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Dose-Effects Models for Space Radiobiology: an overview on Dose-Effect Relationship.

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Abstract

Space radiobiology is an interdisciplinary science that examines the biological effects of ionizing radiation on humans involved in aerospace missions. The dose-effect models (DEM) are one of the relevant topics in space radiobiology. Their knowledge is crucial for optimizing radioprotection strategies, the risk assessment of the health hazard related to human space exploration, and reducing damages induced to astronauts from galactic cosmic radiation. This area of research necessary in the past arose as crucial with the restart of the Beyond Low Earth Orbit human space exploration missions planned by all the national space agencies in the following decades (e.g. ARTEMIS lunar exploration program). DEM will allow predicting the possible damage to human health in space exploration. Since 2017 the authors, mostly taking part in the Alpha Magnetic Spectrometer Roma-Sapienza group, have been investigating the possible synergies coming from the Astroparticle scientific community and medical physics, considering the DEM one of the most promising topics of research. One crucial step done in 2020 was, an assessment of the state of the art on the Dose-Effect relationship (DER). DERs describe the observed damages to normal tissues or cancer induction during and after space flights. Based on a Pubmed search including the last 10 years of peer-review published papers reporting the collected dose-effect relationships after space missions or in-ground simulations, we identified seven significant DERs (e.g., eye flashes, cataracts, central nervous systems, cardiovascular disease, cancer, chromosomal aberrations, and biomarkers). This paper presents the results of the assessments and recent updates on the state of the art of knowledge in the fields and some possible hints and examples of potential synergies between different research areas to improve it, with particular emphasis on the possible synergies coming from the vast amounts of data and information on cosmic rays collected by the cosmic ray detectors operating in space.

Keywords: Human Space exploration, Space Radiation, Space Radiobiology, Radiation Dose-Effects Model, Cancer Risk, Astroparticle Experiments

Acronyms/Abbreviations

Low Earth Orbit (LEO)
particles emitted by the Sun (SPE)
galactic cosmic rays (GCRs)
cardiovascular disease (CVD),
central nervous system (CNS),
overall reliability(OR),
research priority(RP)
dose-effect model (DEM)
dose effect relationship (DER)

1. Introduction

Space radiobiology (SPRB) is a fascinating field that has fostered a growing interest in the recent years, thanks to the increased technological capability to travel and operate in space and the consequent renewed interest from the national space agencies to plan exploratory and colonization space missions.

Manned space missions in this and the next decade will see the presence of humans on the Moon and Mars surfaces. One of the space Agencies' aims is preparing

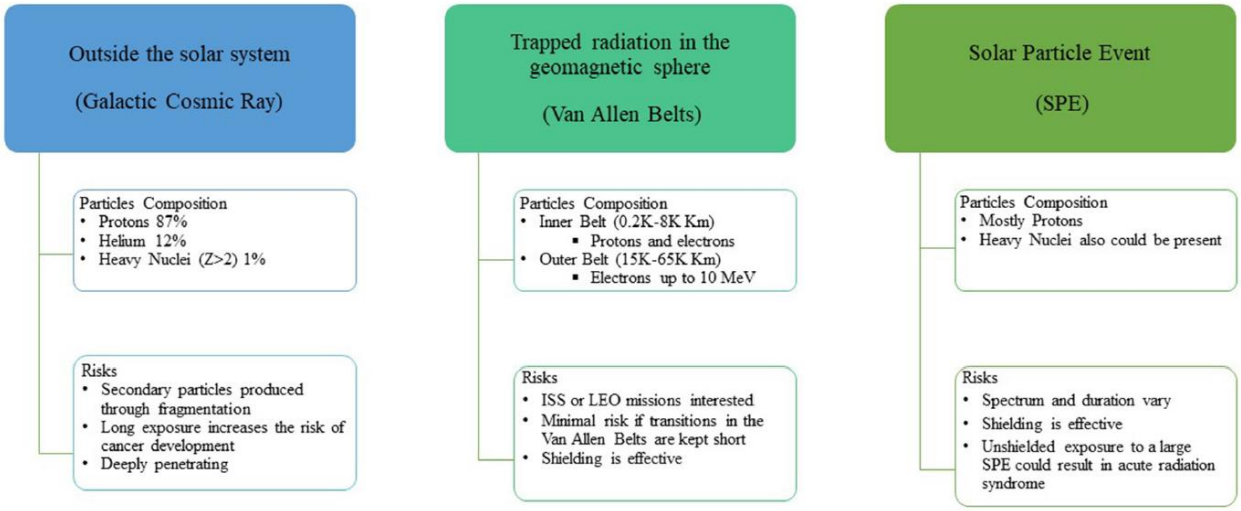

Fig. 1. Scheme of the origin of space radiation particles and consequent risk. ISS, International Space Station; LEO, Low Earth Orbit[3]

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the safe human exploration and colonization of space outside the Low Earth Orbit (LEO).

The space radiation environment is a complex mixture of radiation species dominated by highly penetrating charged particles from three different sources (see Figure 1) : particles emitted by the Sun (SPE) due to the solar activities, particles trapped in the magnetic field of the Earth (i.e., Radiation Belt), and galactic cosmic rays (GCRs) coming from outside the solar system. GCRs, while approaching our planet, interact with Earth's magnetosphere, which stops/deflects most particles (99%) while the rest lose most of their energy going through the atmosphere before reaching the Earth's surface [1]. In particular, the geo magnetosphere shielding is equivalent to one of 1-meter thick metal. Completely different is the situation in space where the GCRs might interact with the human body, and the absorbed doses to tissues can be dangerous for human health.

In this context, all the different components of space radiation have been extensively studied and measured during the last decades by several astroparticle experiments operating in space, and the information contained in the data taken by such experiments can be used to improve the radiation health risk assessment for humans in space missions. Thus, the biological effects of ionizing radiation represent one of the issues potentially affecting the health of astronauts/space workers. In this context, the information derived from astroparticle experiments presently operating in space is crucial to accurately predict the expected dose thresholds and optimize the shielding dimension and technology to be implemented.

This paper highlights the state of the art of space radiobiology models, while [2] illustrates the past and present astroparticle experiments.

2. Material and methods

2.1 Resource Identification Search Strategy

The PubMed search used the following query strings of [3] to identify the proposed models for acute and late effects related to space mission/exposure and compare these effects with the threshold reported in the diagnostic or therapeutic applications using ionizing radiation.

Query search included the following keywords/string: space[title/abstract] model[title/abstract] radiobiol* [title/abstract]. For each detrimental health and tissue effect, an additional search have to be implemented e.g., (model[title/abstract] OR relationship[title/abstract]) AND (radiotherapy[title/abstract] OR space[title/abstract]) AND (radiobiol* [title/abstract] OR dose [title/abstract]).

The research had been restricted to the last 10 years to include only the most recently published studies. The last search was completed on April 30th, 2022.

Full articles in English were retrieved when the abstract was considered relevant. Papers published before 2011 were considered eligible when reporting models and dose-effect correlations considered as the reference in the recent studies.

3. Results

Analyzed effects included, among others, eye flashes, cataracts, CNS effects, cardiovascular disease (CVD), biomarkers including chromosomal aberrations, cancer

Table 1. dose-effect models and type of endpoint studied for space exploration and colonization

Model	Study Type	Dose range/threshold or LET	References	Overall Reliability	Research Priority
Eye flashes	Spaceflight	LET> 5–10 keV/µm	[4-7]	****	*
Cataract	Spaceflight	8 mSv	[8-12]	***	***
CNS	Ground/Simulation	100-200 mGy	[13-24]	**	*****
CVD	Spaceflight	1000 mGy	[25-28]	*	***
	Ground/Simulation		[29-36]		
Cancer	Spaceflight	<100 mGy	[37,38]	***	*****
	Ground/Simulation	<100 mGy	[39-47]		
Biomarkers or Chromosomal Aberrations	Spaceflight	5-150 mGy	[48-58]	***	*****
	Ground/Simulation	<10000 mGy	[59-62]		
Other Risks	Ground/Simulation	~2000 mGy	[63-64]	*	***

induction (including mortality), and other possible risks never evidenced in astronauts but investigated as possible long-term irradiation for future missions to Mars and Moon (Table 1).

Several effects occur during the space exposition (Eye flashes or biomarkers changes) and are transient; others occur after several weeks or months, depending on the absorbed dose and dose rates (e.g., central nervous system (CNS) or cardiovascular disease (CVD) effects), while others require several years and could happen from 10 to 30 years (e.g., cancer).

More details on the biological consequences of space radiation exposure on human cells are reported in ref. [3]

3.1 Tables

Table 1 summarizes the analysed effects, including, among others: eye flashes, cataracts, CNS effects, CVD effects, biomarkers including chromosomal aberrations, cancer induction and cancer-related mortality, and other possible risks never evidenced in astronauts but

investigated as possible long-term effects of irradiation expected for future missions to Mars and Moon. In the last columns of Table 1, the overall reliability (OR) and research priority (RP) rates are reported using a 5-point scoring system from very low (*) to very high (*****) values, according to the definition reported in [3].

The reliability of models has been reported considering the number of revealed effects, statistical approaches, and information on dose and GCR spectrum and its modification through shielding materials. We also include an attempt to score the priority for future research considering the possible impact on a long-term mission in deep space, the availability of advanced facilities, and the possible synergies with related medical fields using ionizing radiation.

3.2 Eye flashes

The first description of the biological consequences of the space radiation exposure on human cells was the subjective sensations of lights on eyes, commonly called eye flashes, first observed by Apollo crews[4].

Primary or secondary neutrons and possibly heavy ions, rather than mesons, were suspected of causing eye flashes. Observations on helmets of Apollo astronauts revealing numerous tracks of metallic ions as heavy as zinc and nickel, which are very rare in space, suggesting that the technical environment of spacecraft itself adds extra complexity to the actual spectrum of secondary particles. Secondary particles, generated by the interaction of very high-energy particles with metallic stuff of spacecraft, having a LET greater than 5–10 keV/µm was suspected of causing eye flashes [5-6].

Preliminary studies indicate that light ions are the most probable particles for generating eye flashes [7]. The measured rate of ions in the eye produced an average rate of 5 × 10–2 eye flashes per minute (20 in about 420 min of observation).

3.3 Cataract

Cataract risk from space radiation seems linear with no apparent threshold and caused by genetic damage leading to aberrant cellular differentiation of lens epithelial cells [8-9]. However, questions on the definition of clinical significance and the progression of cataracts with time must still be addressed for the risk assessment [10-12]. Preliminary analyses of 5 years of data with an average of 3.8 exams per subject found no relationship between radiation exposure and progression rates for posterior subcapsular cataracts and nuclear cataracts, e.g., the estimated median progression rate from space radiation being 0.25 ± 0.13% lens area/Sv/year (P = 0.062).

3.2 CNS

CNS effects during a mission include; cognitive function (e.g., detriments in short-term memory, reduced motor function, and behavioural changes), while late CNS risks comprise neurological disorders, such as premature ageing and Alzheimer's disease or other dementia.

CNS risks are of concern for long-term exploration missions to Mars or other destinations, while the possible observation of CNS effects in astronauts participating in past NASA missions is highly unlikely because in LEO astronauts are partially protected by the Earth's magnetic field, the lengths of past missions are relatively short, and the population size of astronauts is too small to reveal a statistically significant association [13-24].

3.2 CVD

There is no consensus on the relationship between CVD risk and low-dose cardiac exposures after a space mission, likely due to the statistical limitations of cohorts of astronauts[xx] pre-selected among health subjects with appropriate life habits. However, associations between CVD and whole-body doses of <1Gy among atomic bomb survivors and the experience from radiotherapy are of potential clinical importance and provide a foundation for assessing astronaut health [25-36].

3.3 Cancer

Based on spaceflight-based studies, a 3% risk of exposure-induced death is generally used as a basis for setting age- and gender-specific dose limits for astronauts based on the NCRP report n.132 [37]. After adjusting US cancer rates to remove smoking effects, radiation risks for lung and other cancers, the radiation mortality risks for NS were reduced compared to the average US population by more than 20% and 50% in the mixture model and multiplicative transfer models, respectively.[38]

Based on ground/simulation-based studies, cancer is a stochastic risk and for this reason may occur even at very low doses (defined as doses < 100 mGy) which is currently estimated using the Linear-No Threshold model (LNT) according to UNSCEAR [39], ICRP recommendations [40], and NCRP commentary [41]. However, the debate on the accuracy of the LNT model is still open [42-47].

3.4 Blood based biomarkers

Spaceflight-based studies suggested that high-LET radiation is more efficient in producing complex-type chromosome exchanges than sparsely ionizing radiation, and this can potentially be used as a biomarker of radiation quality [48].

Astronauts' blood lymphocytes were analyzed before and after 3-4 months long duration missions to investigate the complex chromosome exchanges, revealing that chromosomal aberrations of long-duration in blood samples of astronauts increase with absorbed doses [49].

Ground/simulation-based studies investigated some of the proposed biomarkers to predict the risk of carcinogenesis, including complex clustered DNA damage, persistent DNA repair foci, reactive oxygen species, chromosome aberrations and inflammation. Other biomarkers discussed, often assayed for at longer points post-exposure, include mutations, chromosome aberrations, reactive oxygen species and telomere length changes. [50-62]

3.5 Other risks

Potential induction of mucositis in astronauts after long-term exposure to high LET/high Energy particles (such as Carbon ions) during extended space flights has been described as related effects, along with effects on skin, being epithelial tissue an ideal model to study radiation-induced effects [63-64].

Total Space Radiation Dose (mGy)	<0.2	0.2–1.99	2–3.99	4–10.99	≥11	Total
# Astronauts	14	19	11	15	14	73
# Cancer Deaths	2	2	1	0	2	7
# Cardiovascular Disease Deaths	1	4	1	1	0	7
# Accident Deaths	6	5	0	0	1	12
# Other Deaths	1	0	1	0	1	3
# Unknown Deaths	1	0	0	3	1	5
Mean Medical Dose (SD)	2.4 (6.4)	27.7 (13.6)	34.4 (20.8)	29.1 (15.6)	32.5 (21.7)	25.1 (19.4)
Mean Year at Birth (SD)	1932.6 (4.1)	1931.7 (5.2)	1931.6 (2.5)	1932.2 (4.4)	1931.5 (3.3)	1931.9 (4.1)
Mean Age at Entry into Astronaut Corps (SD)	31.6 (2.7)	32.2 (3.4)	33.0 (2.5)	31.8 (2.8)	32.5 (2.2)	32.2 (2.8)
Mean Follow up Time (SD)	29.3 (23.6)	40.3 (15.0)	46.4 (12.9)	50.7 (7.8)	48.1 (7.5)	42.8 (16.1)
Total Group Person Years	409.9	766.5	510.1	760.8	673.4	3120.8
Mean Age at Death (SD)	57.7 (23.8)	65.7 (15.9)	64.5 (14.9)	78.2 (19.9)	74.9 (10.2)	65.2 (19.1)
Mean Current Age of Living Astronauts (SD)	79.9 (2.9)	82.1 (3.9)	84.9 (3.1)	83.6 (3.6)	83.8 (2.3)	83.4 (3.4)

Fig. 2. Early astronauts cohort demographics binned by total space radiation dose category as reported in by Elgart et al in [64]

4. Discussion

Some points of discussion arised from the above literature analysys are presented here

4.1 Space Radiation DEM for a New Space Exploration Era

For many years, astronauts have been exposed to space radiation comprised of high-energy protons, heavy ions, and secondary particles produced in collisions with spacecraft and tissue. However, going deep in numbers, only a few astronauts participating in the Apollo missions in the late 60s and early 70s were exposed to the BLEO space radiation[65]. Further such space missions last for a short time, days to a few weeks, with significant uncertainties in projecting risks of late effects from space radiation, for the space explorations coming in the following years (e.g. cancer and cataracts) due to the paucity/corrected epidemiological data and levels of absorbed doses. Several open issues have to be addressed in the following years.

4.2 Space Radiation DEM for shielding design

New space missions will require new starships, short-term exploration, and long-term colonization will require the design of safe bases and specific villages or homes.

Interactions of the galactic cosmic rays in these expositions scenarios require a demanding shielding solution that considers the effects on the health of astronauts and inhabitants of the nuclear interactions of the GCRs with the shielding that depends on the composition and thickness of the hull material. These interactions will result in fragmentation products and particles of reduced energy but higher LET that contribute to the radiation dose within the spacecraft. Also, DEMs should add such secondary radiation components to reduce the uncertainty in health risk assessments. Integrating the DEMs in a unique software shielding design tool is another objective to reach.

4.3 Space Radiation Solar Modulation

One aspect that characterizes the IR in space is that any radiation fluxes of any type are not fixed in time. Near the Earth and in the heliosphere, radiation is modulated by the activities of SUN and Earth magnetic fields. Radiation modulation effects are present in DEMs, accounting for them through a best/worst case approach usually referred to as solar minimum or maximum conditions since most of the analyses refer to situations where only the Sun is relevant. This approach is safe and reliable when the exposition scenario is limited to the LEO and will require significant improvement as the complexity and duration of the space mission will increase. Most information on IR modulation, even at the daily level, is available (e.g. the daily proton fluxes at different energies as measured by the AMS02 detector are shown in figure 3.) and will become crucial the produce more precise DEMs.

4.5 IR interaction with other potentially toxic agents in space

Another critical aspect of DEM development is that up to now, most of the literature and all the experience from the clinical field move their ansatz in modelling, considering only the IR environment. No inclusion in modelling is done for other toxic causes present in the

space environments. Naturally, all the experiences coming from the hypothesis in modelling experience and data from the clinical field are the same. Peculiar is the case, for example, of IR and radiation and microgravity or altered gravity [66].

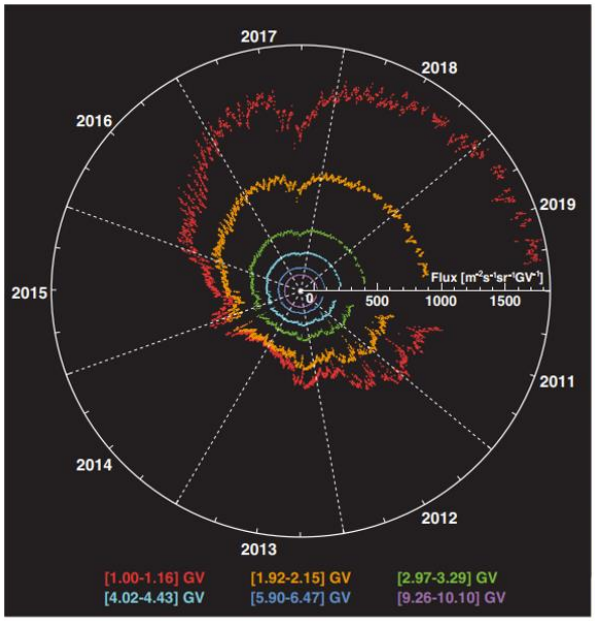

Fig. 3. The daily AMS02 detector, onboard the ISS, proton fluxes for six typical rigidity from 1.00 to 10.10 GV measured from May 20, 2011, to October 29, 2019, which includes a significant portion of solar cycle 24

Both are recognized as primary and inevitable risk factors for humans travelling in the possible and part evidenced space context. However, the reports regarding their synergistic effects remain inconclusive [52-54], and such interactions between different toxic agents must be considered in futures DEM development.

4.6 Space radiations complexity in the labs

A focal point for improvement in DEM is the possibility of recreating the complexity of the space radiation environments in the laboratory. Some endpoints (e.g. CNS) that cannot benefit from using IR in the clinical fields have a poor possibility of having data from previous space missions in BLEO. The main direction consists in creating particles and ions testing facilities where researchers can recreate that mix of particles and fluences characteristics of the BLEO, Lunar or MARS environments. Many countries are modifying or updating particle/ions accelerators facilities, previously used only for research in particle or medical physics in such a way.
Also, NASA created a similar ground-based testing laboratory Galactic Cosmic Ray Simulator [76]. This facility enables a new era in space radiobiology research due to its capability to generate a spectrum of ion beams that approximates the primary and secondary GCR field experienced at human organs locations within a deep-space vehicle.

4.7 Sinergies and collaboration for DEM improving

Taking about the number one health risk for humans, cancer, the first and most important field of synergy, comes from the experience made in cancer research during the last decade. Many are hints that could be peculiar for space IR effects. For example, there are hints that low dose radiation could lead to various alterations in immune system parameters, including natural killer cell activation modulation of blood cytokine levels, which plays a crucial role in cancer development [95-98]as well as in cancer control [77]. Also data from radiotherapy might help to improve the risk models for space radiation [79] as for radiological or nuclear attacks due to precise knowledge of absorbed dose and objective determination of effects [79]

Fig.3. Galactic Cosmic Ray Simulator at Brookhaven National Lab (US). A GCR simulator uses new technology that allows to test multiple ion beams at one time to accurately represent the radiation conditions that an astronaut is exposed to in a spacecraft. Studies on the effects of radiation on CNS and other endpoints has been done only on ground at the accelerator facilities or through simulations. (Photo Courtesy of NASA).

Another is the experience of evidence of supra-linear effects at low doses for the non-target bystander effects that could be relevant to the fluences expected in space[80]. These issues are examples of issues to be further explored for long-term missions. In that context and since 2017, the authors, mostly taking part in the Alpha Magnetic Spectrometer Roma-Sapienza group, have been investigating the possible synergies coming from the Astroparticle scientific community and medical physics, considering the DEM one of the most promising topics of research.

6. Conclusions

Cancer and toxicity risks remain not accurately quantified despite the technological developments and conceptual advances of space radiation biology and considerable efforts. Early estimates of the uncertainty on cancer mortality risk due to space radiation examined in the discussion (4.2, 4.3, 4.4) ranged from 400% to 1500%, with more precise estimates showing uncertainties at the 95% confidence level of 4-fold times the point projection [81]. Relevant improvements have been observed in estimating absorbed dose-effect models, and novel facilities are available for the ground-based Galactic Cosmic Ray Simulator. Technological advancements might realize the dream of human space exploration, and crewed spaceflights are on the agenda of space agencies. Radiological devices or linear accelerators might help conduct in vitro or in vivo ad hoc experiments or analyze the available information from (cancer) patients' cohorts, thus reinforcing our knowledge of cancer and non-cancer space-radiation-induced effects. Unfortunately, the number of events helpful in modelling the radiobiological effects is still limited.

Consequently, functional dose-effect relationships, models, and their uncertainties need further improvement. In the discussion paragraph, we suggest implementing future research in different ways to increase the understanding of this topic, but one principle should drive the research activities: unification. DEM development is an interdisciplinary scientific activity requiring competencies and knowledge from different fields and focusing on creating synergies between scientific experts. Implementing scientific and technological tools according to this unification principle is mandatory in achieving the DEMs improvements goal.

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