Dose-Effects Models for space radiobiology: an overview

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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. One of the relevant topics of space radiobiology is represented by the dose effect models. Their knowledge is crucial to optimize radioprotection strategies (e.g. spaceship and lunar gateway shielding, lunar/Mars village design,…), the risk assessment of the health hazard related to human space exploration and to reduce the damages potentially induced to astronauts from galactic cosmic radiation.

Dose-effects models are used to describe the observed damages to normal tissues or the induction of secondary tumors during and after space flights and are developed for the various dose ranges and radiation qualities characterizing the actual and the forecast space missions (International Space Station, solar system exploration,…).

The manuscript aims at providing an overview of the published dose-effect relationships in order to identify future research able at improving the model prediction capability and reduce their uncertainty levels. These strategies require an accurate characterization of the space radiation quality, the conduction on Earth of radiobiological studies in vitro and in vivo and the reinforce of the actual knowledge using dose-effect relationship developed at doses typical of diagnostic or radiotherapy exposure.

Novel research in the field are of paramount importance in order to reduce damages to astronauts from cosmic radiation before Beyond Low Earth Orbit (BLEO) exploration in the next future.

INTRODUCTION

Space radiobiology is an intriguing field that has fostered a growing interest in recent years thanks to the increased human capability to realize space activities/missions.

The space radiation environment is a complex mixture of radiation species dominated by highly penetrating charged particles from different sources (see Fig.1). On this regard, three different types of particles are present: particle emitted by the Sun (SPE) due to the solar activities, particles trapped in Earth's magnetic field (i.e. Radiation Belt) and Galactic Cosmic Rays (GCR) coming from outside the solar system.

The energy spectrum and abundances of radiation species is modulated by planetary magnetic fields and long-term solar activity, but also is characterized by short-term solar particle events[1].

In addition, the presence of shielding on the space stations or spacecraft modifies the incident spectrum and related exposure due to particles production by the interaction (spallation) with such structures.

Such particles can penetrate several tens of centimeters of materials such as aluminum or tissue/water producing lower Z secondary particles through nuclear interactions. The secondary particles are characterized by lower linear energy transfer (LET) which confers greater penetration range than the primary particles [2].

In ionizing radiation protection, several technical solutions are generally applied to reduce the worker exposure: increase the distance from the radiation source, reduce the exposure time and implement an ad hoc shielding[3].

Distance is not useful in space, being GCR substantially isotropically distributed. Time in space is accurately reduced as low as possible according to the plans of exploration and colonization or decreasing flight time. Therefore, shielding materials are not able to fully absorb all space radiation due to the presence of very high-energy component of the GCR spectrum. In addition shieldings need to be optimized considering both their efficacy and cost to reduce the unavoidable exposures to the minimum acceptable level. More in detail, passive or active shielding may significantly contribute to reduce radiation exposure also considering the time variable contribution of GCR[3]. Nevertheless, dose- and equivalent dose- rate to astronauts are around 0.3–0.6 mGy/day corresponding to 1–1.8 mSv/day, respectively[4].

In the space radiation environment, both acute and late effects are the most frequent and important life-threatening adverse events associated with ionizing radiation exposure. Acute radiation syndrome (i.e. short-term risk of radiation sickness) are

caused by intense SPEs in case of crews unable to reach areas with adequate shielding. Late radiation morbidity (e.g. carcinogenesis or central nervous system or cardiovascular induced damage) is associated with chronic exposure to GCR, which is substantially different both qualitatively and quantitatively from the Earth's radiation natural background depending on various above described factors (i.e. long- or short-term solar activity and magnetic field features).

Dose-effect relationships models have been proposed to explain, model and predict clinical and subclinical effects registered during spatial mission mainly on human subjects and confirmed in in vitro/in vivo studies. In addition, the possibility to use clinical diagnostic or radiotherapy devices is recognized as an important tool for improving the radiobiological model understanding for space exposure due to the similarity of dosage and available type of particles. Moreover, the full understanding of non-targeted effects induced by charged particles becomes mandatory[5] due to the interaction of secondary particles with several human tissues. In addition, several investigations are still ongoing to take into consideration the possibility to hibernate astronauts for guarantee as additional protection against space radiation effects[6].

Our study aims at reviewing the space travel acute and late adverse effects to be compared/discussed to ones currently observed after diagnostic or radiotherapy exposure to similar dosage/radiations.

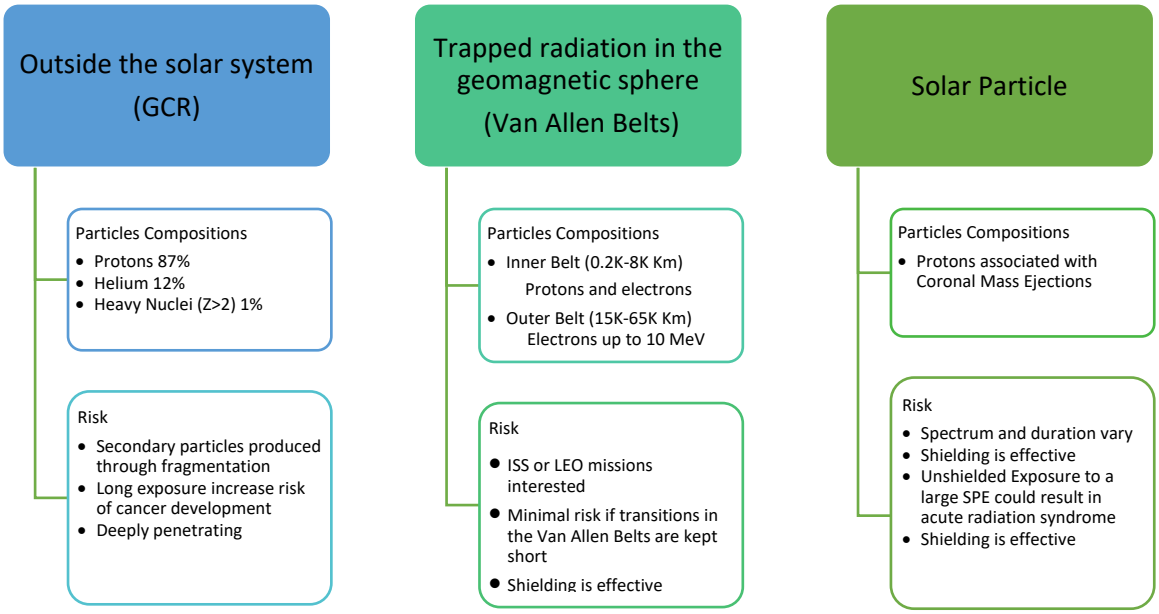

Figure 1: Scheme of the origin of space radiation particles and consequent risk.

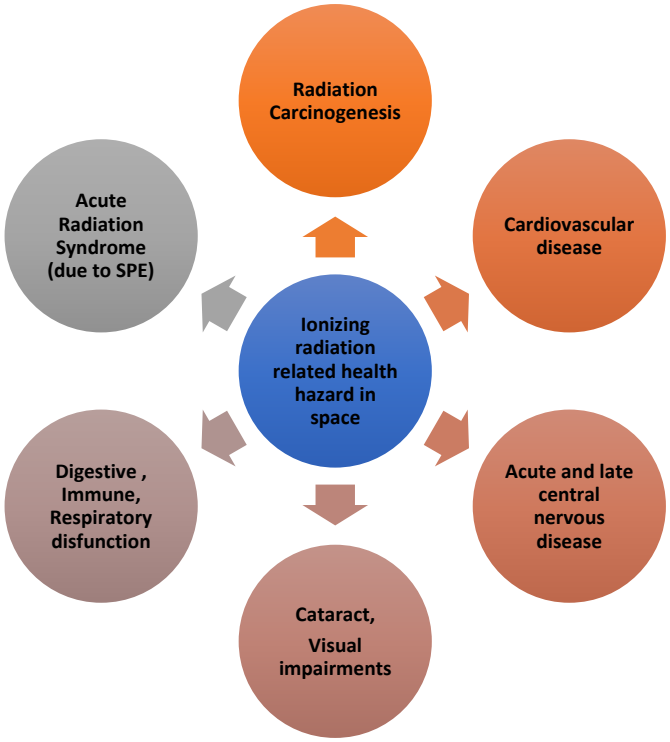

Figure 2: Possible Ionizing Radiation related health hazard in space.

MATERIALS AND METHODS

A PubMed search was performed using the query string reported below to identify the proposed models for acute and late effects related to space mission/exposure and compare these effects with the threshold reported in diagnostic or therapeutic applications using ionizing radiation.

Query **search** included the following keywords/string: **space[title/abstract] model[title/abstract] radiobiol* [title/abstract]**.

https://www.ncbi.nlm.nih.gov/pubmed/?term=space%5Btitle%2Fabstract%5D+model%5Btitle%2Fabstract%5D+radiobiol*+%5Btitle%2Fabstract%5D

The research was restricted to the last ten years in order to include only the most recently published studies. The search was done on 23th October 2019. Titles and abstracts were independently reviewed by the authors in order to decide study inclusion. Full articles were retrieved when the abstract was considered relevant and only papers published in English were considered. The bibliographies of retrieved and reviewed papers were also examined to identify other relevant articles to be included. Papers were considered eligible when reporting models and dose effect correlations.

RESULTS

Based on Pubmed/Medline search, 51 papers have been found. Twenty-nine were original papers retrieved reporting/proposing radiobiology or dose-effects models have been reported while 22 reviews (which were screened for including additional papers). The proposed models have been described (table 1) to provide an overview on available relationships and present their performance, characteristics, limitation and uncertainties discussed in the following paragraphs.

Study Reference	Model	Dose range/threshold or LET	Experimental Validation
7-10	Eye flashes	LET> 5 – 10 keV/µm	Yes
11-17	Chromosomal aberrations	5 - 150 mGy	Yes
18-24	Cataract Risk	8 mSv	Yes
26-27	CNS Risk	100-200 mGy	No
28-29	Oral mucositis	2000 mGy	No
30-32	Cardiovascular disease (CVD)	*1000 mGy*	in Japan atomic bomb survivors
28, 32-34, 36,38	Cancer	*<100 mGy*	Yes

Table 1: investigated model for predicting dose effect relationship in humans involved in space missions.

More in details, 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[7]. Secondary particles, generated by interaction of very high-energy particles with metallic stuff of spacecrafts, having a LET greater than 5–10 keV/µm was suspected to cause eye flashes [8,9]. Preliminary studies seem to indicate that light ions are the most probable particles for generating eye flashes[10]. 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).

Chromosomal aberrations in blood samples of astronauts has been reported to increase with absorbed dose[11].

After doses received in space ranged from about 5 to 150 mGy the mutant frequencies of blood of cosmonauts were 2–5 higher than unexposed controls. The frequency of dicentric aberrations in lymphocytes (5.78×10^{-3}) was also related to Mir-18 expression in crew member ($6.4 \pm 2.0 \times 10^{-3}$) demonstrating good agreement [12,13]. Moreover, the yield of chromosome aberrations decreases some years after a first flight but without reaching the unirradiated values while a second flight does not increase in proportion the yield of aberrations. This behavior suggests a non-additive or even and infra-additive effect, supporting the fact that a radio-adaptive response could occur [7,14]. The bio-dosimetry based on the dicentric chromosome aberration analysis has been

developed and validated[15,16,17] and represents a fast and reliable tool for dosimetry assessment of populations exposed at radiological incidents for triage purposes.

Cataract risks from space radiation seems to be linear with no apparent threshold and is caused by genetic damage leading to aberrant cellular differentiation of lens epithelial cells[18,19]. However, questions on the definition of clinical significance and the progression of cataracts with time must still be addressed for the cataracts risk assessment. A dose effect threshold of about 8 mSv [20,21] has been reported lower than the previous reported threshold of 2 Gy [22,23,24]. A decreased dose effect threshold has been also reported for occupational exposure[25]. Indeed, the current framework of radiological protection of occupational exposed medical workers reduced the eye-lens equivalent dose from 150 to 15-20 mSv per year [25].

Central nervous system (CNS) risks depends on multiple mechanisms leading to synapse changes[26]. The average lifetime of synapses varies in different brain regions and depends on exposure time. In addition, the microgravity effects have also to be considered. In this regard, a simplified 3D neuron models with properties equivalent to realistic neuron morphology has been developed using GEANT4 with the purposes of describe the effect observed in rats after dose 0.1 to 2 Gy delivered to the hippocampus[27].

A 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 effect[28]. The effect in terms of cell density/compactness, double strand breaks and induction of NFkB or interleukins have been investigated using doses ranging from 2 to 10 Gy [29].

Cardiovascular disease (CVD) from low dose radiation exposure represents an important issue for Space radiobiology [30] but also for RT being experienced by an ever-growing number of cancer survivors[31]. Low-dose cardiac exposures have not been convincingly linked to CVD, but associations between CVD and whole-body doses of <1 Gy among atomic bomb survivors are of potential clinical importance. Unfortunately, the development a comprehensive risk prediction model is has not yet been achieved, although strongly recommended [30].

Cancer is a stochastic risk and for this reason may incur even at very low doses. Cancer risks following exposures to low doses of radiation (defined as doses < 100 mGy) are currently estimated using the Linear-No Threshold model. However, the use of this model has been widely criticized and its use remains controversial [32,33,34]. Furthermore, multicellular models of tumors due to carbon ions compared to X-rays has been also investigated [28]. In addition, the uncertainties of cancer risk predictions to exposure to GCRs have been recently described within the linear-additivity model using the approach of Monte Carlo sampling from subjective error distributions[20]. One of the sources of uncertainties is related to the behavior of Quality Factors (QF) for the particles constituting the GCR at low doses. This issue represents the major gap of knowledge to quantify the overall uncertainty in risk projections. The QFs as a function of particle type or charge number and energy have been deeply investigated using the models of track-structure[35]. Moreover, the QF extrapolation to low dose has been verified using the large radiation-induced cancer rates from the UNSCEAR (2008). In addition, the overall probability distribution functions of the NASA QF function for solid cancers and leukemia versus kinetic energy for iron particles have been recently reviewed [36].

Discussion

Research Areas for improvements for health hazard related to space exploration.

Due to this new interest in the human space exploration the European Space Agency (ESA) is currently expanding its effort in identify all the necessary research activities to create a European Space Radiation Risk Model(ESRMM)[37], and to reach in the future a harmonized set of criteria of maximum allowable exposure between all the space agencies (NASA, Jaxa, ...). The needed research areas to increase the knowledge in the field was recently identified from a team of ESA experts (Topical Team) (Fig. 3)

Figure 3: Space Radiation research areas to be investigated in order to reach a European Space Radiation Risk Model as stated from the ESA topical team in 2019[37].

Among this area, the development of new dose-response model as part of the "missing biology for risk assessment" has a crucial role. In this context, the ESA Topical Team recommends exploring the shape of dose-response relationship for radiation induced health effects and understand the potential impact of individual susceptibility. In this regard, the Topical Team also identified the outcomes to be considered including not only the cancer risk induction but also acute and late effects on normal tissues, as well as cardiovascular and neurological disease and lens opacification (Fig.3).

Substantial efforts have been made to delineate biological mechanisms and health related outcomes of low-dose radiation. These include a large, department of energy (DOE) funded, Low Dose program operated in the 2000s, as well as the EU funded programs, previously NOTE and DOREMI and currently MELODI. Nevertheless, QFs still demand further investigation to improve the design of radiobiological dose effect model.

To explore this topic an overview of available dose effect models for SPRB has been conducted to identify potential improvements in this expertise field.

Chromosomal aberration has been largely investigated in both SPRB and radiotherapy studies. In particular, ionizing radiation produces a significant effect in increasing of chromosomal aberrations and chromosome break, productions of dicentric and ring. For this reason chromosome gaps are very sensitive and useful biomarkers to predict radiation induced acute and late effects[38],[39],[40].

Cataract risks for astronauts has been reported at doses (8 mSv) lower than ones proposed in the European Directive 53/2013 (15-20 mSv) for workers.

Dose range for the induction of oral mucositis (2-10 Gy) for astronauts are largely lower to the one reported for grade 2 or more toxicity using carbon ion therapy (i.e. 43-54Gy RBE-corrected [41]) or cumulative doses of 32-42 Gy[42],[43] using photon therapy.

Cardiovascular disease is of paramount interest in radiotherapy due to higher conformal capability of modern devices able to spare cardiac tissues. It depends not only from dosage to heart but also to lungs [44] and from hypertensive heart disease[45].

In external beam radiotherapy, radiation induced effects to CNS might be mitigated reducing the mean and maximal doses to hippocampal under 10 and 17 Gy, respectively [46] , while for the astronauts the doses should be reduced under 0.1-0.2 Gy. The impact of reducing these doses in external beam radiotherapy has been recently investigated in terms of risk for peri-hippocampal recurrence in patients with brain metastases.

CNS and cardiovascular diseases may affect astronauts' health although the uncertainty on these radiation-induced effects is even higher than for cancer[37].

Obviously, being astronauts healthy workers pre-selected for many factors including cardiovascular performance and vision, lowers risks of cancer, circulatory, and pulmonary diseases, the dose effect models developed for the general population are expected to be too cautionary[3].

In addition, radiation risk during long-term space flights is associated to a very high level of uncertainties due to space radiation environment and magnetic field, but also due to the presence of shielding with different capability of reducing the incident radiation thus producing heterogeneous secondary radiation particles. Early estimates of the uncertainty on space radiation cancer mortality risk ranged from 400% to 1500%, with more precise estimates showing uncertainties at the 95% confidence level of 4-fold times the point projection[47].

To remark that one of the most important uncertainty sources is the limited number of subjects involved in the spatial missions as well as the number of astronauts/crews with acute or late effects. This leads to a limited statistical power (<6%) for cardiovascular and mortalities[29]. Due to the low power, further adjustments for other time-related parameters such as age at first exposure and latency time were not considered although these factors are expected to change the risk of damage manifestation.

The NASA uses a 3% risk of exposure-induced death as a basis for setting age- and gender-specific dose limits for astronauts. Because astronauts are considered as healthy workers and include never-smokers subjects, the expected cancer risks are 20% and 30% lower for males and females, respectively, for never-smokers compared to the average U.S. population[48].

On the other hand, different space missions and irradiation conditions allow investigating the dose effect relationship in a wide range of absorbed doses and microgravity conditions. Microgravity and ionizing radiations alter the gene sets when used alone while they did not alter the gene sets when used in combination indicating a complex interaction between these factors[49].

In addition, the uncertainties in estimating the risks for late effects (including cancer) from space radiation exposures arise from the variability and complexity of the radiation fields due to multiple interactions with the vehicular space craft or human tissues. Moreover, the limited radiobiology data using high energy and/or high LET particles increase the uncertainty of the radiation quality and the expected dose-rate effects[50,51].

In addition, estimation of the biological risks from space radiation remains a difficult

problem because of the many radiation types including protons, heavy ions, and secondary neutrons, and the absence of epidemiology data for these radiation types. In contrast to conventional dosimetric methods[52], the biophysical description of heavy particle tracks has been addressed in the context of the interpretation of both space radiation dosimetry and radiobiology data in order to provide insights into new approaches to these problems. Modern Instrumentation allows the estimation of absorbed dose with a greater accuracy thanks to the recent availability of alpha magnetic spectrometer (AMS02[53]) experiment installed on the ISS that is measuring data since 2011 and is approved to operative for all the life cycle of the ISS. data useful for validating and comparing ad hoc Monte Carlo calculation tools[54]. This aspect could be relevant also for the improvement of countermeasure including shielding evaluation and dosimetry of a specific astronaut irradiation condition.

Remarkable progress made in cancer research during the last decade indicated that low dose radiation (LDR) can 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 [55,56,57,58] as well as in cancer control[59].
Very promising preliminary results have shown that blood cytokine levels and in general the alteration of immune system parameters can be considered biomarkers of LDR exposure.
Further studies are mandatory to guide the development towards novel medical applications as well as to protect astronauts during space exploration.

In addition, in-flight experimentations on intestinal microbiota showed a significant change without alteration of mucosal integrity[60].

These first data reinforce the critical need for further studies exploring the impact of spaceflight on intestinal microbiota in order to optimize long-term space travel conditions.

Conclusion

Relevant improvements have been observed in the estimation of absorbed dose effect models. Technological advancements will lead to realize the dream of the human space exploration and manned spaceflights are in the agenda of space agencies. Radiological devices or linear accelerators might help conducting in vitro or in vivo ad hoc experiments or analyzing the available information from (cancer) patients' cohort thus reinforcing our knowledge on cancer and non-cancer space-radiation induced effects. Unfortunately, the number of events useful for modeling the radiobiological effects is still limited. Consequently, available dose-effect models and their uncertainties need further improvement and suggest implementing future researches to increase the understanding of biological mechanisms.

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