Concerns About Applying Animal Irradiation Experiment Results to Human Space Missions

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Radiation Testing of Laboratory Animals on Earth May Not Accurately Reflect Space Radiation Effects on Astronauts

Abstract

Ground irradiation experiments on Earth that study the effects of radiation on rodent brain function may not allow prediction of expected radiation effects on astronauts in space. Though cognitive impairment was reported in the test animals, the conditions of the irradiation differed significantly from the observed space radiation environment. The high doses of irradiation and the spectrum of rays provided to the smaller surface area of the rodent brains do not duplicate the observed impact of identified space radiation on the larger human brain and body, and do not take into account the biological processes of healing and annealing that have mitigated the damage from astronaut radiation exposure.

In contrast to the serious health effects reported that have been attributed to the absence of gravity, such significant radiation effects on cognitive status have not yet been identified in multi-year cosmonaut space missions. This paper addresses some possibilities for this disparity.

Concerns

In recent years, many ground irradiation experiments have been conducted on rodents, which have attempted to mimic the environmental conditions that astronauts would face in orbit and during interplanetary travel through space.

This review addresses concerns related to the methodology of such experimental findings [1, 2, 3 ,4, 5], the observed effects of the studies on the test animals, and the attempts to apply the findings to humans who would travel in space. Specifically, the test rodents are helpful to evaluate the radiation effects of human space travel, specifically as they were diagnosed of having developed cognitive impairment (brain damage) from intense, excessive, and “un-natural” laboratory radiation exposure vastly different from the radiation existing in space in terms of type, intensity, and energy. Such effects, if they were to occur among astronauts, would impair their ability to safely and reliably control and survive their mission.

Though well intentioned, such animal ground irradiation experiments, unfortunately have serious shortcomings and limitations which affect the validity of their results, because conditions in space have not effectively been duplicated in the laboratory on Earth. Differences between the space radiation environment and the Earth laboratory result because Earth radiation facilities typically provide only:

- A single radiation source at a time (protons, electrons, neutrons, heavy ions).
- A single energy at a time
- A single (standard) beam direction
- A single intensity at a time.

Variations in size, purity, and consistency of the beam, may affect the results.

To mimic the radiation dose to which a human crew would be exposed **over several years in space**, the laboratory radiation is applied at an **enormously accelerated rate** via very large doses and within very short time intervals. These short-term high-rate irradiations are significantly different from those that would be experience by humans during long-duration space missions, in which the ray dosage and frequency are much lower.

In space, additional differences would be observed, including:

1. The generation of secondary daughter products within a spacecraft by the interaction of the primary cosmic rays with the various vehicle materials, equipment, instruments, the astronauts' suits, and the human body.
2. These daughter products are not present in the lab and would change the composition and value of the incident radiation.

The exposure of the test targets in the laboratory (biological samples, small animals) is confined to a **dense**, **focused**, **high intensity**, **unidirectional**, and **mono-energetic** beam of (at most) a few select ion species, **one at a time**. In contrast, in interplanetary space, the cosmic ray incidence is of **low intensity, omnidirectional**, **isotropic**, and **instantaneous for all ion species**, and occurs **simultaneously for all energies** (complete spectra).

- **The absence of a healing mechanism in the targets of the lab experiments**. During long missions in space, healing (annealing) would ameliorate the radiation effects by repairing inflicted damage. The laboratory experiments do not provide the opportunity for self repair of radiation damage, which mitigates negative long-term effects in human astronauts.
- The fact that results obtained from experiments on specific animal organs or tissues may not reflect correctly corresponding effects on a human being, whose anatomy and physiology are significantly different.
- The impact, if any, of the zero gravity environment in space, which is not addressed in the laboratory.

- The impact, if any, of the absence of a strong magnetic field in space, not duplicated in the laboratory.
- The combined (synergistic) effects of these parameters on the human body in space.

Galactic cosmic rays and periodic solar flares or Coronal-Mass- Ejection particles (intermittent only, if applicable) of varying intensities, are continuously and simultaneously incident on a spacecraft from all directions. Hence, ground test simulations are not equivalent to space reality, which may result in large uncertainties and lead to erroneous conclusions.

Cosmic-Ray Abundances

In an attempt to better simulate specific space conditions, facilities may adjust beam species, energies, and rates, one at a time in each case.

At the lab, the selection of a beam's ion species would affect the experiment's outcome. As the interplanetary cosmic ray environment is composed approximately of **90%** Hydrogen (**H**), **9%** Helium (**He**), and **1%** all other heavier ions combined, the **HZE** elements of the periodic table selected for the referenced tests, namely ^{26}**Fe**, ^{16}**O,** and ^{48}**Ti,** may not be the best choice, considering that the effects of a given dose derived exclusively from **HZE** particles may not be identical to the effects of the same dose from the **H** and **He** ions. These two ions are orders of magnitude more numerous than the **HZE** ions of the beams. Figure 1 [6] lists the relative abundance of cosmic rays in terms of their charge number. It shows that the **H** and **He** particles are at least **2-3** orders of magnitude more numerous than **Oxygen**, **3-4** orders of magnitude more numerous than **Iron**, and over **4** orders of magnitude more numerous than **Titanium**.

The respective flux levels of the ions that are important for this review, are approximately: **H**=$2x10^4$, **He**=$4x10^3$, **O**=$8x10^1$, **Ti**=$1x10^0$, **Fe**=$8x10^0$. Thus in space for every single incident

Titanium ion, the corresponding approximate number **of H** is about **20,000,** of **He 4,000,** of **O 80,** and of **Fe 8** particles**.**

It is obvious from these numbers that the selection of ^{16}**O,** ^{48}**Ti,** and ^{26}**Fe** for the referenced experiments, is a reason for concern. As their incidence is extremely low in the interplanetary environment, they would not contribute significantly to the dose accumulation, over a multi-year-long space mission.

For example, Figure 2 is a plot of the cosmic ray **Oxygen** spectrum as a function of kinetic energy, for solar min and solar max conditions [7]. At the selected lab energy of 600 MeV/n, the flux is only a very few particles per **cm^2 per day**. That is, approximately **2.2x10^{-3}** particles/(cm^2-d) for solar maximum and about **6.0x10^{-3}** particles/ (cm^2-d) for solar minimum.

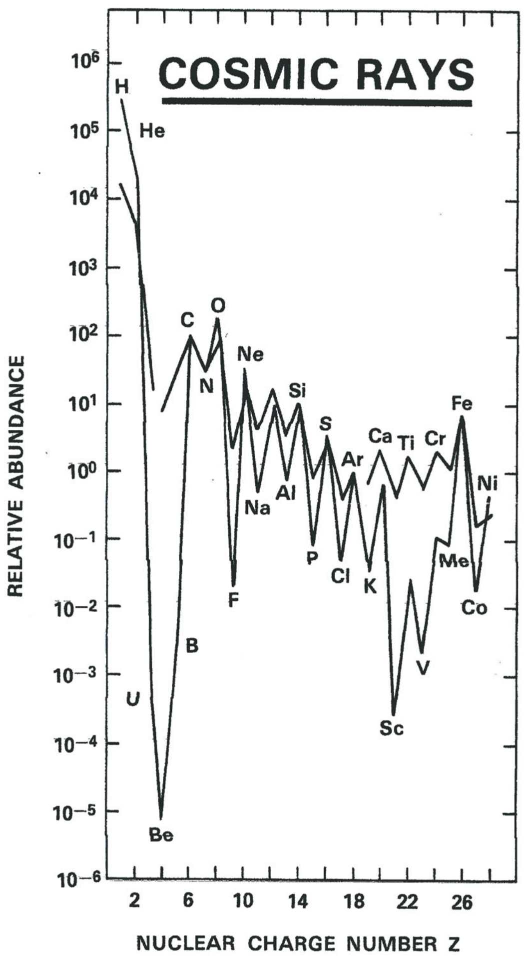

Figure 1: Relative abundance of cosmic ray

Converting the **cm^2** unit to the cross-sectional area of the human brain, which is approximately **(12 cm)^2,** the flux of Oxygen ions at 600 MeV/n is about **1** particle per human brain <u>**per 3 days**</u> for solar maximum , and approximately **1** particle <u>**per 1 day**</u> for solar minimum. This incidence of **Titanium** and **Iron** ions is even lower than **Oxygen.**

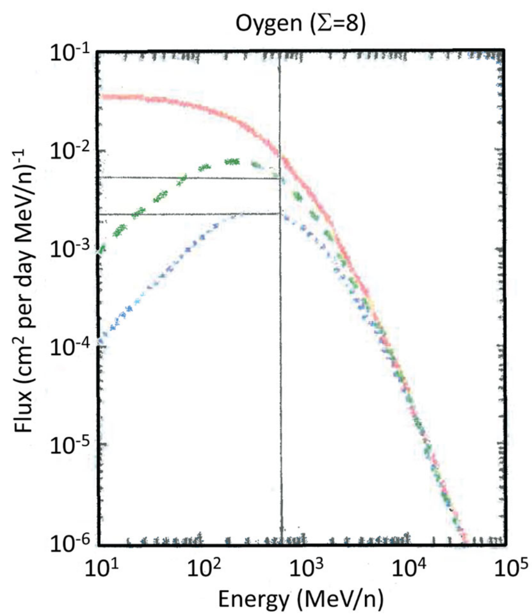

Figure 2: Oxygen spectrum as a function of kinetic energy for solar min and solar max

Human to Rodent Perspective

To gain a more realistic perspective of the applicable effects of the rodent experiments in relation to a human brain, basic physical parameters need to be considered:

	Human	**Rodent**
Brain mass	1,000 gr	1 gr
Brain neurons	$8.6x10^{10}$	$7.1x10^{7}$
Brain CSA*	$(12\ cm)^2$	$1\ cm^2$

*Cross-sectional area

Thus, if a focused beam of high intensity heavy-ion radiation affects a large percentage of the rodent's brain neurons, the exposure of a human brain **to that same radiation** would probably affect a larger number of neurons, because of the longer path lengths of the ion tracks in the larger human head. But percentage wise, assuming for arguments sake that 50% of the rodent's tiny-brain neurons were affected, twice that amount would still correspond only to less than **0.001%** of the human brain neurons. **This ratio is not likely to produce consequences and effects in humans, analogous to those reported in rodents.**

These experiments therefore do not effectively duplicate the conditions of space in regards to radiation type, dose, duration, and effects.

Additionally, the differences in mouse and human physiology may undermine the applicability of the rodent data to human interplanetary radiation exposure.

A further item of concern is that cosmic ray intensities below energies of approximately **1-2 GeV/n** are anti-correlated with the solar cycle phases, for all cosmic ray particle species, i.e. lower fluxes are observed during solar maximum and higher fluxes during solar minimum, by a factor of approximately **2.7**, Figure 3 [8].

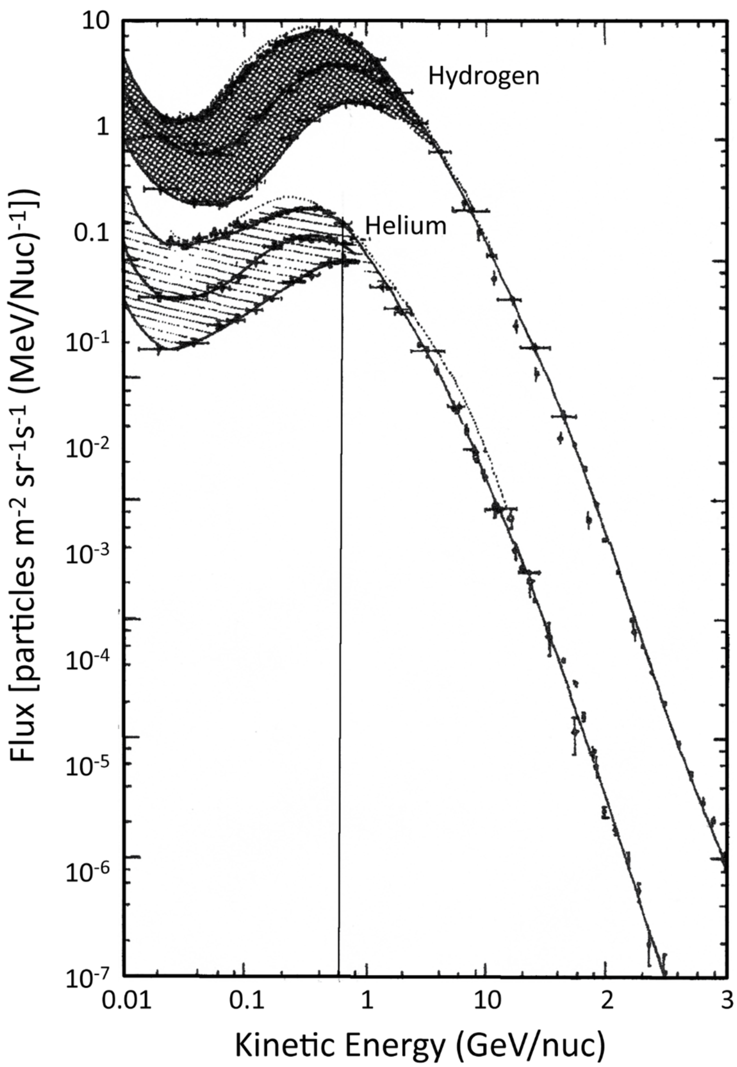

Figure 3: Primary cosmic ray differential energy spectrum. The upper envelope indicates the solar minimum while the lower envelope indicates the solar maximum spectrum. The shaded area indicates the range of the solar modulation over a solar cycle. The hydrogen spectrum in this figure has been multiplied by a factor of 5 so the modulated portion of the spectrum avoids merging with the top of the helium spectrum.

This variation is significant for calculations that include particles below the critical **1-2 GeV/n** energy level, because of the larger fluxes in that part of the spectrum. However, cosmic rays with greater energies are not affected by solar cycle variations.

It is also advisable to remember that the nominal solar cycle length of **11** years is only an average value. In reality, solar cycles may vary from **<9** years to **>13** years, as documented for five actual cycles in Figure 4 [9].

The pink colored areas denote the constant-per-cycle 7 years-long solar maximum periods. The areas in between are the solar minimum intervals, that are of variable length.

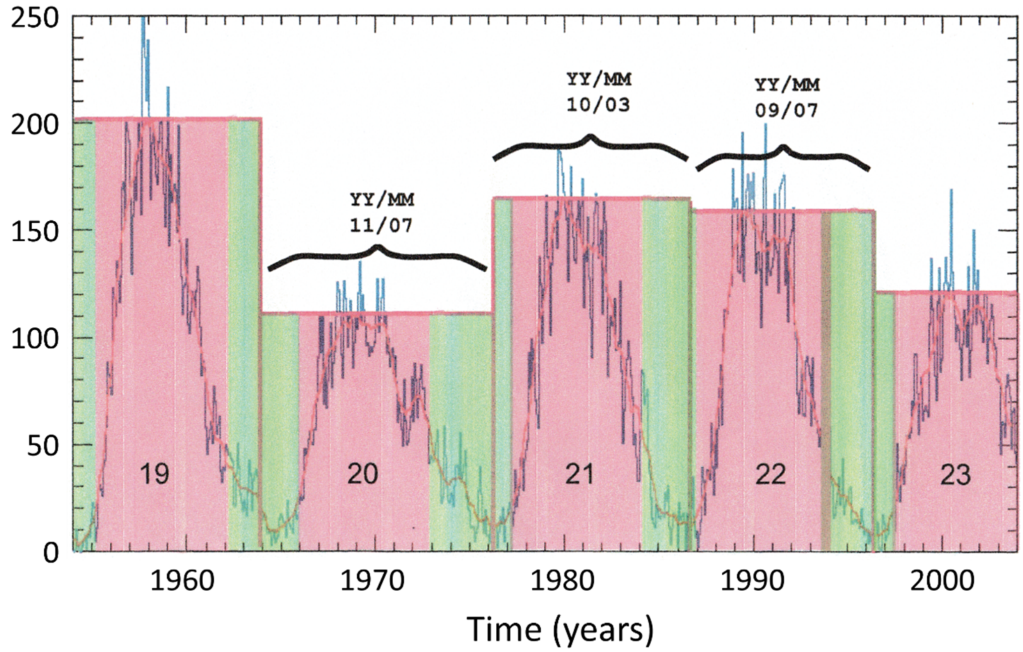

Figure 4: Recent Solar cycle phases.

To obtain a more realistic measure of the actual levels-of-effectiveness of the cosmic ray ion species, the application of a relative **'dose equivalence'** is essential.

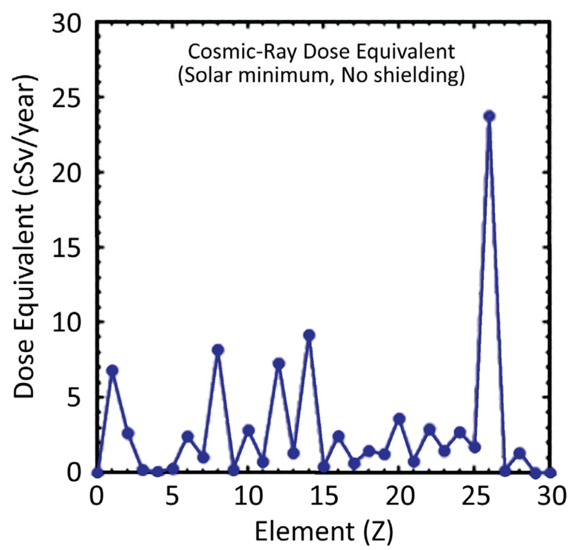

Figure 5: Cosmic-Ray Dose Equivalence.

Figure 5 is a plot of the **'Cosmic Ray Dose Equivalence'** for the first 30 elements of the periodic table [10], under solar minimum conditions, without shielding interference, in terms of **cSv/year**. **Fe** Ions have the greatest impact in this group. However, as a contributor to human dose accumulation in space, the relative importance of the **Fe** ion is **minimal,** as is also the case with the **Oxygen** and **Titanium** ions, used in one of the experiments [1]. This is indicated in Table 1, which includes the relative cosmic ray '**Dose Equivalence'** effect of five ions (**H, He, O, Ti, Fe**), by combining it with the abundance of these ions. This evaluation, in terms of **cSv/year**, confirms that, **proportionally**, **HZE** cosmic ray particles, in spite of their larger mass, larger charge, and greater ionization capacity, **contribute minimally** to a total absorbed dose in space, when compared to the contribution from the vastly more populous **99%** low-z ions (**H** and **He**).

Table 1: Relative Cosmic Ray Dose Equivalence.

Element	**Abundance**		**Equivalence**		**Effect**
H	20,000	x	7	=	**140,000**
He	4,000	x	2	=	**8,000**
O	80	x	8	=	**640**
Ti	1	x	2	=	**2**
Fe	8	x	24	=	**192**

Another factor to consider when using heavy energetic particles in lab experiments, is their respective track size, which correlates with ionization effectiveness. The ionization capacity of a cosmic ray along its track depends on the mass and the charge of the incident ion, as illustrated in Figures 6-12.

In Figure 6, as mass and charge increases, the tracks of the heavy ions become systematically denser and wider, increasing their ionization capacity [11] . Figures 7-12 provide a more detailed depiction of this, indicating the charge concentration and the radial distribution around the center of the track [12].

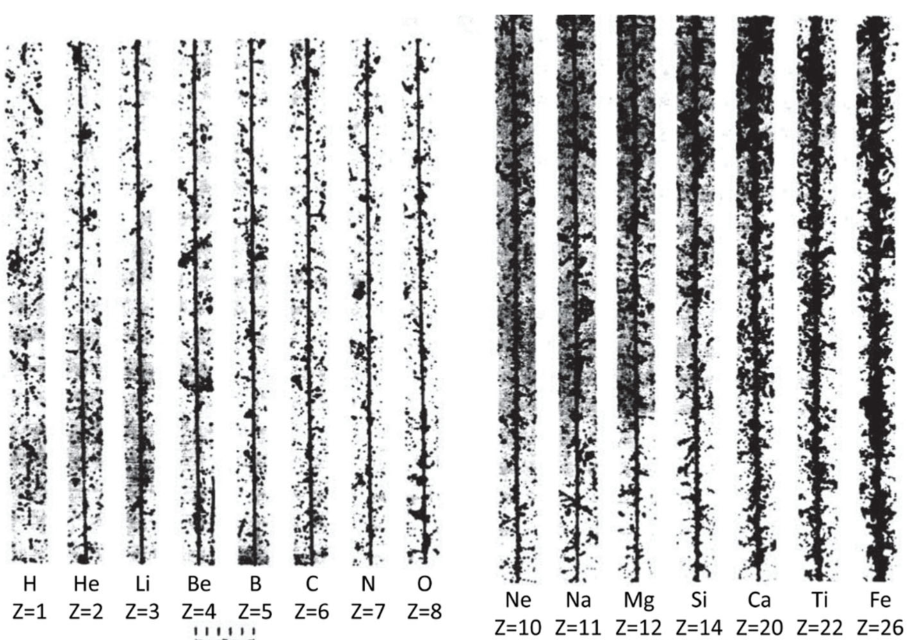

Figure 6: Reproduction of tracks of primary cosmic rays of hydrogen to iron in nuclear emulsions.

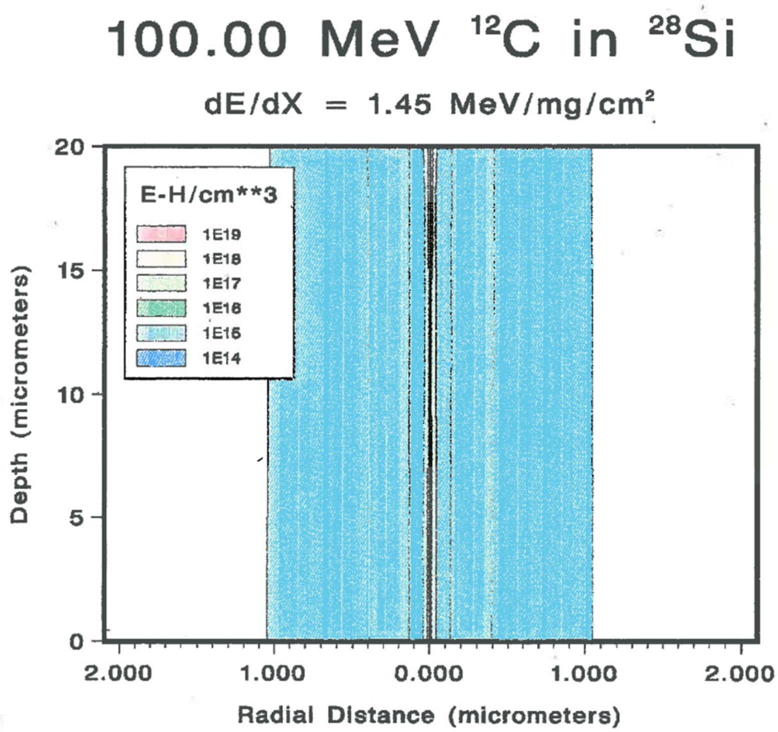

Figure 7: Ionization capacity of a cosmic ray at 100MeV.

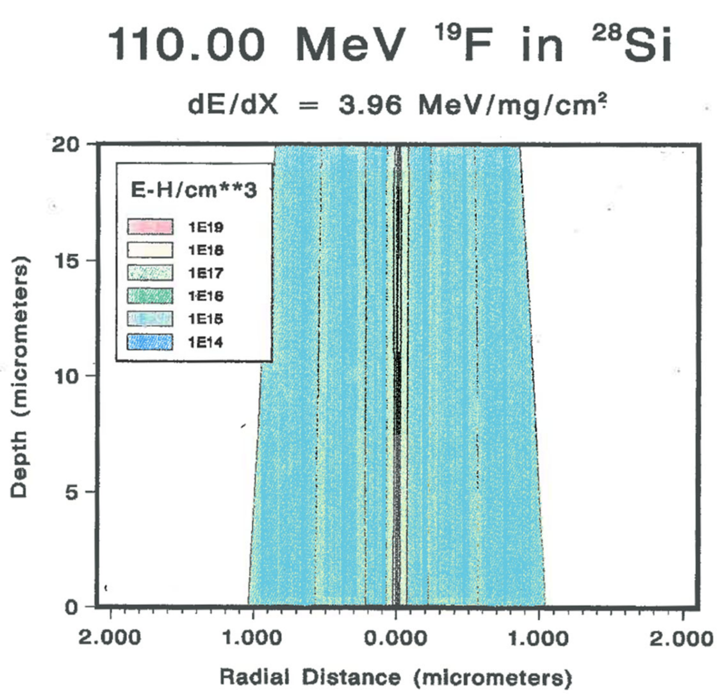

Figure 8: Ionization capacity of a cosmic ray at 110 MeV.

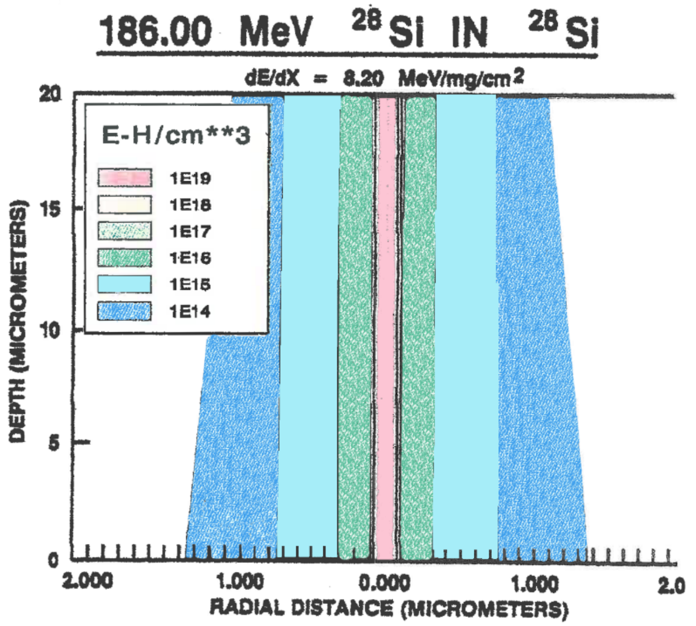

Figure 9: Ionization capacity of a cosmic ray at 186 MeV.

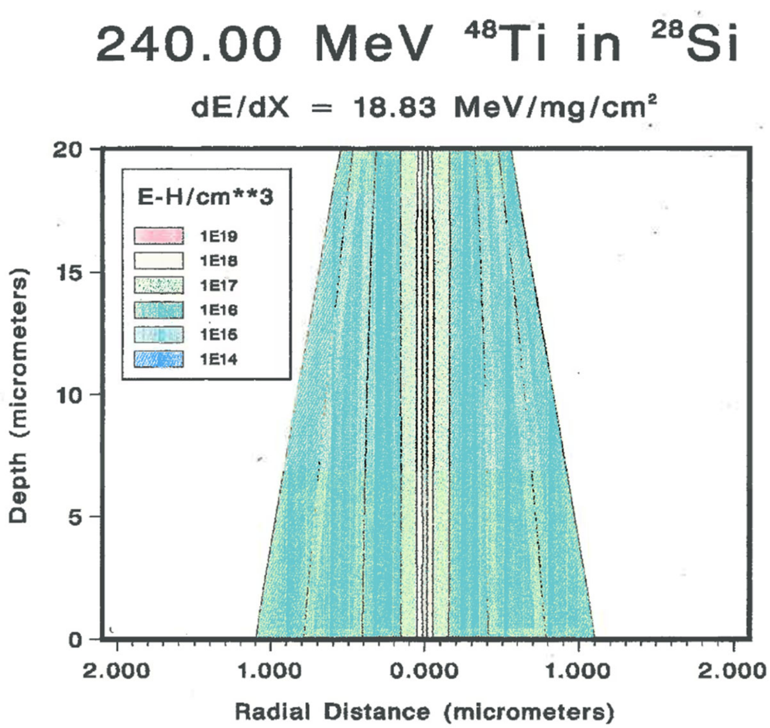

Figure 10: Ionization capacity of a cosmic ray at 240 MeV.

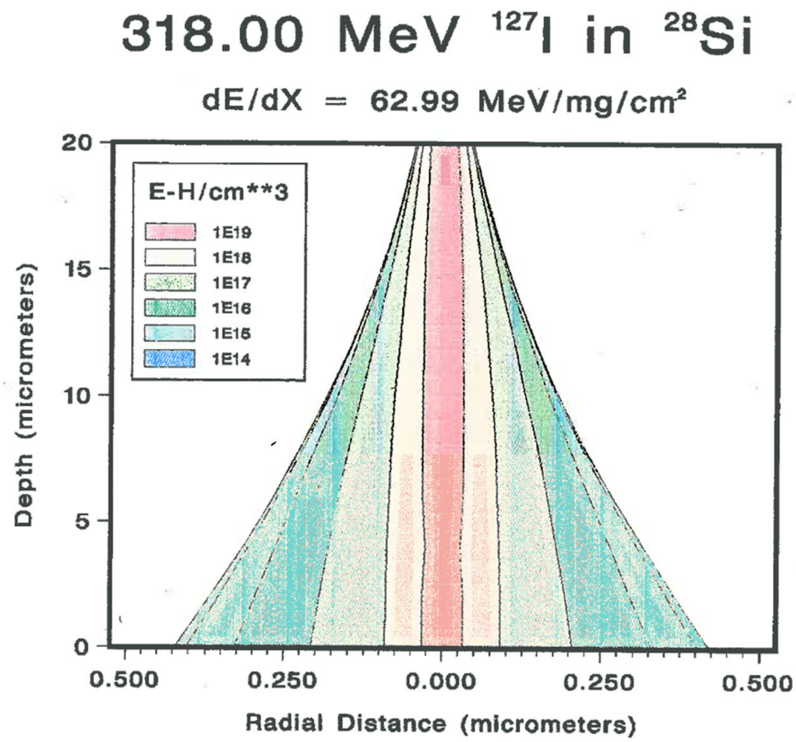

Figure 11: Ionization capacity of a cosmic ray at 318 MeV.

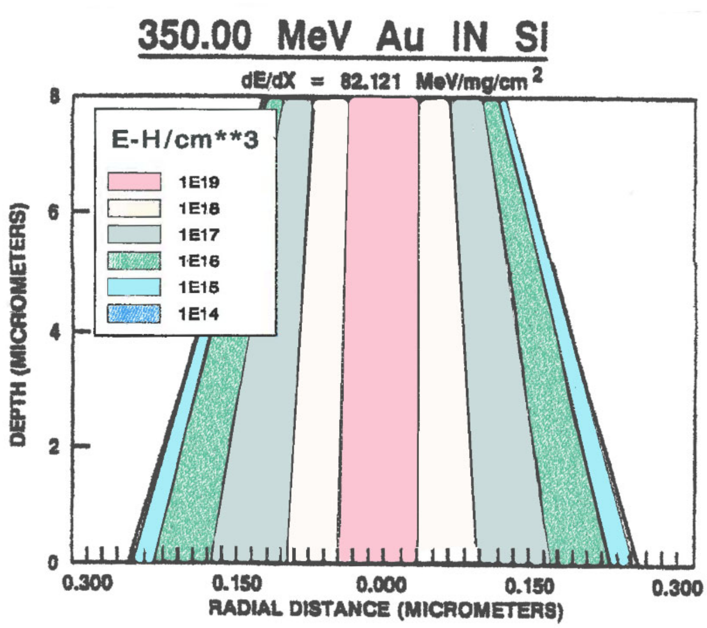

Figure 12: Ionization capacity of a cosmic ray at 350 MeV.

Although it has not been determined whether a given dose imparted to a biological target in the lab with environmentally low-incidence high-z particles, produces the same effects as a similar dose from the low-z but high-incidence **H** and **He** ions, prevailing in space, it is to be expected that a radiation exposure evaluation based exclusively on **Iron**, **Oxygen**, and **Titanium** ions, would not be equivalent and would not reflect accurately the effects and conditions of an actual multi-year space mission in the interplanetary environment.

Another serious matter of concern regarding these experiments is that the assumed long–duration mission-dose was imparted to the animal targets in the lab at an enormously high rate of over <u>**780,000 times greater**</u> than that measured on the journey to Mars, in an extremely short time of just a few seconds [1,2]. The respective test parameters of the **Oxygen** and **Titanium** experiments, in terms of doses, rates, and exposure duration, are listed in Table 4. It is not surprising that the rodents suffered cognitive brain damage from such an extreme exposure**. The major problem is that these results are totally irrelevant to human space travel, and astronauts would never experience such un-natural extreme conditions.**

Table 4: Rodent Experiment Parameters [1,2].

<table>
<tr><th></th><th>Experiment Dose</th><th></th><th>Rate</th><th>Duration of exposure</th></tr>
<tr><td rowspan="2">a.</td><td>^{16}O : 30 cGy</td><td>at</td><td>0.5 Gy/min</td><td>36 sec</td></tr>
<tr><td>^{48}Ti : 30 cGy</td><td>at</td><td>0.5 Gy/min</td><td>36 sec</td></tr>
<tr><td rowspan="2">b.</td><td>^{16}O : 30 cGy</td><td>at</td><td>1.0 Gy/min</td><td>18 sec</td></tr>
<tr><td>^{48}Ti : 30 cGy</td><td>at</td><td>1.0 Gy/min</td><td>18 sec</td></tr>
<tr><td rowspan="2">c.</td><td>^{48}Ti : 5 cGy</td><td>at</td><td>0.5 Gy/min</td><td>6 sec</td></tr>
<tr><td>^{48}Ti : 5 cGy</td><td>at</td><td>1.0 Gy/min</td><td>3 sec</td></tr>
<tr><td colspan="5">Actual Mars Measurements
Solar Maximum
Mars Surface Rate: 0.64 mSv/day
Mars Journey Rate: 1.84 mSv/day
(Solar Minim approximately 2.7 times larger)</td></tr>
<tr><td colspan="5">Experiment Irradiation Rate</td></tr>
<tr><td colspan="5">0.5 Gy/min = 390,875 times the Mars journey rate</td></tr>
<tr><td colspan="5">1.0 Gy/min = 781,750 times the Mars journey rate</td></tr>
</table>

An actual dose evaluation of a potential Mars mission can now be confidently estimated from data obtained by the **RAD** instrument on the **CURIOSITY** rover, which landed on the planet in August 2012 [13]. The detector experienced approximately **1.84 mSv** average <u>per day</u> during its 240-day journey to Mars, and approximately **0.64 mSv** average <u>per day</u> on its first 300 days on the surface[1]. Since the rover's mission occurred during the active phase of the solar cycle (solar maximum), the corresponding measurements would be more than double during the solar minimum **(x2.7).**

[1]Footnote: The reduced dose on the surface is due to a 2π shielding provided by the body of the planet, as well as to the partial attenuation by Mars' tenuous atmosphere of the low-angle incident cosmic rays.

Another minor element that can influence radiation experiment results or calculations, is the "*Inequality of the LET*" effect in the generation of Delta rays, which are produced by heavy ions in the target. The kinetic energy of a cosmic ray determines the value of its stopping power, the **LET**, and as the ion penetrates the target, its **energy, and consequently its LET** changes.

Thus, when the energy of a particle increases, the initial value of the **LET** also increases, from a relative low to an absolute high and then decreases to a final low at the highest energies. Figure 13 is a plot of this relationship for elements from Hydrogen (**H**) to Gold (**Au),** in a tissue medium. A similar pattern prevails, when the **LET** is evaluated in another medium, such as water.

In that process, a horizontal **LET** line across the **Figure 13** will eventually encounter an element's curve for a second time, at a discrete higher energy. At every such **LET-Energy** pair, the ionizing particle produces Delta rays in the target, but at different energies. An example of this is presented in Figure 14 **[14],** which plots **LET** versus energy for a Copper ion in a Silicon medium. At the two energy levels of the Copper ion, **25 MeV** and **395 MeV**, the **LET** has the identical value of **26 MeV-cm^2/mg**, but the corresponding Delta rays produced are **1 keV** and **14 keV,** respectively.

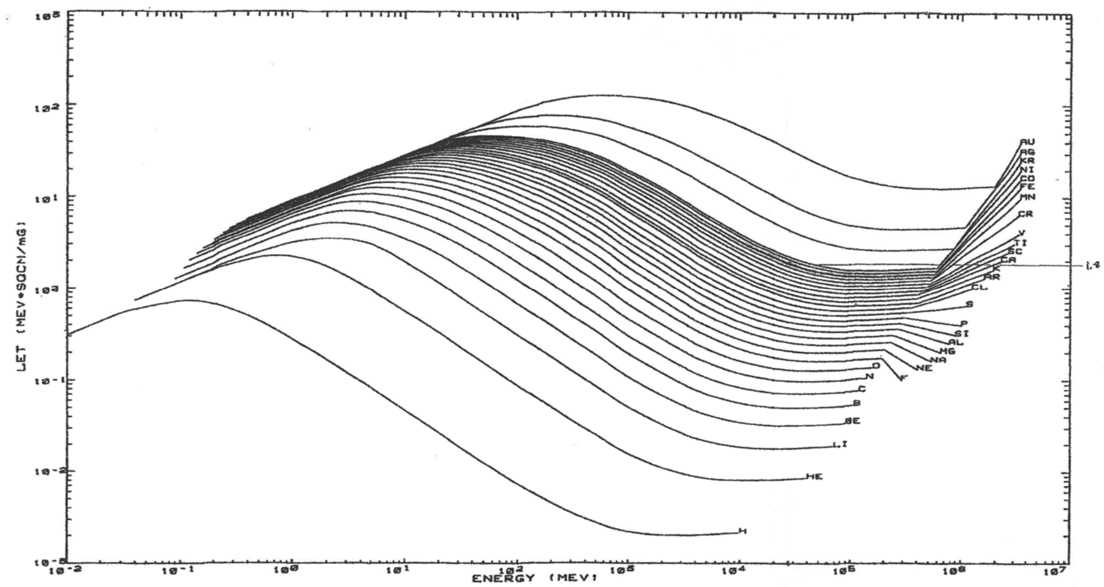

Figure 13: Cosmic Ray Heavy Ion LET in Tissue.

Conversion Rate of Deposited Energy for Si:
3.6 eV/e-h

Maximum Delta Ray Energy
From Cu Ions: in Si

E_{Cu} = 25 MeV $E\Delta$ = 1 keV
E_{Cu} = 395 MeV $E\Delta$ = 14 keV

Stopping Power of Cu in Si

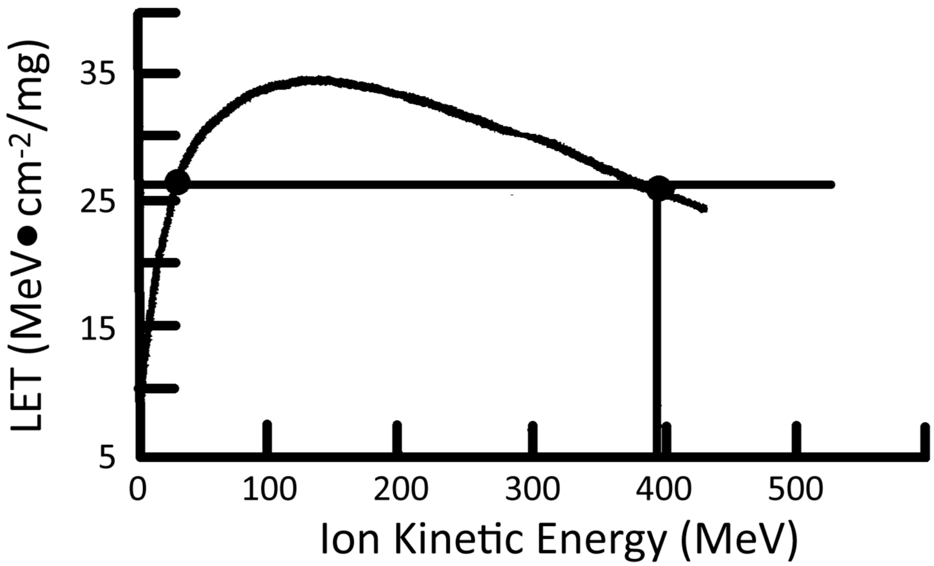

Figure 14: Inequality of LET Effects.

But this effect **does not impact significantly** the total dose experienced by the target.

However, it is important to realize that in contrast to the radiation effects, **<u>the greatest possible harm</u> inflicted on biological systems in space, derives <u>not from radiation</u> but from extended periods of time spent in zero or low gravity regions [15],** as listed in Table 5, that were identified by systematic observations, tests, and research linked to space effects over decades of manned missions by **NASA, ESA,** and **Roscosmos**. No brain damages has been observed in astronauts, such as those reported for the rodents in references [1,2,3, 4, 5]*

*<u>Footnote</u>: (a) "*Russian cosmonaut Mikhail Koronenko and astronaut Scott Kelly, on landing in Kazakhstan, could barely breathe: after a year of weightlessness, their lungs and chests were weak and once they landed, they could barely walk. The ground crew carried them from the capsule, for fear they might stumble and brake a bone* [15]". These serious effects were suffered despite the ISS having been supplied with exercising equipment designed specifically for use in a zero gravity environment for two-and-a half hours daily. The

corresponding health status of crews to Mars, after a 2.5 year journey, would be much worse, **but not from radiation**.

(b) "*In an experiment that charted the changes in the quadrupeds of rats flown in space, more than a third (1/3) of their total muscle bulk* <u>*was lost within 9 day*s</u> [16]".

Table 5: Space Induced Human Health Problems

The listed problems are primarily the consequence of zero- or low-gravity effects:

- Vision impairment
- Bone loss
- Mass-losing muscle atrophy
- Shrinking spines
- Cardiovascular alterations
- Immunological functions impairment
- Teeth susceptibility to cavities
- Behavior health effects
- Digestive and pulmonary systems impairment
- Decrease of red blood cells (space anemia)
- Mental health

Further experiences have been:

- Headaches
- Loss of sleep
- Loss of balance
- Nausea
- Rashes
- Post flight kidney stones
- Stress induced herpes

Unknown possible health effects from:

- Zero magnetic field

Hazards on Mars from:

a. Toxic soil
b. Toxic un-breathable atmosphere
c. Toxic global dust storms
d. Radiation exposure to ultraviolet radiation

Regarding astronauts well-being, numerous studies and experiments have systematically evaluated and quantified the effects of long- duration exposure to space conditions on the health of crew members. Particularly important in this research effort have been the exceptionally long missions of many cosmonauts, Table 6.

Table 6: Duration of Cosmonaut Missions.

Continuous single-mission stay		**Total Days**
Valery Polyakov 1994-1-03 to 1995-3-22		437.7
Sergey Avdeyev		397.6
Vladimir Titov & Musa Manarov		396.0

Multi-mission stay		
Gennady Padalka	5 missions	879
Yuri Malenchenko	6 missions	828
Sergei Krikolov	6 missions	803
Alexandr Kaleri	5 missions	769
Sergey Avdeyev	3 missions	748
Victor Afanasyev	4 missions	556
29 Others	Multiple missions	From 652 to 365

The absence of specific information in the relevant literature about radiation effects, may be because there were no such effects noticeable in crew members. **Therefore, the effort to apply the results of the rodent experiment to human brains, is particularly troubling, without a valid basis for this correlation.** The interpretation of these rodent effects, and the conclusions presented, must first be independently verified by a different experiment, i.e. one that also considers the critical points and special conditions reviewed above, which are more relevant to the experience and exposure of humans in space.

In conclusion, tests at irradiation facilities on the ground will not produce results that are automatically transferable to humans in space. In addition, the presence of **gravity and magnetic field** on Earth could confound ground research data, and undermine their validity to evaluate the effects on astronauts.

The knowledge gained from studying conditions of space travel on biological samples in Earth labs, may provide scaffolding for future tests with humans. However, applying conclusions from current animal experiments to human estimates of health is premature and unreliable, and the serious limitations of the research should be identified. The rodent irradiation is an interesting and valuable animal experiment, but cannot meaningfully relate to astronaut health or performance, especially when it does not include the healing/annealing process that can significantly reverse the effects of radiation-induced damage in biological systems.

Therefore, the results from these experiments cannot automatically be applied to astronauts. The opportunity exists to use current space flights, including long-term residence on the **ISS**, to perform in vivo studies on humans that more closely duplicate some of the conditions of extended space travel, instead of attempting to correlate outcomes from a different species under different conditions in the laboratory on Earth with interplanetary mission effects.

Appendix

A special note on ground-test results vs. space reality.

In the early years of space missions, a disparity was identified regarding radiation effects on sensitive electronic parts and devices, particularly when device performance was compared to testing and characterization data from tests with high exposure rates at irradiation facilities on the ground. When the lab results were compared to the radiation effects observed in space, a significant rate effect was discovered. In order to simulate multi-year exposures in just a few minutes in the lab, accelerated testing had been performed to provide operational data. However, it was observed in space that irradiated parts were performing and functioning surprisingly well, and lasted about 20% to occasionally 100% longer, than the ground test results had predicted. This phenomenon has also been observed in biological targets. In electronics, it is called 'annealing', for biological targets it is referred to as 'healing'. In electronic parts, the difference in performance, that is, the 'annealing' benefit, was facilitated by a slow recovery process, which repaired some of the damage inflicted by radiation. In humans, the similar process of 'healing' can repair some of the damage induced by the low rate of heavy ion cosmic ray space radiation encountered during long duration missions.

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