

Once we know all the radiobiology we need to know, how can we use it to predict space radiation risks and achieve fame and fortune?

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Abstract

It has been over 40 years since occupational radiation exposures to NASA's astronauts began and more than 300 individuals have been exposed to low and intermediate doses of trapped protons and galactic cosmic rays (GCR). The International Space Station (ISS) will add substantially to this number and significantly increase average lifetime doses. We review these exposures in this report. After many years of investigation, the method used to assess risk have not changed significantly. However, molecular biology and genetics have made enormous progress in establishing the mechanisms of cancer formation, damage to the central nervous system, and individual variation in sensitivity to radiation. We discuss critical questions and possible new approaches to the prediction of risk from space radiation exposures. Experimental models can lead to testable theories that along with extensive biophysical and informatics approaches, will lead to fame and fortune by allowing for accurate projections of astronaut risks and for the development of biological countermeasures.

KEYWORDS: Space radiation, Radiation Carcinogenesis, high-LET, HZE ions.

1. Introduction

In this paper, we consider the past and future of space radiation risk assessment. In the first part, we review the historical exposures of astronauts from different radiation sources and discuss limitations of verifying any adverse health effects due to the actual population size of space workers. The second part of the paper considers how new information from radiation biology studies should be used to improve our estimates of the risks to astronauts from space radiation. NASA has received guidance on risk assessment for space radiation exposures since the early 1960's in the form of major reports from the National Academy of Sciences [1, 2, 3] and U.S. National Council on Radiation Protection and Measurements (NCRP) [4].

Risk assessment for astronauts is distinct from terrestrial workers and the general public in several ways. First in space, astronauts are exposed high-energy protons, helium and heavy ions and their secondaries produced by nuclear reactions including neutrons and high linear energy transfer (LET) recoil nuclei. Terrestrial workers are most frequently exposed to low LET gamma rays or x-rays with only a small neutron dose, with the exception of miners exposed to inhaled alpha emitters. Since epidemiological data for providing a basis for risk estimation for protons and heavy ions is non-existent, risk estimates must rely entirely on model systems and biophysical considerations. It is well established that energy deposition in DNA, cells, and tissues produced by nuclear particles is qualitatively distinct from low LET radiation [5] and that there is an important role for correlated nuclear reaction events produced by charged particles or neutrons in tissue [6]. Astronauts are also subject to

other types of exposures including diagnostic x-rays during selection and flight readiness protocols, the use of internal isotopes in experimental protocols, and atmospheric radiation during air training. Temporal patterns of exposure for space and terrestrial workers are distinct with NASA astronauts receiving more fractionated and higher dose-rates. Dose limits recommended for astronauts [7] are higher than those recommended for most terrestrial workers. Also, average doses received by astronauts will continue to rise due to the occupation of the ISS in reverse of the trend for workers on the ground.

The current approach to risk assessment does not differ drastically from that recommended to NASA in 1970 [1]. There have been changes in epidemiology data [4] that have led to higher projection of risks for a given dose of radiation. These changes included a higher projection of risks for solid cancers than in 1970 [1] when leukemia was expected to be the major risk. Because of the inclusion of female astronauts and the development of the space shuttle which led to career radiation workers, in 1989 the NCRP recommended [4] age and sex dependent dose limits. Less consequential changes to space radiation risk assessment were the assignment of linear energy transfer (LET) quality factors, and improvements in the accuracy of organ dose projections and spaceflight dosimetry. Molecular biology and technology have progressed over the same period and there is an expectation that fundamental changes to risk assessment will take place. Also, for the first time a large number of ground-based facilities capable of accelerating protons and heavy ions to the energies that occur in space are in operation or will be in the next few years. This will allow a radiobiology database to be accumulated and for advancements in the basic understand-

ding of the radiobiology of space radiation. The genetic basis for the diseases of concern following radiation exposure have been elucidated [8, 9] and this knowledge should be used to guide future risk approaches for astronauts. We discuss these issues in this paper.

2. Re-evaluation of astronaut career risks

NASA limits an astronaut's career radiation exposure to a projected risk of 3% excess cancer fatality. Short-term dose limits (30-day and 1-year) are also imposed to prevent clinically significant deterministic effects where dose thresholds are expected to occur. Recently, we have performed a re-evaluation of the career exposures incurred by NASA astronauts. Herein, we discuss preliminary results of this re-evaluation. This re-evaluation was undertaken for several reasons: first, to include organ equivalent doses as evaluated using the most recent radiation quality factors or weighting factor's recommended by the ICRP 1990, [10] and NCRP 2000, [7]. Second, dose to risk conversion factors are re-evaluated every few years as epidemiological data matures, and have indicated an increased level of risk for a given radiation exposure. Finally, radiation transport codes and active spaceflight dosimetry have been developed allowing for accurate estimates of the LET spectrum at individual organs and to isolate the contributions from trapped and galactic cosmic rays (GCR).

For space exposures, we have estimated organ doses using environment and transport codes [11], ICRP-60 quality factors, and shield models of spacecraft and organs. Calculations of organ dose are re-normalized using the ratio of measured to calculated dose at skin where the astronauts badge is worn. Area dosimetry on specific missions are used to scale the ratio of the trapped to GCR contributions. The efficiency of TLD's as a function of LET is taken into account using accelerator data. We note that an alternative approach using radiation

weighting factors provides many ambiguities for space applications because of the values assigned to high-energy protons and relativistic ions such as helium and carbon, and because of the complicated relationships between primary and secondary radiation inside the spacecraft and tissue. Calculations using weighting factors are more than a factor of two higher than the present method.

Table I shows a breakdown of the collective doses from individual sources for each decade over the 40 years of the NASA programs. For each exposure type, the collective and average effective dose equivalent using tissue weighting factors [10]. The highest space exposures have occurred in the 1970's and 1990's because of the long duration Skylab and NASA-Mir missions, and the Apollo missions. Average quality factors in low Earth orbit (LEO) range from about 1.5 for missions dominated by trapped radiation to 2.5 for missions dominated by GCR. The exposures from diagnostic X-rays decreased dramatically by the mid-1980's due to a Presidential Directive ordering improvements in procedures. On the Apollo 12 through Apollo 17 missions a ^{238}Pu source was used for a lunar surface experiment [12] and led to a small neutron dose with higher doses occurring on the aborted Apollo 13 mission because the experiment was not delivered to the lunar surface. For air-travel, the listed values are preliminary estimates using the approximate number of hours of training required for pilots and mission specialists and the typical flight routes. Although, space radiation is the dominant component of collective doses, clearly other types of exposures make significant contributions individual astronauts.

Figure 1 and 2 show doses and projections of the probability of excess lifetime cancer fatality, respectively for all NASA astronauts. Of note is that because of the age-dependence of risk coefficients, diagnostic X-rays performed during or soon after selection into the astronauts corps often make a higher contribution to the accumulated risk of an

Table I – Historical collective and average occupational doses from individual sources amongst NASA astronauts.

Historical Collective Doses over time period-					
Source	1957-1969	1970-1979	1980-1989	1990-1999	Total
Space					
Collective, cSv-PY	20	111	42	273	446
(Average, cSv)	(0.46)	(4.0)	(0.26)	(0.73)	(0.74)
Pu-source					
Collective, cSv-PY	–	2.8	–	–	2.8
(Average, cSv)	–	(0.2)			(0.2)
Diagnostic X-rays					
Collective, cSv-PY	141	179	52	15	387
(Average, cSv)	(0.095)	(0.082)	(0.027)	(0.007)	(0.05)
Air-flight	20	32	50	65	157
Collective, cSv-PY					
Total Collective	181	324.8	134	353	992.8

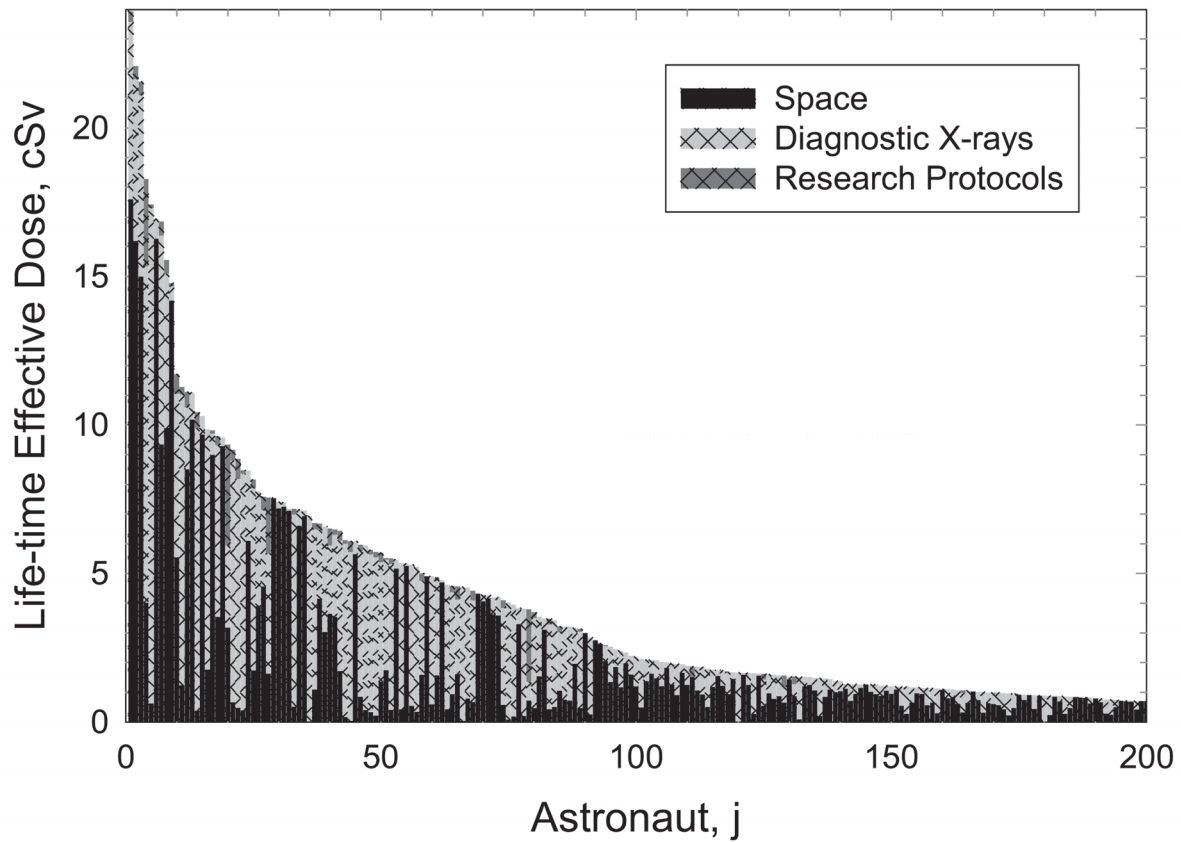


Fig. 1 – Preliminary results for re-evaluation of life-time effective doses for astronauts showing contributions from space radiation, diagnostic X-rays, and research protocols. Air-flight exposures of astronauts are not included.

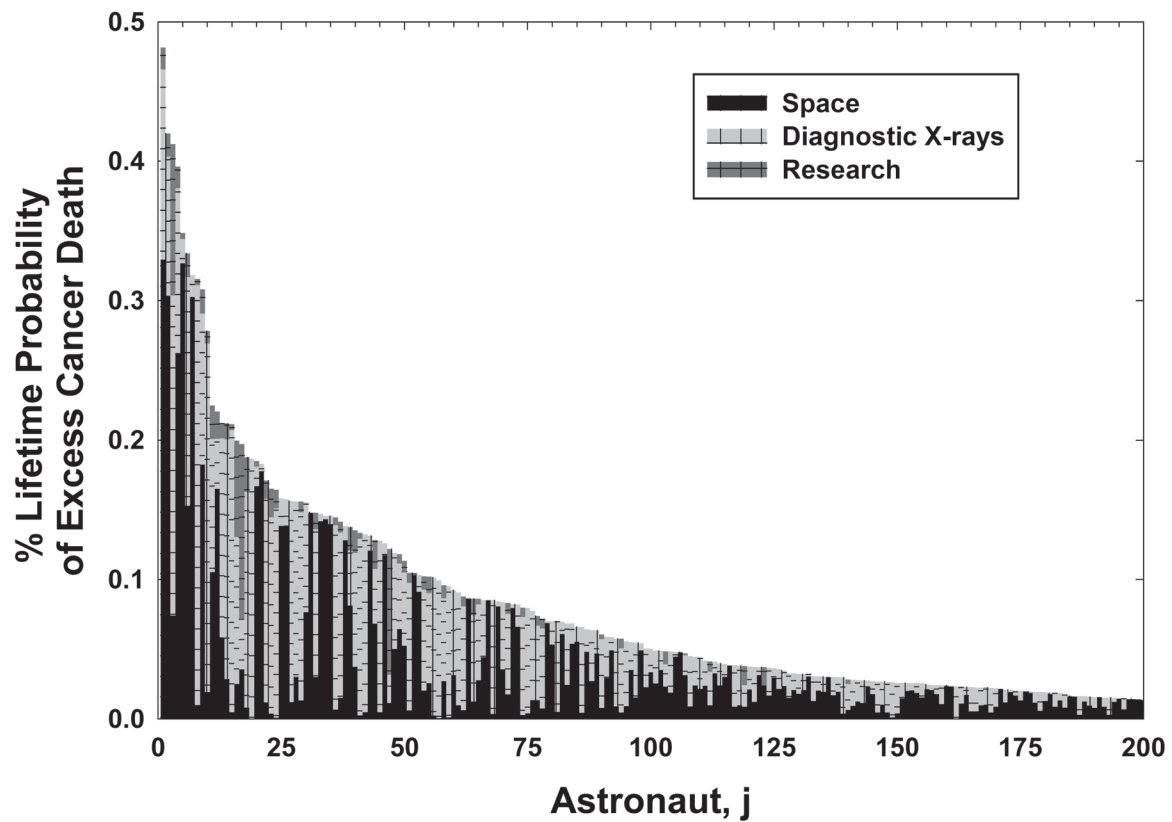


Fig. 2 – Preliminary results for re-evaluation of fatal cancer risk from radiation exposures for astronauts evaluated using NCRP recommended age and sex dependent dose to risk conversion factors. Air-flight exposures are not included.

individual. Doses have been well below career limits consistent with the ALARA principle (As Low As Reasonably Achievable) and no individual has exceeded more than one-third of their career limit. However, for long-term missions a major concern is place on how reliable are the current projection models for late effects from heavy ions and neutrons. Improved validation of the accuracy of space dosimetry and radiation transport codes, especially for estimating the neutron components in space, is also needed. Biodosimetry is used to verify previous radiation exposure. In recent years, the application of chromosome painting techniques have become routine after long-term space flight (> 30 days) [13, [14] and improvements in the accuracy of these approaches will continue in the future.

3. Astronauts cohort size and individual based risk assessment

Because of the small number of astronauts it will extremely difficult to verify any excess cancer risk amongst space workers. About 14 astronauts per year will occupy the ISS and the mission lengths of 4-6 months will lead to doses of 8-20 cSv. For astronauts traveling beyond LEO, higher doses will occur, however the small cohort size of perhaps 6-12 astronauts will prevent any excess cancer from being attributable to radiation using epidemiology alone. In order to illustrate this point, Table IIa shows calculations of the total number of person-years after radiation exposure in the cohort of NASA astronauts participating in the longitudinal study of astronaut health (LSAH). The study contains 295

living or deceased astronauts. About 35 other persons have ventured into space in NASA's programs, however do not participate in the LSAH study. As a comparison group, we can consider other radiation workers [15], the low dose atomic-bomb survivors (< 0.5 Gy), and a cohort of workers as NASA Johnson Space Center (JSC) participating in the LSAH. Table IIb shows power calculations of the minimum level of relative risk sufficient to verify an excess risk with 95% confidence intervals. These estimates ignore possible biases or confounding factors that would limit statistical proof of an excess risk. Clearly, an excess cancer risk even 5-fold above the current limit of 3% excess fatality would be difficult to verify using statistical methods alone. Such statistical limitations support the development of new individual-based approach to risk assessment.

A challenging task will be to develop individual biomarker's of radiation sensitivity and assays that indicate an increased risk from prior exposure that directly correlates with the early stages of a disease [16, 17]. The expectation is that knowledge of genetics and the molecular interactions involved in DNA damage, DNA damage processing, and cell cycle regulation and growth controls can be used to develop assays that measure a signature of the earliest stages of a disease progression or of an enhanced level of radiation sensitivity or resistance in an individual. One important area of study is gene polymorphism's [8, 17] which occur in a much larger fraction of the population than for e.g. the population that is null or heterozygous for a tumor suppressor gene. Such changes may alter expected resistance or susceptibility through functional chan-

Table IIa – Population size and collective doses of Astronauts compared to other occupational exposed groups.

Cohort	Hanford Workers	Atomic-Bomb	Astronauts Year 2000	Astronauts Year 2010	JSC Control Group
No.	32,595	~6,000	295	450	910
Person-Years	781,549	140,000	5,500	8,600	18,000
Collective Dose (PY-Sv)	877	–	10.1	16	0
Average Dose (mSv)	26.9	–	35	40	0
No. > 50 mSv	600	–	60	120	0

Table IIb – Minimal relative risk needed to establish an increased occurrence of cancer with a 95% confidence interval (C.I.) for astronauts relative to other cohort sizes.

Comparison Cohort	Minimal Relative Risk to assure 95% C.I. in year 2000	Minimal Relative Risk to assure 95% C.I. in year 2010
JSC Control Cohort	3.7	2.9
Cohort of 100,000 PY	2.3	2.1
Cohort of 1,000,000 PY	2.0	1.9

ges in genes known to be important in DNA damage processing or downstream cell cycle controls. Important related questions are the legal and ethical ones related to the use of such methods which must be answered before such knowledge and technology could be applied for risk assessment.

4. Radiobiology research and risk assessment

Health risks from radiation include cancer, late effects to the CNS, cataracts, hereditary effects, and acute radiation sickness that might occur after a solar particle event. By the early 1980's, many lifetime studies of tumor induction in mice and rats had been concluded using gamma ray and neutron exposures. Reviews of the motivations, and strengths and weakness of these studies have been given by Fry and Storer [18] and Ainsworth [19]. Few animal studies aimed at understanding the dose response for tumor induction by proton and heavy ion beams have been made [20, 21]. In recent years, the focus of risk assessment has emphasized mole-

cular approaches that attempt to answer traditional risk assessment questions such as the extrapolation to low doses and dose-rates and the variation of effects with radiation quality. However, at the present time there is no assurance that these approaches will be sufficient to reduce uncertainties in risk assessment, and most likely a combined approach using molecular and animal data is needed. Throughout the 1990's, the NASA annual radiation health investigators meeting has held round-table discussions that have produced a set of critical questions whose answers are expected to lead to reductions in risk assessment uncertainties and to lead to the discovery of biological countermeasures [22]. Table III lists the most recent version of critical questions related to radiobiology research. Clearly, there is a consensus from the scientific community that basic understanding in radiobiology can aid in space radiation risk assessment as indicated by this list of critical questions.

In order to discuss how progress in understanding basic radiobiology may be used to improve risk assessment we consider two areas; studies of DNA

Table III – Critical Questions in Radiobiology for Improving Risk Assessment.

Molecular Biology
1. What are the probabilities of GCR to produce radiation damage at specific sites on DNA?
2. How are processes like oncogene activation and oncogene suppressor inactivation involved in the carcinogenic effects of GCR radiation?
3. What mechanisms are involved in modulating radiation damage at the molecular level (repair, errors in repair, gene amplification, etc.)?
4. How can molecular mechanisms of radiation damage be used to understand effects in whole cells?
Cellular Biology
1. What is the probability of initiating neoplastic cell transformation or other steps leading to a cancerous cell?
2. How do cellular repair mechanisms modulate damage produced by energetic charged particles?
3. How can the radiation effects on cells in culture be related to radiation effects in 'normal' cells and tissues?
4. How can cellular mechanisms of radiation damage be used to understand effects in whole organisms?
Animal Models
1. How can animal models be used to extrapolate probabilities of radiation risk to humans in space?
2. What is the relative biological effectiveness of different types of radiation for the relevant endpoints such as cancer and cataracts?
3. How can protection against the effects of galactic cosmic rays and the proton radiation of solar events be improved?
4. What is the age dependence of relevant radiation effects in animals (cancer, cataractogenesis, life shortening, etc.)?
Humans
1. What should be the radiation "dose limits" for manned deep space missions?
2. What is the probability of cancer as a function of dose, dose rate, radiation quality, gender, age at exposure, and time after exposure?
3. What is the effect of GCR at different stages of the carcinogenesis process?
4. What is the probability of cataract formation as a function of the same quantities?
5. What is the probability for genetic and developmental detriment incurred as a consequence of radiation exposure in space?
6. What pharmacological agents should be developed and tested as prophylactic agents for low LET?

damage processing [23] and genomic instability [24, 25]. The elucidation of the roles of both homologous and non-homologous DNA recombination in mammalian cells is leading to important implications in the extrapolation of effects to low doses and dose-rates [23]. Of note is the large number of gene products now known to be involved in DNA damage processing are potential targets for identifying inherent resistance and sensitivity as well as biological countermeasures. Mathematical models of DNA recombination using biochemical reaction theory have already been developed [26] and are replacing old paradigms that used purely geometrical and physical concepts to describe gene mutation and chromosome aberration data. Such models suggest that the curvature in dose-responses occur due to competition between damage processing pathways [26] and provide a biological based theory for the extrapolation of radiation responses to low doses and dose-rates.

Genomic instability refers to delayed effects observed in the progeny of irradiated cells including chromosome aberrations, mutations, cell death, and persistent reactive oxidative damage (ROS). Cytogenetic approaches have been used extensively for understanding genomic instability and have begun to define relationships to carcinogenesis. Khadim et al. [24] observed instability in the form of delayed chromatid aberrations in primary bone marrow stem cells using high LET alpha particle irradiation. An increase in the number of aberrations occurring beyond 30 cell divisions from radiation exposure was found with alpha particles, however instability was not found following x-ray exposures. Studies by Ullrich and co-workers [25, 27] have used mouse mammary stem cells irradiated *in vivo* and observed chromatid type aberrations for up to 40 cells divisions after neutron irradiation. An important observation from these studies is that a relative risk model for instability in the mouse mammary stem cell is strongly correlated with relative risk factors for mammary tumors in the same strain of mice. Such systems could potentially serve as a surrogate for large-scale animal studies, providing a cost-effective approach to establish relative risk factors as a function of radiation quality, shielding, dose, or dose-rate.

Several studies [25, 24, 28] have indicated that for high LET radiation there is a very shallow or non-existent dose-response at low doses for many mutagenic or oncogenic endpoints. These effects have suggested extra-cellular mechanisms including oxidative damage to the cytoplasm, release of extra-cellular factors, or aberrant cell signaling. These observations have potentially large implications for NASA because they suggest that the expensive costs of adding spacecraft shielding may provide little or no benefit. Clearly, such approaches are needed because of the difficulty in costs and interpretation

in performing a large animal study at low doses and dose-rates.

One area of risk assessment that has made little progress is the possible effect's to the central nervous system (CNS) during or after long-term spaceflight. Damage to terminally differentiated cells in the CNS were noted by NAS [1, 2, 3] as one of the highest priority research questions for space exploration [29, 30]. These concerns were prompted by observation of light flashes by astronauts on both the Apollo and Skylab missions. Light flashes continue to be observed by astronauts in LEO, especially on high inclination missions. Although not fully explained, flashes are related to the passage of high charge and energy (HZE) or high LET recoils through or near the retina [2]. This led to a concept of a microlesion to describe an HZE track near the end of its range severely damages a column of cells. Similar effects may be possible after high-multiplicity nuclear reaction events in the brain. Figure 3 shows calculations of the number of micro-lesions per year from GCR using differential models of cellular sensitivity. Table IV estimates, the number of micro-lesion for various space missions assuming one occurs for particles with cell killing densities above 20% over at least 50 cell layers. Clearly, a significant fraction of the brain would be traversed by such heavy ions on a Mars mission. We note that the use of the number of particle traversals per cell ignores the effects of lateral damage to adjacent cells by delta-rays [31] and provides no indication of the differential damage severity of nuclei of a given charge and velocity.

Can the destruction of a small number of unreplaceable cells lead to late effects in the CNS? Effects that have been observed in animal models include altered motor function or performance [32], accelerated striatal aging [33], late degradation of DNA [30], and altered dopamine function [32]. Little progress has been made in understanding if these effects could occur following low dose-rate exposures to humans. A recent review by Tolifon and Fike [34] noted that as the survival times of patients treated with radiation for primary and secondary brain tumors have improved, the frequency and severity of abnormal changes to the CNS have become more apparent. These findings and observations using animal models irradiated with heavy ion beams are a large concern if theories of late tissue damage are correct. One such theory developed by Casarett [35, 30] predicts that late CNS effects could occur many years after radiation exposure in what has been called "radiation accelerated aging" and would have an increasing severity and decreased latency with increasing dose or heavy ion flux. It appears that the largely unknown late effects to the CNS from heavy ions tracks, first noted by NAS in 1970 [1], still carries the largest uncertainty in risk assessment for exploration missions.

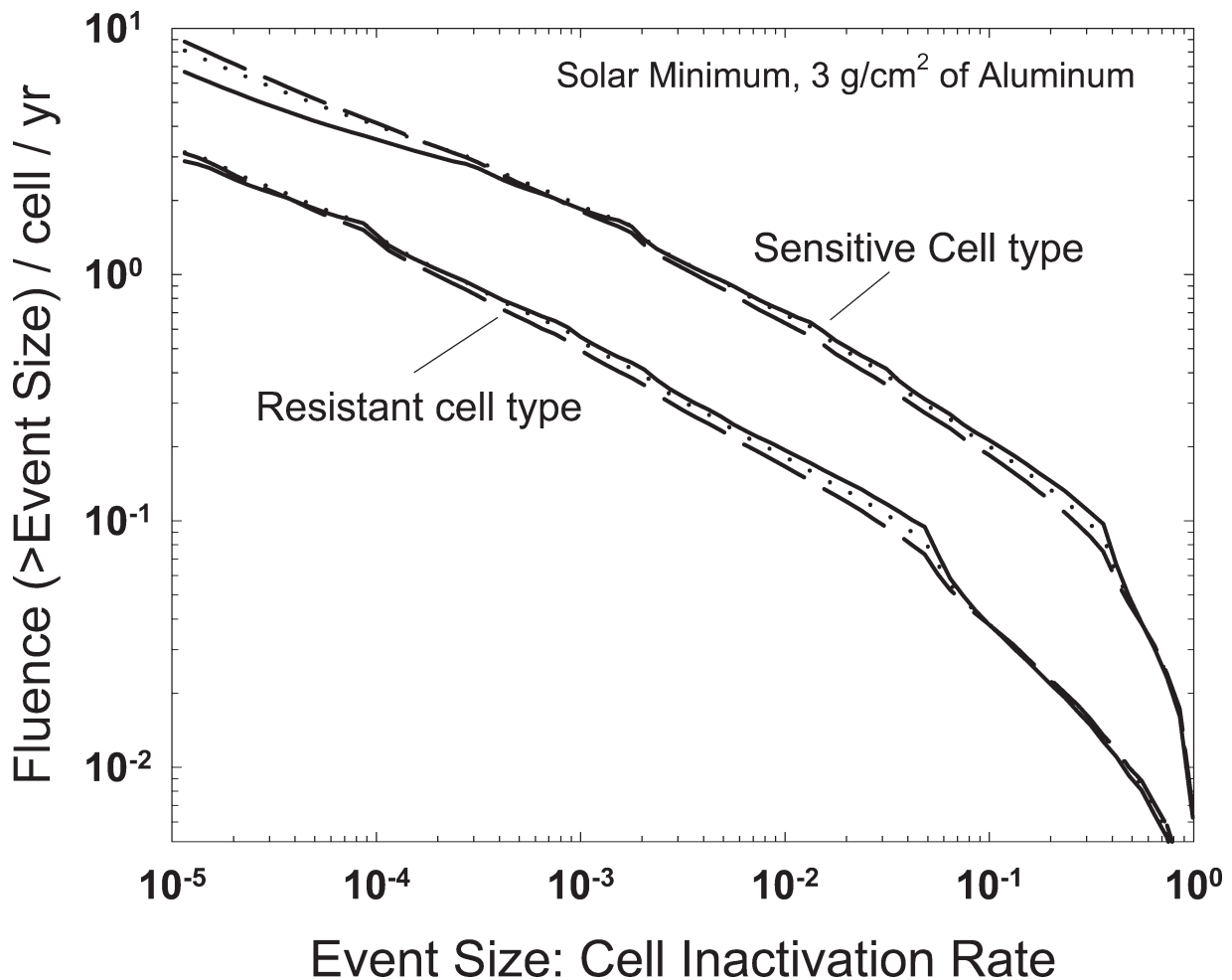


Fig. 3 – Calculations of the integral number of GCR ions that inactivate cells above a given rate assuming a cell size of 100 μm². Calculations are made for several depths in tissue behind 3 g/cm² of aluminum shielding and for a sensitive and resistant cell lines. Solid line is for 1 cm tissue depth, dotted line for 4 cm, and dash line for 8 cm.

Table IV – Estimates of the probability per cm pathlength of a microlesion for various mission scenarios near solar minimum.

Mission Type	Dose, cGy	Eq. Dose, cSv	%Probability of Microlesion/cell
ISS (120 d)	6	13	0.3
Deep Space (120 d)	7	30	1.3
Lunar Base (120 d)	4	19	0.8
Mars Surface (120 d)	5	21	0.6
Mars Mission (1000 d)	35	150	6.7

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