | 102 | 131 |
| Dosimeter 2 | 54 | 31 | $.91 \times 10^{-6}$ | $.48 \times 10^{-6}$ | 107 | 139 |

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September 30, 1992

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