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Review

Radiation risk mitigation in human space exploration: a primer, a vision, and the state of the art

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Abstract Human exploration beyond low Earth orbit poses unique health and operational challenges, with space radiation recognized as one of the most significant hazards. This comprehensive review examines the complex nature of the space radiation environment, its biological effects on humans and life support systems, and current strategies for risk assessment and mitigation. It details the composition and properties of galactic cosmic rays (GCRs) and solar particle events (SPEs), their interactions with spacecraft shielding, and the resulting biological impacts ranging from DNA damage to systemic effects including cancer, cardiovascular disease, and central nervous system impairments. Special emphasis is given to the combined effects of radiation and microgravity, which together alter cellular function and influence health outcomes. The paper also explores the effects of radiation on plants and microorganisms as biological components of bioregenerative life support systems (BLSS). The issue of radiation-induced degradation of food and pharmaceuticals is also considered. Existing and emerging countermeasures, encompassing passive and active shielding, pharmacological agents, nutrition, physiological adaptations like synthetic hibernation, and personalized risk assessment through targeted crew selection are critically reviewed. Additionally, the work highlights the importance of high-fidelity analog studies, space-based experiments, and advanced risk models integrating physical, biological, and operational data to inform future mission planning. Finally, the paper reviews existing infrastructures, experimental platforms, and European research programs, emphasizing the critical role of ground-based accelerators, space analog environments, and in-flight studies in advancing our understanding of radiation risks. By identifying key knowledge gaps and proposing a structured mitigation framework, this study presents a strategic roadmap for protecting human health and sustaining life during long-duration missions to the Moon, Mars, and beyond. (The review work described in the paper stems from the discussions within the working group on Radiation sponsored by the Italian Space Agency.)

Narici Livio, Ottolenghi Andrea, Tabocchini Maria Antonella, and Cotronei Vittorio are retired.

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1 Introduction

Radiation is one of the five main stressors firstly recognized by National Aeronautics and Space Administration (NASA) for human spaceflight (see Fig. 1). To enable human deep space exploration, radiation risks, identified and quantified by a comprehensive risk model, should be mitigated and minimized under a pre-defined threshold, by means of the application of proper countermeasures.

This review work provides an account for the direct and indirect effects of the space radiation environment on human beings and bioregenerative life support systems, and for the best approaches to study these effects, to propose and develop ad hoc countermeasures.

The paper is presented within the framework of the current worldwide investigations and programs to identify the major open issues where efforts should be focused at. The availability of the needed infrastructure and devices in the world is also considered.

The radiation mitigation workflow is described in Fig. 2: The left part is showing the sources of the space radiation, while the right part the effects of radiation on humans; in the center, we have positioned the countermeasures and the risk model.

Radiation measurements and validated radiation models provide the needed detailed physics parameters to be fed into the risk model [1, 2] that translates these physical quantities to risk levels. For this purpose, the risk model needs also an exhaustive input from the right side of Fig. 2: the "RadBio/Physiol" area, often generally referred at as space radiobiology. This area provides the knowledge to translate the radiation inputs into risk of damages (temporary, permanent, acute and chronic, deterministic (tissue reactions), stochastic, etc.). The risk model will therefore use the radiation inputs and the radiobiology knowledge to produce a risk evaluation. The need to consider different organs, genders, personal histories, etc. makes this output multidimensional.

This output is strongly needed for the development of countermeasures. These are either physics (passive or active shielding) or bio-/physiological countermeasures. All must be designed, developed, and optimized to minimize the final risk. This can be individually tailored, so that, for example, it could provide the needed information for a running optimization of the mission plan (lower portion of Fig. 2).

The complex multivariate response of the risk model can be simplified in a first rough approximation which is provided by the dose equivalent. This variable takes into account the radiation qualities and their effects on the astronaut health with a single, linear energy transfer (LET)-dependent parameter (Q, see [3, 4]), or with a more detailed input energy- and LET-dependent Q [5, 6].

The structure of the paper also ideally follows the workflow described by Fig. 2: In Ch. 2, we first present experimental (detection) and modeling (simulation) approaches to provide all the needed detailed physical parameters to characterize the space radiation environment. Integration and smart management of radiation data are proposed as near future requirements, at the basis of a long-term strategy to make deep space missions as independent as possible from ground mission centers. In Ch. 3, we discuss which are the health risks associated with the human exposure to space radiation, starting from changes induced at the molecular level, leading to cancer and non-cancer effects, as well as leading to traces of radiation action on biological systems (biomarkers), possibly

Fig. 1 Recognized 5 most relevant hazards of human deep space exploration (NASA courtesy)

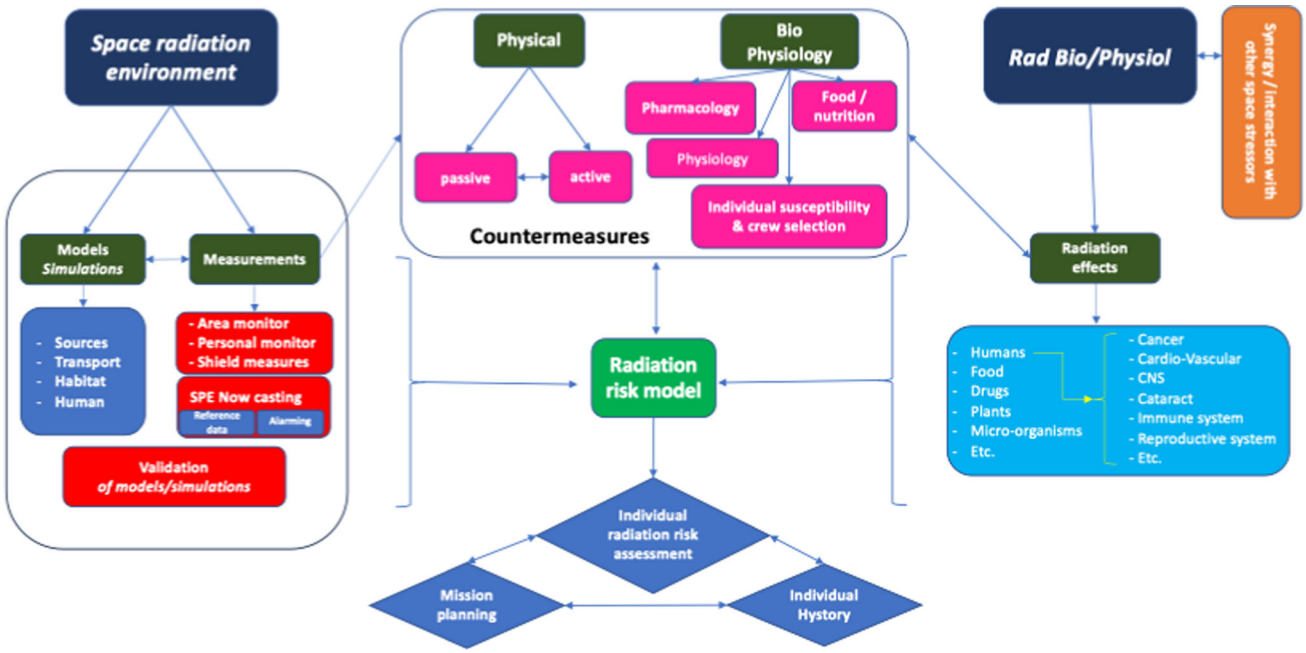

Fig. 2 Tasks involved in the process aimed at mitigating radiation risk for astronauts during space exploration missions

allowing to estimate radiation doses (biodosimetry). Also, the possible synergy of radiation with other space stressors as, e.g., microgravity is discussed. Given the variety of biological effects covered, we decided to focus on more recent findings, again delineating which are the knowledge gaps to be filled to achieve a better understanding of radiation-induced mechanisms and how they lead to health detriment. Ch. 4 deals with space radiation action at the level of the life support system, including effects to food, drugs, and plants. Ch. 5 presents the effects of radiation on microorganisms in both human health and life support system. Ch. 6 briefly introduces the currently established exposure limits to control the risk, which are the advancements deemed critical for development and optimization of a risk model. Ch. 7 is dedicated to the different countermeasures that can be set in place to mitigate the risk, including promising approaches as synthetic hibernation, as well as delineating a vision based on crew selection and smart management of their health records in view of operation planning. In Ch. 8, we review the needs and current availabilities of tools and infrastructures both on ground and in space to perform studies fostering advances in space radiation risk mitigation. Finally, Ch. 9 briefly presents two research programs quite relevant in this area.

2 Radiation

2.1 The path of radiation in space

As shown in Fig. 3, the radiation from space sources is modulated by several items in its path to the astronaut body.

The components of space radiation that are most hazardous for astronauts' health in deep space are galactic cosmic rays (GCR) and solar particle events (SPE). The formers are composed mostly by fully ionized nuclei, mostly from $Z = 1$ (hydrogen) to $Z = 26$ (iron). The GCR fluxes drop significantly for $Z > 26$, as iron is the heaviest nuclei produced in stellar nucleosynthesis. About 85% of GCR are protons, 14% are helium ions, and 1% are heavier ions [3]. GCR fluxes are isotropic, and their intensities are modulated by their interaction with the heliospheric environment, resulting in rigidity-dependent anticorrelations with the 11-year solar cycle (maximum GCR flux intensity at the minimum of the solar activity, and vice versa) and with the fainter solar regular time structures [8, 9]. The heavier ions are more effective in damaging living tissues, resulting in contribution to the health risks that is comparable to the one of protons, even if their flux is much lower [10]. The spectra of all ions peak at about 1 GeV/nucleon [11] and extend from low energies (a few MeV) well beyond the TeV region. At these two ends, the low flux intensities result in negligible direct effects in space health hazards, and at the low end, the ions are most likely stopped by the habitat shield. The radiation flux (number of hits per unit of time, unit surface) is as small as few hits per centimeter squared per second. Recent measurements show that the average dose equivalent in the ISS (0.647 mSv/day [12]) is very similar to the one measured on the surface of Mars (0.64 mSv/day [13]) and about one-third of the dose equivalent measured during Earth to Mars transit (1.84 mSv/day [14]). For a more careful comparison of these measurements, the specific shielding situation and the solar cycle effects should also be considered (see also [15]).

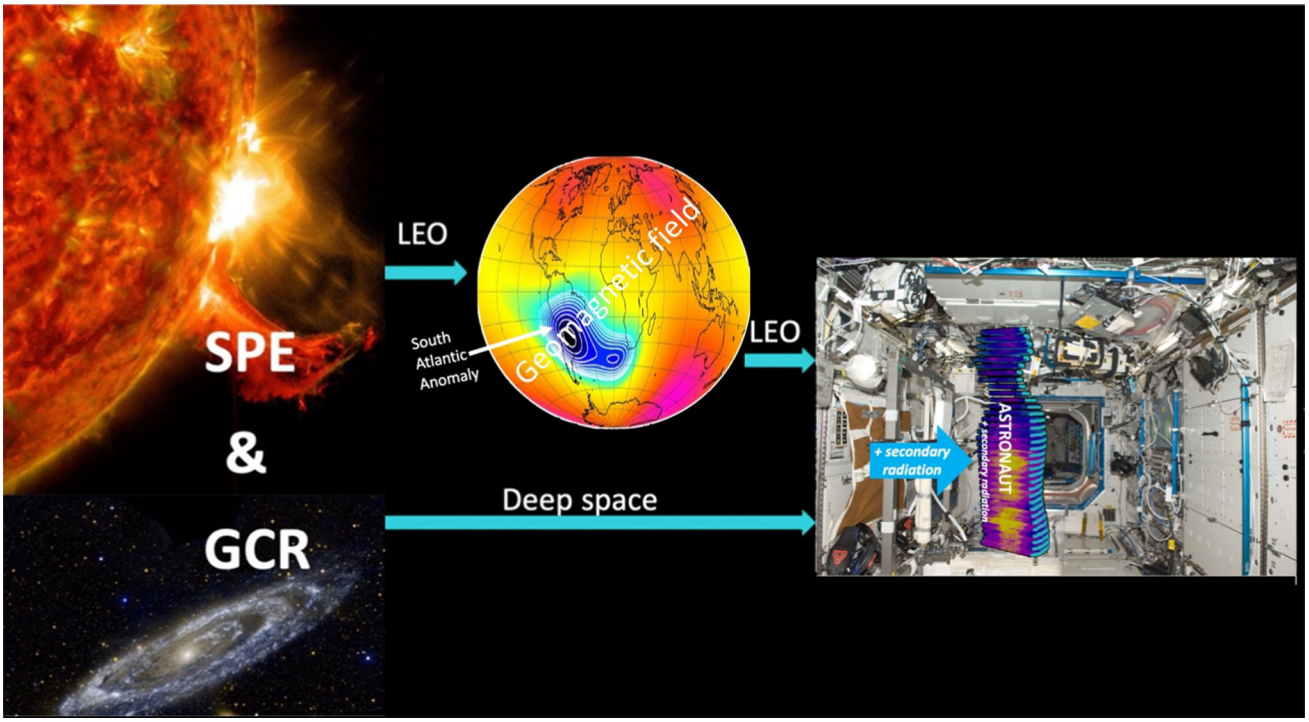

Fig. 3 Schematic view of the radiation path from sources to target (astronaut silhouette adapted from [7])

SPE are sporadic and abrupt increases of the flux of energetic particles originated from the Sun. SPE feature short duration (hours, days), intense fluxes (orders of magnitudes higher rates than GCR), are non-foreseeable and are mostly constituted by protons with energy spectra peaking at about one order of magnitude lower than GCR.

During GCR and SPE propagation in LEO, the primary fluxes are modulated in terms of intensity and directions by the Earth magnetic field. (This is relevant only for low Earth orbits, LEO, and it is not relevant for deep space.) Then, they traverse the shield of the habitat (hull of the spacecraft/base as well as the shield provided by all the items in the habitat). Even during extravehicular activity (EVA), the astronaut will be in a "mobile" habitat: her/his space suit. Finally, the radiation reaches the astronaut skin and start producing damages. The interactions of the radiation with all these materials produces secondary radiation: lighter ions, protons, electrons, photons, and neutrons. The latter deserve probably the most careful considerations for radiation protection issues [16].

Understanding radiation up to the astronauts' skin is a matter of physics; when radiation reaches the skin, radiation biology comes at play: The biological response is, however, elicited by physical interactions, and it has to be recalled that radiation keeps interacting with body tissues, further producing secondaries.

Finally, to enable deep space exploration it is mandatory to mitigate the radiation effects also on any other target relevant for the astronaut life, such as the bioregenerative life support systems, which include, for example, plants, food, and drugs.

Most of the radiobiological experiments are performed on ground, mainly using particle accelerators as "space radiation analogs" [17–20]. The fidelity of these "analogs" is poor. There are four major points where the characteristics of the irradiation with an accelerator do not match the space relevant quantities: (i) distance in time between two subsequent ion hits (rate); (ii) geometrical distance between two subsequent hits; (iii) radiation composition (linked to the possible nonlinearities of the effects due to different ions (Z) or/and energies); and (iv) directions of the impinging radiation. Point (iii) is solved by the recently introduced GCR simulators. Finally, we should consider the issue due to the need to use doses and rates often significantly higher than what is actually observed in space, to measure the effect under study at particle accelerator facilities.

2.2 Radiation physics

2.2.1 Radiation

Modeling space radiation physics is fundamental to assess risk and for the development of countermeasures. It requires:

1) *Modeling of the radiation field*, i.e., modeling the composition (in space and time) of the energy spectra of GCR and of the SPE. Most of the models were proposed in the 1990s, with developments in the following years. For GCR, examples are the Nymmik's model, CREME-96 model, CHIME model, Badhwar and O'Neill model (BON), and DLR model.

- The Nymmik's model originally proposed by Nymmik [21, 22]—MSU, Moscow State University—is a semiempirical model used by Russian Space Agency, DLR and ESA. Starting from Nymmik et al. publications, in the 2010s Matthiä et al. from DLR, developed a new simplified and promising approach [23].
- The CREME-96 [24] model is an update of the CREME-85 model developed at the Naval Research Laboratory, USA. It also includes geomagnetic transmission calculations. For the GCR, the CREME-96 code is based on Nymmik's model.
- The CHIME model [25], ESA, requires satellite observations and does not have predictive capabilities.
- The Badhwar O'Neill (BON), recently updated to the BON2020 issue [26], is a galactic cosmic ray model used at NASA as input into radiation transport codes for vehicle design, mission analysis, astronaut risk analysis. It has had several revisions, all based on the same framework.
- The DLR model (Matthiae et al. 2013) describes the galactic cosmic ray spectra of nuclei using only a single parameter to be derived by the specific solar modulation conditions, from measurements of the Advanced Composition Explorer (ACE) spacecraft and Oulu neutron monitor count rates.

Besides details on the various models available in the cited references, overviews on most of these models, together with comparisons, can be found in the NCRP Report No. 153 [27], or in a very recent review [28]

For SPE, there is a need of developing forecasting and prediction models possibly including the time evolution and the fluence spectra.

2) *Development and validation of radiation transport codes*.

Examples of transport codes are used for space radiation research are:

- HZETRN2020, a deterministic transport code specifically developed by NASA for space radiation transport (https://software.nasa.gov/software/LAR-19979-1)
- SHIELD, developed by ROSCOSMOS, the Russian State corporation in charge of spaceflights and cosmonautics programs (http://www.inr.ru/shield)
- GEANT4 (https://geant4.web.cern.ch/) and PLANETOCOSMICS (ESA, application linked to GEANT4)
- FLUKA (https://fluka.cern/)
- MCNP (https://mcnpx.lanl.gov/)
- PHITS (https://phits.jaea.go.jp/)

Radiation transport codes are essential also to predict the effects of radiation shielding and to design planetary habitats and spacecraft characteristics. Further ground-based benchmarks and validation of the available codes for specific particle types and energy ranges are also still needed, together with validations through spaceflight measurements.

3) *Track structure codes* (see Sect. 2.4).

4) *Criteria to develop and implement countermeasures* in different mission scenarios, including advanced shielding materials and the development of active shielding (see Sect. 6).

Taking advantage of tools of these kinds, a very recent and interesting paper is, e.g., showing that it is possible to predict radiation in a space habitat with a good accuracy if models are well validated and knowing the geometry of the habitat [2].

2.2.2 Detectors

Introduction Besides feeding the risk models, there are three major goals for the measurements of the radiation in space habitat: (i) monitor the radiation environment; (ii) running validation of radiation and transport models; and (iii) checking specific radiation parameters for warning issues.

Without considering constraints, the ideal radiation detector for human space exploration would be a real-time spectrometer with an acceptance range able to measure different types of ionizing radiation, from high-energy photons (for the external detectors) to electrons and all the ions (protons up to iron). For internal measurements, a neutron detector able to measure neutrons from a few MeV to the GeV region will also be needed. External detectors are needed to support detailed radiation–matter interaction model validations, for assessing the actual shielding effectiveness of the various solutions adopted and, most importantly, to provide needed real-time measurements for in situ alarming purposes (see later).

Mass, size, and power considerations imply severe limitations on the detectors. This is even more relevant for personal detectors. For a review of detectors, see [29, 30] and references therein.

Ideally, all the detectors should be connected to some centralized "radiation center" (see 2.2.2.5).

The measurements relevant to human explorations in space habitats performed with these detectors are cited in the same mentioned review, most recent ones can be found in Narici & Berger 2023, and others can be found in Sect. 7.3, when briefly mentioning the space analogs. Much of the data are available in RadLab (part of the Open Science data Repository from NASA [https://osdr.nasa.gov/bio/]) at the link https://visualization.osdr.nasa.gov/radlab/gui/overview/ (see also 7.6).

External External detectors, coupled with internal ones, are needed to support: (i) detailed model validations of the radiation fields in outer space and of the radiation–matter interaction processes (including the expected fragmentation by-products); and (ii) an

in situ assessment of the actual shielding effectiveness of the various solutions adopted (either in spaceships, in permanent stations or in crew spacesuits). In these cases, the optimum would be to have the same detector inside and outside the habitat shielding layer, approximately in the same location and with the same orientation, simultaneously monitoring the radiation flux.

Most importantly, external detectors are needed to measure the SPE precursors providing real-time measurements for in situ alarming purposes. This will be described in 2.3.

Habitat These detectors, often called "area" detector, are the least limited by the quoted budget consideration, but they are still limited by other technical constraints. However, they can feature some nuclear identification capability, produce real-time output, and provide LET spectra, measuring from protons to heavy ions, including iron. These detectors should also be able to measure the real-time integrated dose.

As far as the habitat is concerned, neutron detectors are needed, while the need for photon and electron detectors is still under investigation, since their relevance for risk assessment appears very low. Neutrons are produced by fragmentation processes induced by the interaction of the primary radiation with the ISS or spaceship walls. Their energy spectra and delivered dose must be studied and monitored to provide inputs for the assessment of radiation effects on humans.

Finally, microdosimeters, currently used mostly in radiation therapy centers, could provide an assessment of the energy deposited in a cell size volume and therefore could be useful to help characterizing the radiation field quality.

Personal phantoms Small active detectors are taking the place of the personal passive detectors, used up to now. The real-time, active features should also be paired with wireless connections to a centralized "radiation center." Due to the stringent size and power limitation these detectors should accept several performance compromises about features. It should be noted that a battery life lasting several days is a key requirement, impacting also on the size–mass issue.

Similar "personal" radiation detectors could be used in ground measurements with phantoms, to study the radiation behavior at different depths and in different positions in a virtual body. These experiments have also a quite important space counterpart where phantoms are used in the ISS to best study the radiation within the human body with a real space radiation field [7, 31].

Integrating and managing radiation data External detectors, area detectors, and personal detectors provide a network of relevant information about the dynamic of the radiation environment. To make the best use of these data, exploiting also the cross-check capabilities, and providing the crew with a set of information, they can use proficiently even during emergencies, and a centralized radiation center (CRC), possibly managed by smart applications and algorithms, is now considered a near future requirement.

Given the CRC mentioned above, the possibility arises to devise a strategy utilizing multiple smaller devices, such as area or external detectors, each tailored to specific radiation targets and applications. By exploiting their functions and their synergies through the CRC, all collected data can be integrated and harnessed to maximize the capabilities of the detection system.

The amount of information provided by the different detectors (external, area, personal, but also in a base, rover, etc.) can become overwhelming during emergencies, especially in situations where fast communication with the mission control center (MCC) is not possible. It is now agreed that one of the requirements for the Mars voyage is the full migration of the decision processes from Earth to space. In this frame, the output of the radiation monitoring must be provided also in space directly to the crew, and due to the large amount of data, it should be properly reduced and processed to provide relevant suggestions. This requires analysis systems based on smart technologies that could help the crew, namely the radiation officer, in making the proper decisions.

2.3 Now-casting

The most dangerous radiation events are the SPE. As mentioned, these are relatively short, low-energy, high-rate fluxes of particles (protons), totally unpredictable in time. Being of lower energy, they can be more easily shielded than GCR. However, the amount of needed shielding for a vessel is still far from being feasible from the mass point of view. The strategy would be to build a shelter in the vessel: a small space, with the proper shielding, where the crew goes when a SPE is hitting the spacecraft. The effectiveness of this strategy relies on the promptness of the alarming for the crew.

Eventually, breakthroughs in solar physics will provide enough accuracy to forecast these events, but right now it is not possible to achieve it when predictions directly involve the safety of the crew. So, the crew will have to be dependent on now-casting: measuring specific SPE precursors (such as photons or electrons), predicting from these the level of risk of the incoming event, so to issue proper warnings/alarms.

In this view, the crew will withstand the initial part of the SPE (receiving an average dose that must be estimated) but will be shielded for the longest and most dangerous part of the event. The duration of the SPE is an issue, also considering that the shelter will not have all the life supports for a long permanence.

Also, a time interval longer than foreseen to reach the shelter once the alarm has been issued, or the need to exit the shelter during the SPE should be taken into account. These considerations lead to the need of ad hoc designed countermeasures as, e.g., personal shielding vests [32].

In perspective, external photon and electron detectors will therefore be mandatory in the future: Their presence would allow data to be sent in real time to a possible CRC and properly analyzed using algorithms based on previous SPE history, to issue, when and if needed, a warning. The use of data from geostationary satellites might, in some situations, be of help [33–38].

2.4 From dose to track structure, microdosimetry and beyond

The induction of radiobiological damage is a stochastic multistep process involving several orders of magnitude both at a spatial level (from atomic dimensions to cellular and organ dimensions) and at a temporal level (from the 10^{-15} s of the physical interactions to the hours, and possibly years, of the biological processes). As for any perturbation to a biological system, different modeling approaches can be adopted, depending on the purposes for which they are developed; however, no clear boundaries between approaches can be drawn, e.g., between phenomenological and mechanistic models.

A mechanistic stochastic approach typically starts from track structure, studied using Monte Carlo methods to describe (and possibly predict) biological damage, at the subcellular and cellular scale. It includes radiation-induced DNA damage and repair processes (and their relevance in inducing other biological endpoints), These early events lead to effects appearing at the tissue, organ, and systemic levels, which (at least to some extent) can also be studied with mechanistic approaches including intra- and extrasignaling perturbation (bystander effect), and their anti- and procarcinogenesis implications.

The relevance of the spatial distribution of energy deposition events by radiation at the subcellular and cellular scales (radiation quality) in driving the biological response has led to the success of approaches based on nanodosimetry, microdosimetry, as well as approaches based on track structure properties [39–41].

Starting from initial energy deposition, the basic information needed for track structure calculations is the knowledge of the probability (expressed as cross sections) for the relevant processes that may occur in matter. Data on cross sections have to be previously processed to obtain the mean free path for subsequent collisions for primary and secondary particles and the relative probability of each interaction process. The time-dependent evolution of ionizing radiation tracks at short times (up to 1 microsecond after irradiation) is usually divided into three main stages. The "physical" stage (up to 10^{-15} s) involves the energy depositions due to the interaction of the impinging radiation with target molecules. This stage produces a primary spatial distribution of excited and ionized molecules and of sub-excitation electrons. Ionized and excited molecules dissociate, relax, or auto-ionize during the "physicochemical" or "pre-chemical" stage (from 10^{-15} to 10^{-12} s after irradiation), whereas sub-excitation electrons either recombine, or thermalize and become solvated, i.e., bound to a cloud of water molecules. A spatial distribution of new chemical species is therefore produced at the end of this stage. At 10^{-12} s after irradiation, when the “chemical” stage is usually assumed to begin, the various species start diffusing, reaching an intra-track equilibrium state at about 10^{-6} s. During this stage, chemical species—in particular water radicals—can react among them, or they can attack other cellular constituents such as the DNA, but not only [42].

Track structure-based approaches become fundamental when dealing with different qualities of radiation (when different types of initial damages are involved), different dose rates and inhomogeneities of energy depositions, such as in the case of space radiation.

Several Monte Carlo track structure codes are currently being adopted for radiation biology studies (in some cases with applications to the space radiation scenario), as, e.g., Geant4-DNA [http://geant4-dna.org/], PARTRAC [43], PTra [44]. In some cases, radiation transport codes have also been (or are in the progress of being) extended to include options for nanodosimetry/track structure calculations and also for the evaluation of microdosimetric quantities (as, e.g., PHITS) at the physical stage of radiation action.

When codes include the simulation of all the above-described stages of radiation action and a software representation of the target cell and its genomic content (biophysical track structure codes as Geant4-DNA and PARTRAC), they provide a framework to quantify the initial DNA damage, its complexity, and, in some cases, also its evolution (e.g., with modeling of DNA repair processes and formation of chromosomal aberrations). Alternative models like the LEM [45] do not include the full representation of radiation tracks (but mainly consider a radial distribution of the dose around the particle track core and are referred to as amorphous track structure models) and can also be successfully used to simulate DNA damage and cell survival (e.g., for particle therapy applications).

The potential of all these approaches to establish a direct link between physical features of radiation tracks and the biological outcome in terms of RBE (at least for DNA damage induction, though this is certainly non-exhaustive of radiation-induced biological effects) makes them a valuable tool to inform risk models for stochastic effects related to space radiation.

3 The space radiation risks for human health on the basis of the endpoints

3.1 Basic changes at molecular and cellular level

The chronic exposure to galactic cosmic rays (GCRs) may have late health effects such as induction of cataract, cancer, or degenerative diseases of the central nervous system or other organ systems [46]. Severe effects can be also caused by the exposure to SPEs if not properly shielded. Therefore, the comprehension of the biological effects of GCRs and SPEs is fundamental for planning spaceflights. An additional concern is the exposure to ionizing radiation that occurs at very low dose rates in deep space. As seen above, measurements showed that astronauts will be exposed to approximately 1.84 mSv/day of GCRs in interplanetary space and

0.64 mSv/day of GCRs on the Mars surface (see Sect. 2.1), amounting to a total mission dose equivalent of ~ 1 Sv for a round trip to Mars with 180 days (each way) cruise, and 500 days stay on the Mars surface for a particular solar cycle [13]. Thus, understanding the health effects caused by chronic, low-dose-rate radiation exposure is also central for planning space missions [47]. At the molecular level, space radiation from high-energy photons and atomic nuclei has been shown to damage cellular components determining biological responses that are indicated below.

3.1.1 DNA damage

Ionizing radiation induces DNA breaks, through either direct interactions with the DNA molecules or indirect radiolysis [48]. Unlike low-LET radiation, high-charge-and-energy (HZE) particles in the space environment deposit their energy along densely ionizing tracks, traversing thousands of cells and delivering elevated local doses in the cell nucleus [49]. This creates a tightly clustered and complex mixture of DNA damage (double-strand breaks, single-strand breaks, base damage, etc.), which is challenging to repair. Damaged DNA, if inadequately repaired, can lead to mutations and chromosomal aberrations that potentially lead to cancer. Directional genomic hybridization has recently revealed an increase of chromosome aberrations (intra-chromosomal inversions and translocation) in astronauts' lymphocytes during and after spaceflight. Importantly, the astronaut with the most accumulated time in space had the highest yield of inversions, indicating also that the inversions could be informative biomarkers of space radiation exposure [50–52]. Finally, the post-flight rise of inversion and translocation frequencies is indicative of instability that likely reflects GCR-induced cytogenetic damage in stem cell compartments [53].

3.1.2 Oxidative stress

Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of reactive oxygen species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products [54]. Elevated levels of ROS can damage proteins, lipids, and DNA, eventually triggering and leading to DNA mutation and/or cell death. ROS can result from indirect effects of ionizing radiation as a consequence of radiolysis of water. The oxidative stress can be self-perpetuating and could contribute to inflammation at the tissue and organ levels thus worsening the overall levels of cellular damage. Exposure to space radiation, as well as to hypoxia and microgravity, has been demonstrated to enhance the cellular production of ROS and nitrogen species (RNS) [55, 56]. It has been recently reported that oxidative stress response in human peripheral blood mononuclear cells depends on LET during simulated deep space radiation [57]. Thus, further investigations are required to understand whether these studies can explain the physiology of some spaceflight-related system deficits including the immune system dysfunction.

3.1.3 Mitochondrial dysregulation

Strictly related to the oxidative stress, mitochondrial dysfunction is an additional major feature of biological responses to space missions. Mitochondrial dysfunction arises from an inadequate number of mitochondria, an inability to provide necessary substrates to mitochondria, or a dysfunction in their electron transport and ATP synthesis machinery. Ionizing radiation can induce leakage of electrons from the electron transport chain and then result in the generation of an excess of ROS, which could ultimately induce mutations in mitochondrial DNA, change the mitochondrial DNA copy number and/or damage proteins required for essential mitochondrial roles in the cells [58]. Mitochondrial ROS also modulates the function of the DNA damage protein ATM, linking DNA damage and mitochondrial function. Changes in the mitochondrial DNA copy number and the expression of genes involved in the regulation of oxidative stress were detected in biological samples of astronauts [50, 59] and are likely to represent additional health risk factors for crewmembers of space missions. However, assessing whether these alterations are a direct consequence of exposure to GCR or are caused by other factors of space environment (i.e., microgravity, which also induces mitochondrial oxidative stress) still deserves further investigations.

3.1.4 Epigenome alteration

The different heavy ions that make up the GCR spectrum each have distinct effects on gene expression patterns in cultured cells, via mechanisms that remain poorly understood [60]. These differences in gene expression may reflect modifications to the epigenome affecting the local patterns of DNA cytosine methylation, posttranslational modifications of histones, nucleosome positioning, long-range chromatin organization, and modulation of ncRNAs. ^{56}Fe and ^{28}Si ion exposures are known to affect methylation of chromatin regions relevant to human cancers. Therefore, high-LET radiation-induced modification of epigenome should be taken into account for the cancer risk analysis of astronauts [61]. Radiation also affects the expression of miRNAs, which regulates gene expression. miRNAs increase was observed in human immune cell samples exposed to simulated deep space radiation, as well as immune cells from the NASA Twin Study. Interestingly, these samples showed the same differentially expressed miRNA classes as those found in rodents flown to International Space Station indicating the existence of a conserved spaceflight relevant miRNA signature [62]. However, this deep space radiation-induced modulation of miRNAs expression was not caused by changes in chromatin condensation indicating that cosmic radiation influences the epigenome through different mechanisms.

3.1.5 Telomere maintenance

Chronic exposure to space radiation could influence chromosome stability affecting also telomere maintenance. Indeed, telomeres were found significantly longer in three unrelated astronauts aboard ISS compared to the average telomere length measured before spaceflight, but they shortened rapidly upon return to Earth, and overall astronauts at the end had shorter telomeres compared to preflight [63, 64]. Persistent DNA damage response (DDR) to ROS production by mitochondria, as well as replication stress could activate both telomerase-dependent and alternative lengthening of telomeres (ALT)-dependent shift in telomere dynamics [65, 66]. As changes in telomere length dynamics could be linked to genome instability, aging and ultimately cancer [67], a better understanding and monitoring of mechanisms that underlie this effect should be taken into consideration for preserving crewmember general health.

3.2 Cancer

Cancer is one of the main late risks of deep space exploration and different national space agencies have set career effective dose limits for astronauts on the basis of recommendations from the International Commission on Radiological Protection (ICRP) or from national space radiation risk assessment models [1]. However, several gaps in knowledge concerning the effects of space radiation on astronauts need to be filled and a major issue is to reduce the uncertainties on the effectiveness of GCRs at low doses/dose rates for causing carcinogenesis.

On Earth, cancer risk evaluation can be only based on particle radiotherapy-induced secondary tumors. In adult cancer hadrontherapy, which mainly deals with relative high doses/dose rates of protons and C-ions and with secondary neutrons, both severe late normal tissue damage and radiation-induced second cancers are rare [68]. Other information coming from epidemiological studies is mainly related to exposure to acute doses of low-LET radiation and has to be scaled by using the RBE (relative biological effectiveness) and the DDREF (dose and dose rate effectiveness factor) concepts. Both RBE and DDREF values are under debate and varies for different exposure scenarios and different tumor types.

In model systems, due to the low dose rate and the technical complications in performing radiation experiments in LEO, most of our knowledge is derived from ground-based accelerator experiments [69]. Due to the similarity between rodent and human radiation-induced cancer incidence, simulations of GCR components on Earth have been extensively applied to rodent models. High RBE of HZE particles has been reported for induction of mammary tumors, Harderian gland tumors, skin tumors, intestinal colorectal cancer, leukemogenesis, and hepatocellular carcinoma. On the other hand, HZE ions are no more effective than gamma rays for inducing acute myeloid leukemia and ovarian cancer, which might indicate different underlying mechanisms for induction of these tumor types. Importantly, no novel tumor types have been observed in rodents exposed to HZE ions in comparison with spontaneous and low-LET-induced tumors. Additional data are required to better understand the effect of dose fractionation on carcinogenesis, given current inconsistencies ([46] and references therein).

In an attempt to better simulate the space radiation scenario, experiments on cells and animal model systems have been carried out with mixed beams [70–72]. More recently, the Brookhaven NASA's Galactic Cosmic Ray Simulator based on fast beam switching and control system technology made possible to generate a spectrum of ion beams that approximates the primary and secondary GCR field experienced at human organ locations within a deep space vehicle [19, 73]. Data so far obtained have shown that exposure to a multiple ion beam of protons (20 cGy), helium (5 cGy) and silicon (5 cGy) at a dose rate of 0.5 cGy/min elicits significant changes respect to a different sequence or to protons alone in lung cancer initiation. This effect can be mitigated by CDDO-EA, an anti-inflammatory antioxidative radioprotector [74]. Other experiments have been carried out on other cancer relevant systems [75, 76], and more data is expected to be available in the near future.

3.3 Cardiovascular disease (CVD)

Exposure to various types of radiation can lead to radiation-induced CVD, involving the development of new CVD or the exacerbation of existing CVD. It is possible to distinguish between acute complication of radiation exposure, mostly being acute pericarditis, and chronic progressive damage that involve multiple disorders of the heart and vasculature, such as myocardial remodeling and fibrosis, accelerated development of atherosclerosis, cardiomyopathies, valve abnormalities, arrhythmias, and conduction disorders. These effects can develop over more than 10–15 years after exposure. Several underlying mechanisms for radiation-induced cardiovascular disease have been identified, but many aspects of the pathophysiology are still unclear.

In relation to space radiation, the deleterious effects of ionizing radiation have been extensively studied in animal models, while there is a paucity of data in humans; a subgroup analysis of Apollo astronauts firstly indicated a greater proportional mortality from CVD compared to both astronauts from low-lying orbits, non-flight astronauts and those of the general population, even if these kind of study might contains different bias related to confounding variables such as lipid levels and physical exercise, sample size, tobacco use, and fitness levels that may have influenced overall results.

Nonetheless, animal models within the literature have clearly indicated the negative effects of radiation sources; for instance, rats exposed to high-energy ^{56}Fe-ion radiation (0.1 to 1 Gy) were found to have significantly higher aortic stiffness over a 6-month exposure, with high levels of endothelial dysfunction, myocardial remodeling, pressure decompensation. Oxidative stress has largely

been implicated as an underlying mechanism of pathophysiology with increased ROS production, activation of xanthine oxidase (XO) in the aortic samples. Moreover, the reduced bioavailability of NO from superoxide-forming XO and its correlates remains a likely pathway for endothelial dysfunction and vascular stiffness [77].

Proton and γ-irradiation have also shown impaired cardiac function as well as increased cardiac fibrosis in adult male C57Bl/6NT mice, with iron-ion radiation-producing longer-lasting damage. Disrupted cardiac homeostasis appears as the result of radiation-induced dysregulation of various intrinsic pathways including the handling of Ca^{2+} by SERCA2a and cardiac hypertrophy signaling via MAP kinases. Aggregates of persistent inflammatory responses were measured by levels of oxidative DNA damage. The increase in genomic injury here may act as both an analog for ROS and cytokine recruitment as well as a predictor of future cardiovascular disease.

Lastly, irradiation of the aortic arches and carotid arteries of apolipoprotein E-deficient mice with ^{56}Fe-ion particles demonstrated accelerated progression of atherosclerotic, with upregulation of transforming growth factor beta (TGF-b) and NFKB following microvascular damage. Since carotid artery plaques independently predict cardiovascular events, the potential consequences of radiation seem especially pertinent [78].

The role of space radiation in potentiating CVD is still in its infancy while more data are present in relation to microgravity effects on cardiovascular system [79], and while animal and cellular-based studies are important, it is also necessary to understand whether these changes translate to the human condition.

Results from existing studies and exposure risk indicate the need for more research into the crucial role of radiation in cardiovascular pathophysiology as well as prospective countermeasures.

The estimate of a linear increase in major adverse coronary artery events of 7.4% per Gy administered, with no detectable lower or upper threshold, and the prediction that a radiation dose of cumulative ~ 1.0 Sv will be experienced by an individual traveling to Mars clearly indicates an increased lifetime risk of death from radiation exposure between 1.3 and 13% for a 40-year-old male [80].

3.4 Central nervous system (CNS)

Cosmic radiation can affect the CNS including sensory systems ad retina, thus compromising astronauts' safety and quality of life [81, 82]. Recent studies have proved the connection between the reduction of the functional behavior and the space radiation-induced damage to the neuronal structures in astronauts. These effects were also observed 1 year after the journey, implying a persistent damage to the brain [83–85].

Space radiation can also affect visual activity. Beside the anectodical reports of anomalous phosphenes perceived in space in dark conditions (see [86, 87] and references therein), astronauts on long-term mission to the International Space Station (ISS) reported some ocular damages [88]. Retinal damage is due to several factors, such as fluctuation in oxygen tension, oxidative stress, or increased ocular pressure. The causes of spaceflight-associated neuro-ocular syndrome (SANS), however, are still unclear. In particular, this syndrome can lead to several optical damages, such as the unilateral and bilateral optic disk edema, choroidal and retinal folds, and nerve fiber layer infarcts [89, 90]. A recent study has shown the space radiation-induced apoptosis in vascular endothelial cells of the retina. This effect can, in turn, compromise the intraocular pressure regulation and astronauts' visual acuity [91]. Therefore, further studies are necessary to investigate the effects of space radiation on the central nervous system, with particular attention to the SANS development.

3.5 Cataract

The mechanisms of cataract formation [92, 93] are not precisely known. However, it is assumed that they originate from genetic damage in lens epithelial cells, such as disruptions in cell cycle controls, apoptosis, abnormal differentiation, and cellular disorganization, or other pathways leading to abnormal lens protein fibers.

For over 30 years, astronauts in Earth orbit or on missions to the Moon have been exposed to space radiation, but, due to the absence of epidemiological data, various uncertainties exist in the projection of risks of late space radiation effects on cataracts. The phenomenon of light flashes [86, 87], which continues to be observed by astronauts on the space shuttle and the International Space Station (ISS), suggested that single heavy particles can affect one or more photoreceptor cells in the retina, raising concerns for damage to other tissues, including lens [94–96]. Evidence of early development and higher incidence of cataract in astronauts who are more exposed to space radiation has been reported by [97].

Therefore, the investigation of the space radiation-induced cataract formation is crucial. In particular, the ICRP recommended 20 mSv/year for the eye lens as the equivalent dose limit, averaged over a period of 5 years and not exceeding 50 mSv per year [98]. This drastic reduction in dose limits warrants several radiation protection measures to observe the new regulations, such as lens dosimetry and the design and testing of protective devices.

3.6 Effects of radiation on immune system

Spaceflight can result in effects on the immune system in a complicated pattern. Specifically, the consequences consist primarily of effects on cytokine levels, reduced T and natural killer (NK) cell function, changes in the pattern recognition system of monocytes and granulocytes [46].

In consideration of the radiosensitivity of the lymphoid system, an immunosuppressive effect is attributed to ionizing radiation [99]. However, the actual interaction is currently a matter of debate. In fact, especially on the basis of recent evidence from studies in oncology, it is commonly believed that radiation may have a local immune-modulating effect [100]. Current research in the field of oncology is evaluating the effects of an integrated approach between local radiation therapies and immunotherapy. Two topics of discussion can be introduced on the above subject: (i) the use of heavy particles, which have recently proved to be extremely helpful in current clinical practice; and (ii) the immune mechanisms induced by low-dose radiation [101].

Undoubtedly, immune system reactions to radiation resulting in inflammation are often responsible also for local reactions and effects to radiotherapy treatments. Monitoring gene expression associated with the inflammatory response due to irradiation could be a promising biomarker system related to radiation exposure [102]. One of the main research topics in radiobiology aims to clarify the biological effects of low doses [101], where the observed pathophysiological endpoints are related to mechanisms different from direct cell killing. Ionizing radiation, in addition to direct effects on mature lymphocytes and on the response of T lymphocytes to induced signals, also affects the development of T lymphocytes themselves [103]. The most interesting finding is the response to radiation of thymic epithelial cells, which represent less than 1% of the cells present in the thymus. These cells are involved in the process of generating mature and functional T lymphocytes. These effects are probably involved in the metabolic processes for the T-cell deficiency observed in patients undergoing "total body irradiation" (TBI) prior to bone marrow transplantation [104].

3.7 Effects of radiation on reproductive system

In both males and females, exposure to ionizing radiation can result in infertility. In fact, radiation can affect sperm and egg development. It can also expose the fetus or embryo to birth anomalies and genetic diseases [105]. The testis is one of the most radiosensitive organs, and the damage to the germinal epithelium and Leydig cells depends on the radiation dose and on the age and pubertal status of the male. Doses greater than 0.35 Gy cause aspermia, which may be reversible with recovery time varying with dose. At doses greater than 2 Gy, the effect may be permanent. At higher radiation doses (>15 Gy), Leydig cell function will also be affected [106]. Regarding women, we can report experiences from radiation exposures during diagnostic procedures or during radiation therapy, the main side effects result on ovarian failure and infertility. The response of the ovaries to the effects of irradiation varies with age and dose. An ovarian dose of 4 Gy can cause a 30% incidence of infertility in young women, but 100% incidence of infertility in women over 40 years of age [105]. Pelvic irradiation with radiation therapy can also have an effect on the uterus resulting in miscarriages and premature labor later in pregnancy. Radiation exposure of a pregnant woman can lead to an increased risk of children with deformities or an increased risk of miscarriage. Exposure to 0.1 mGy or more of cosmic radiation in the first trimester may be linked to an increased risk of miscarriage [107].

3.8 Biomarkers

The term biomarker refers to a broad set of objectives, reliable and quantifiable measurements mirroring an interaction between a biological system and a potential hazard which may be of chemical, physical, or biological origin [108]. Biomarkers can be used for dose estimation, and hazard identification in risk assessment as well as diagnostic and/or prognostic tools of disease and disease outcome [109]. At the same time, a deep characterization of affordable biomarkers could enable the development of efficient countermeasures.

Biodosimeters are well-established tools required in the absence and/or to complement physical data for dose and risk assessment in the event of radiation exposure. During space missions, physical dosimeters provide careful estimation of dose. However, in order to estimate the radiobiological effects, measurements of LET and of the dose rate of exposure are necessary. Biodosimeters can help in assessing the RBE as expression of the relative amount of damage that a fixed dose of a specific type of radiation could have on biospecimens, providing measurement of the biologically relevant absorbed dose, tightly correlated to health risk [110, 111]. Cytogenetics analyses are the most developed techniques for radiation dose determination (in the order of 0.1 Gy) from blood samples, revealing chromosome damage. Among them, dicentric chromosome, the gold standard for biodosimetry, and micronuclei assays are largely used being very useful for detecting chromosome aberrations even at short time after exposure. Fluorescence in situ hybridization (FISH) targeting chromosome translocations, provide more reliable measurements in assessing long-term effects. However, by combining premature chromosome condensation (PCC) in lymphocytes with FISH it is possible to evidence aberrations a few hours after exposure, with minimum dose detection limit for this technique of 0.05 Gy [112].

Nonetheless, performing cytogenetic assays routinely or on-site can be limiting due to their inherent labor-intensive nature, the need of multiple and sophisticated instrumentation, and skilled operators. In the last decades, the introduction of automation and machine learning has led to the development of advanced robotic platforms that offer the same or even enhanced efficiency and consistency, significantly increasing the potential throughput for conventional cytogenetic-based biodosimeters [113].

More recently, discoveries on nucleic acids and proteins occurring in blood as circulating factors, paved the way to the development of liquid biopsies based on cell-free DNA (cfDNA) or exosomes as noninvasive biomarkers to assess spaceflight health risks and design targeted countermeasures. miRNAs are stable, highly conserved and small noncoding RNAs occurring in every organism being involved in posttranscriptional regulation and as previously reported, undergo specific profile changes in response to ionizing radiation [62]. miRNA as well as other nucleic acids, lipids and proteins are often found associated with exosomes, nanovesicles secreted by most cell types for long-distance intercellular communication in biological fluids. Although the cargo is dependent on the stress, it has been shown that spaceflight induces an overall hyperproduction of exosomes. Specifically, ionizing radiation promotes exosome excretion and cellular uptake, and most importantly the radiation-induced cargo modification has been related to chromosomal and genomic instabilities, oxidative stress, inflammation, apoptosis [46].

In addition to blood assays, saliva has also emerged as a promising biofluid for assessing the outcomes of radiation exposure as salivary glands sensitive radiation targets displaying acute and chronic responses to radiotherapy [114–116]. Ongoing research aims to unravel the molecular and cellular mechanisms underlying salivary gland dysfunction to identify biomarkers of radiation damage therapeutic targets for lasting restoration [117].

The noninvasive and easily collectible features of these measurements as well as their specific activity make these tools ideal biomarkers laying a foundation for the design of efficient cutting-edge countermeasures.

3.9 Combined radiation and microgravity effects

It is widely recognized that the basic cellular functions are sensitive not only to radiation but also to microgravity [118]. Experiments carried out in space or in ground-based analogs cannot exclude that microgravity alters the cellular response to cosmic radiation [119, 120]. Therefore, potential synergies between microgravity and radiation could arise during spaceflight that can increase the risk for adverse health effects.

Whether exposures to microgravity and space radiation simultaneously produce additive or synergistic consequences has been investigated with several biological endpoints, such as DNA damage response [121]. The biological effects caused by both the factors have been extensively studied for a long period. Most of these studies are based on the concept that each of these factors act independently. Indeed, in combined studies, the focus was mainly devoted to understand if the effects caused by ionizing radiation might be altered by microgravity. This was mainly correlated to the perception that DNA damage caused by space radiation is the major factor for the fate of the cell, resulting in experimental data on DNA repair and its possible influence by microgravity. However, recent researches have highlighted that cytoplasmic damage induced by space radiation is crucial as chromosomal damage; moreover, bystander effect in the cells is a further indicator of cellular mechanisms [122].

Therefore, many data suggest the need to deeply investigate possible combined effects provided by the interaction of microgravity and space radiation that might involve nuclear, cytoplasmatic, or mitochondrial mechanisms.

Ground simulation studies have suggested that microgravity and space radiation interactions might be involved in cellular responses such as gene expression and signal transduction.

It has been reported that the expression of cell cycle-suppressing genes (ABL1 and CDKN1A) decreases and that of cell cycle-promoting genes (CCNB1, CCND1, KPNA2, MCM4, MKI67, and STMN1) increases after C-ion irradiation under microgravity. The cell may pass through the G1/S and G2 checkpoints with DNA damage due to the combined effects of C-ions and microgravity, suggesting that increased genomic instability might occur in space [123].

With regard to bone loss, low doses of high-LET radiation, in conjunction with *partial weight bearing*, appeared to promote the induction of bone loss with an increase in sclerostin-positive osteocytes and Wnt signaling [124]. Moreover, in a mouse model looking at the tibia bone surface, radiation caused a 46% increase in osteoclast number, hindlimb unloading caused a 47% increase in osteoclast number, and the combination of radiation and hindlimb unloading caused a 64% increase in osteoclast number, sustaining the synergy between microgravity and radiation probably related to both condition ability to increases in oxidative stress [125].

Furthermore, it has been reported that interactive nature between microgravity and radiation in spaceflight analog studies differs with time, sex, and age for rodent analog studies, radiation dosage and type, and cell lines for immune markers. It is critical that future study designs more rigorously mimic the spaceflight environment to further investigate the complex immunological health risks arising from microgravity, radiation, and more [126].

4 The radiation risks for life support systems

4.1 Food

Food packaged for future deep space exploration missions may be transported to their final destination ahead of astronaut arrival, remaining exposed to galactic cosmic rays (GCRs) and solar radiation in deep space at higher intensities and different spectra than those encountered in low Earth orbit (LEO), for extended durations that have not been previously experienced.

During these prolonged storage periods, food might undergo chemical transformations, including degradation of vitamins, undesirable changes to texture and flavor, possible release of contaminants from food packages, posing critical risk to human health.

In addition, beyond the Earth's protective magnetosphere, food is exposed to GCRs and solar radiation having higher levels and different spectrums compared to those in LEO.

Preliminary evaluation of five spaceflight foods following 880 days of storage on the ISS did not indicate significant nutritional differences compared to ground controls; nevertheless, during this study the food evaluation was related only to nutritional measures and included only one high-moisture food that would allow for greater diffusion of radicals. Therefore, that study and models based on the limited data set cannot conclusively indicate that there is no risk to the overall food system from radiation beyond LEO [127].

The impact of GCR simulation at two target doses (0.5 Gy and 5 Gy) on the stability of the complete nutritional composition of two high-moisture foods also indicated no difference between the control and samples irradiated at both 0.5 and 5 Gy, but several limitations (exposure time, radiation complexity and dose variability package to package) indicate the need of more data including sensory evaluation of food. Although no differences could be attributed to radiation treatment in these studies, the recorded reductions in vitamins A, B6, and B9 are meaningful indicators of food degradation during storage time. In addition, the effects of ionizing radiation on various food packaging polymers are still unknow and most of the studies in the literature are conducted with high dose levels (up to 50 kGy) for short times. However, radiation may induce undesirable changes in quality, such as softening, browning, and loss of nutritional factors, as well as the release of toxic molecules from food packaging [128].

In conclusion, current studies on the consequences of space radiation on foods suggest that the impact on shelf-stable food may be low risk. However, further evaluation is necessary through deeper simulation studies using space relevant beams and validation assessment of nutritional stability over relevant times and storage conditions in the environment beyond Earth's magnetosphere. Additionally, studies should focus on homogenous, high-moisture spaceflight foods that are good sources of radiation labile nutrients, such as thiamin, vitamins, and antioxidants that might be relevant as nutritional countermeasures [128–130].

4.2 Drugs

Short-duration flights of the Mercury, Gemini, Apollo, and Space Shuttle eras and the long-duration ISS human permanence did not highlight the need for prolonged medication shelf life, due to continuous drug refurbishment, and the minimized need for ongoing medication provision for chronic disease.

Consequently, there are only a few data available for the characterization of medication use, effectiveness, side effects, pharmacokinetics, pharmacodynamics, and long-term stability under space conditions. Looking forward to exploration missions to the Moon and Mars, this issue represents a major concern for human health.

Within this frame, one potential risk to pharmaceutical stability arises from long-term exposure to the space radiation environment. While gamma radiation exposure is used on ground for sterilization procedures in selected pharmaceuticals without effects on molecules and formulations, space radiation that differs considerably for composition, dose rate and time of exposure might represent an important issue. Indeed, is still unknown whether long-term exposure to space radiation may affect stability, alter drug ingredients, or produce potentially toxic by-products, particularly in drugs that have undergone degradation reactions. Preliminary data from NASA Space Radiation Laboratory (NSRL) study performed by [131] demonstrated variable drug sensitivity to radiation exposure for clavulanate and promethazine.

Pharmaceuticals can become unstable through alteration of either their physical or their chemical properties. Alteration of physical properties includes changes in appearance or consistency; alteration of chemical properties includes loss of potency, alteration of excipients, excipient–active ingredient interactions, or toxic degradation. In order to claim radiation-free damage status of pharmaceuticals in spaceflight, studies should demonstrate no significant alteration of the drug's active pharmaceutical ingredient as well as no significant development of degradation products that are either toxic or able to alter the pharmaceutical properties.

The basilar assumption of molecular mechanisms involved in radiation damaging live organisms cannot be assumed for pharmaceutical preparations, due to their formulation, concentration, and interaction with excipients. When the drugs are exposed to any ionizing radiation, the electronic transitions take place in the drug molecules depending on the type of radiation which may lead to decomposition of drugs and excipients. Generated radiolytic species may react with active ingredients or excipients or both resulting in a change of physicochemical properties which leads to an alteration in pharmacological activity or pharmacodynamics in the body.

Several studies have suggested that long-term exposure to spaceflight may promote drug degradation and increase the risk of therapeutic failure. A critical analytical analysis of the obtained data on drugs stability in LEO spaceflight has recently highlighted that while spaceflight introduces some risk to drug stability, the common practice on Earth of repackaging of drugs into light weight packaging to reduce mass and volume introduces additional risks associated with atmospheric factors (e.g., O_2, CO_2, relative humidity (RH)), which are known mediators of drug degradation. Hence, addressing repackaging and protective packaging can help maintain medication effectiveness during exploration space missions [132, 133].

Well-designed ground-based simulation studies and innovative formulation strategies as well as development of radioprotective packaging technologies are needed for extended stability and optimum effectiveness with the minimum toxicity of drugs in space [134].

4.3 Plants in space

4.3.1 Difference between travel and permanence

Plants are essential organisms to bring in space to sustain life. Indeed, plants are the primary producers at the base of the food chain on the Earth and the question arises on why they should be less necessary to support human life in space [135]. Indeed, long-term human permanence in space, either in orbital platforms or on planetary stations (e.g., Moon and Mars), requires Environmental Control and Life Support Systems (ECLSS), also known as bioregenerative life support systems (BLSS), capable of fulfilling all the essential metabolic needs [136–139]. In such artificial ecosystems, plants contribute to the regeneration of resources by removing carbon dioxide through photosynthesis, recovering water through transpiration, and recycling wastes of the crew. If the species cultivated in such systems are crops, they represent fresh food much more appreciated than package food or freeze-dried food to also fulfill a role in the mitigation of the stress of the mission and conditions of isolation [140]. The positive effect of plants on astronauts' psychology relies on the beneficial effects of the space gardening, as well as on the optimization of nutritional intake or the function as "comfort fresh food." The relative importance of the different roles played by plants can vary depending on the different mission scenarios [141]. Indeed, the requirements of life support change according to the mission (e.g., the increase in distance from Earth, thus in duration, determines a shift from refurbishment from Earth toward the regeneration of resources onboard). Moreover, the environmental stressors, and the levels at which they act, also depend on the mission, and must therefore be taken into account in the design of the BLSS compartments.

In the case of short-duration manned missions (e.g., in LEO), plant cultivation is mainly constrained by volume limitations and astronauts' diet is still mainly based on ready-to-eat food refurbished from Earth. In such a case, fresh food produced onboard can be a complement to the astronauts' diet and the species choice would regard vegetal systems easy to cultivate, for direct consumption without processing (grow–harvest–consume), such as microgreens and leafy greens, mainly providing vitamins, minerals, antioxidants.

For long-duration missions, such as the one to Mars, it is not feasible to rely on food and other resources re-supplied from Earth: Therefore, other species need to be cultivated such as potato, soy, wheat, and other staple crops in order to provide the needed amount of carbohydrates, lipids and proteins. Moreover, in a long-term scenario, the opportunity to achieve the seed-to-seed cycle becomes a requirement to guarantee the production of seeds for successive cultivation cycles [142]. In such a scenario, the main constraints to cultivation might be volume limitation and space stressors (e.g., microgravity and radiation) during traveling, while mainly radiation during the permanence on the planetary outpost.

In this framework, to design space greenhouses, it is fundamental to keep in mind, which is the target mission, thus the main associated stressor. It is evident that radiation poses the primary challenge for exploratory-class manned missions, as it can significantly affect the plants' resource regeneration capacity, altering the input/output relations with other compartments, and also impacting the nutritional value of the plants, thereby changing their potential role as a countermeasure.

4.3.2 Growing plants in space and relevant radiation risks

In the last decade, the interest toward the understanding of the effects of ionizing radiation on plants has increased [142, 143]. However, most information still derives from studies that have not been designed for space purposes, but were mainly targeted to the use of radiation in breeding programs or as a decontamination mean, as well as to evaluate the effects of radionuclides at nuclear accident sites [144, 145].

Although less studied compared to animal models, and although the variability of data source has often led to contrasting results, there is common agreement on a few statements that can be considered a valuable starting point to envisage which should be the target objectives of future experiments.

Plant's response depends on many factors either regarding the radiation nature (including radiation type and dose) or the vegetal system (e.g., the species, the cultivar, plant developmental stage, target organs, metabolic and nutritional status, etc.) [146]. As regards radiation, generally, the radiation-induced damage increases with increasing doses; at same dose, the discriminant among LET different deleterious effects becomes the radiation quality: high-LET being more dangerous than low-LET radiation especially because of the higher ability to induce genetic mutations [147–151]. It is also well demonstrated that plants exhibit an intrinsic resistance to radiation due to molecular, biochemical, and structural defenses, making them in general more resistant than animals [152, 153]. Indeed, doses higher than 0.1 Gy are considered already harmful for animals while doses higher than 10 Gy can be still ineffective for plants [152]. In some cases, doses of gamma rays up to 200 Gy have been observed not to induce negative effects on plant growth [154]. Moreover, low doses can induce hormesis, defined as a stimulation of various biological processes (e.g., faster germination, increased growth) occurring when seeds are exposed to pre-irradiation with low doses [155–157]. Such a phenomenon is considered a sort of recovery from irradiation damage, but it has been also found that pre-irradiation of seeds at low doses can determine some morpho-physiological changes favoring germination and growth, while it is not high enough to induce permanent injuries. Indeed, faster germination may be also a secondary response to radiation which instead primarily affect the structure and composition of cell walls [144, 158, 159].

Concerning the exposure time, most of the information in the literature refers to studies performed using brief acute doses with high dose rates, because the experiments in space for the assessment of biological effects of chronic exposure, are not easy to perform. This limitation often leads to contrasting results and lack of knowledge on low-dose chronic outcomes, being the studies in natural and agricultural ecosystems in the regions where nuclear accidents happened the main sources of information [145, 160–162].

The variability of plant responses to radiation is significant and remains not fully understood. Comparing results from different studies is not always straightforward, not only due to the use of different plant species, radiation conditions, and experimental protocols, but also because of interactions with other environmental factors (such as light quality during cultivation and microgravity as the other main space factor) that influence the plants' responses to radiation [163–166]. However, many radiation-induced alterations have been reported, and they occur at different plant levels with strong interconnections. Indeed, morpho-physiological traits are a consequence of genetic/epigenetic changes induced both directly by radiation and indirectly by reactive oxygen species produced during the radiolysis of water [144, 160]. Generally, the exposure to ionizing radiation increases embryo lethality, induces genetic alteration (e.g., inducing mutagenesis and/or alteration of gene expression), alters protein and profiles of metabolites, influences cell cycles, differentiation and morphogenesis (e.g., leading to dwarf architecture), elicits modification of floral elements with consequences on reproduction, influences many physiological processes among which the photosynthesis is one of the most important for BLSS, changes the amount in antioxidant compounds in specific organs which suggests the possible impact of radiation on the nutritional value of edible organs [139, 151, 152, 167, 168]. The alteration of the photosynthetic process is one of the main processes to be understood since the photosynthetic efficiency would directly influence the biomass production and the production of oxygen in the pressurized modules. The effects of low- and high-LET radiation are indeed targeted to many critical points of the photosynthetic processing involving the expression of proteins such as D1, structural alterations of the chloroplasts, and chlorophyll perturbations [169–171].

Most of the information available on the effect of radiation on plants comes from non-space-oriented research, in which high, acute doses of low-LET radiation have been targeted mostly to dry seeds [144]. Toward space exploration, the time is ripe for increasing the efforts to investigate plant responses to most relevant radiation models for space purposes, namely chronic low dose rate and high-LET radiation [141].

5 Radiation and microorganisms

Microorganisms are ubiquitous, and wherever we go, we inadvertently carry them along. Almost 50 years of microbial research in space demonstrated that microorganism are able to live in the closed system of the International Space Station. This adaptation can be either beneficial or detrimental to crew members and spacecraft. Therefore, it becomes crucial to identify the impact of two primary stress conditions, namely radiation and microgravity, on microbial life aboard the ISS. To enable successful and safe human exploration, critical microbial issues concerning occurrence, function, and dispersal of microorganisms with regard to human health and material contamination, as well as to the bioregenerative life support systems (BLSS) and planetary protection requirements issues need to be addressed. Elucidating the mechanistic basis of microbial adaptation to space conditions aids in the development of countermeasures against their potentially detrimental effects and allows us to harness their biotechnologically important properties.

5.1 Microorganisms and human health

Effects of exposure to radiation on bacteria and fungi play a significant role in the pathogenesis mechanisms of these microorganisms. Pathogens with increased virulence and antibiotic resistance in the space environment may be a threat to the astronaut health. Consequently, mutated microorganisms transported by humans may contaminate the space environment, and, after the spacecraft has returned to Earth, mutants with high virulence and resistance could also be a risk to human health on the ground. It is well known that in space the astronauts have a suppressed immune system; therefore, the host–microbe interactions could be substantially affected. The study of the effects of radiations and microgravity on microbial growth and activity is necessary for studying any changes in the normal microbiota of crew members and for predicting the host–microbe interaction [172]. Closed, confined conditions of the habitat challenges crew health, due to potential buildup of microbial contaminants and their products in the atmosphere, in water systems (biofilms) and on surfaces and the possible contamination of spacecraft. Therefore, investigating the effect of space conditions, including radiation, on microorganisms is of fundamental importance for the astronaut health and for spacecraft integrity. Furthermore, more studies on the effect of radiation on human microbiome balance are demanded to prevent perturbations/dysbiosis.

5.2 Microorganisms in life support systems

Microorganisms play fundamental roles in the BLSS being involved in waste degradation, water recovery, and oxygen production which are essential for sustaining life in space. Several studies have shown that fungi, bacteria, and cyanobacteria can enhance vitamin production, water recycling, air decontamination, and waste management under space conditions [173–177]. Microorganisms can pose a threat to plants, potentially, threatening the success of a BLSS [178]. Additionally, the growth of human pathogenic microorganisms on plants in BLSS raises concerns about food safety.

Table 1 Radiation limits (Sv) for the different agencies (Shavers et al. 2024)

Space agency	CSA	ESA	JAXA*	NASA@	RSA
Career exposure limit [Sv]	1	1	0.5–1	0.6	1

*JAXA's career limit is age- and sex-specific, ranging from 0.5 Sv for a female 27y of age at first exposure to 1 Sv for males older than 45 at first exposure
@The NASA Space Permissible Exposure Limits (SPELs) limits each astronaut to 0.6 Sv, calculated as the mean effective dose to a female.

Microorganisms generally recognized as safe, including the cyanobacterium *Arthrospira platensis* (a.k.a. Spirulina) and the green microalga *Chlorella* sp., can serve as direct food supplements for astronauts' diets [179, 180]. Other species have been identified as important sources of proteins, and poly- or oligosaccharides, and have been proposed as potential prebiotic candidates [181]. Microorganisms can also induce a remodeling the host's cellular metabolism and produce bioactive functional metabolites to cope with stressors such as oxidative stress or radiation. These properties can be used to design a balanced diet for astronauts.

Challenges ahead may involve developing a balanced microflora that maximizes life support functions and minimizes the threat to crew health in closed space systems.

6 The radiation risk model

All major space agencies are currently expanding their efforts to identify requirements and promote research toward optimizing radiation protection of astronauts. As seen, radiation is one of the main showstoppers for space exploration because of the health risk, and thus an accurate assessment of this hazard is a high priority for extending the permanence of humans in space.

Prolonged exposure to GCR, secondary radiation, and SPE during long-term space exploration missions could lead to significant organ dose. Furthermore, it is important to understand the long-term effects of chronic and low-dose-rate radiation exposure.

Exposures to ionizing radiation are managed by a combination of exposure limitation and optimization practices that minimize risks, following the general "as low as reasonably achievable" (ALARA) principle. While there is a general agreement on the radiation limits for the deterministic effects (common limits for tissue reaction), different limits have been to consider the stochastic effects. The current approach consists of selecting a dose limit for the entire astronaut career. The European Space Agency (ESA) like the Russian Space Agency (RSA) and the Canadian Space Agency (CSA) use a single career dose limit of 1 Sv for all gender and ages. For NASA, the limit is 0.6 Sv, and for the Japan Aerospace Exploration Agency (JAXA) instead, the career limits depend on age and gender (Table 1).

Setting a dose limit is the only feasible practical approach from an operational perspective. Studies of the excess health risk astronauts face because the space radiation environment must provide the basis for those limits, outlining the health consequences associated with each dose level and thereby supporting the determination of "acceptable" radiation levels. Radiation risk models are the essential tools for establishing reliable dose–risk relationships. This is the reason for their central role in the workflow shown in Fig. 2, where they supply the quantitative foundation for subsequent decision-making.

Progressively, space agencies have increasingly adopted probabilistic frameworks that integrate physics-based radiation transport modeling, tissue- and organ-level dosimetry, understanding of radiobiological responses, and uncertainty quantification to estimate health risks [28, 182].

As a relevant example, the NASA Space Cancer Risk (NSCR) model is currently the most mature integrated radiation risk assessment framework [5, 182, 183]. In brief, space permissible exposure limits are set, requiring that the planned career radiation exposure, adjusted for age and sex, must not exceed a 3% risk of radiation exposure-induced death (REID), related to a fatal cancer, with a 95% confidence level.

The REID and its uncertainty distribution are calculated using as input epidemiological data from atomic bomb survivors and occupationally exposed cohorts. Modeling the dose and dose rate effectiveness factor (DDREF) for scaling, along with the dose delivered to tissues by particles of a given energy E and charge Z, is also needed. Quality factors (QNASA) are then constructed, allowing to apply a biological weight to the physical dose, reflecting different RBE functions. Results are calculated as a function of age at exposure and attained age. Cancer mortality rates for cancer insurgence in a given tissue are finally integrated over the expected radiation environment (considering the predicted particle fluence spectra, and exposure duration in the mission scenario) and over all tissues. Final uncertainties are obtained with explicit propagation of model and parameter uncertainties. Recent updates have further integrated Monte Carlo-based uncertainty sampling and harmonization with NASA's permissible exposure limits, enabling consistent mission-specific assessments.

Within this framework, as it can be inferred from many recent works (see, for example [13]), the total equivalent dose for a Mars mission could be around 1 Sv. So it could appear that we are close to respect these limits. However, such limits refer to the entire career, and most likely, the Mars crew will have flown in space already many times.

The roadmaps of most agencies include a return to the Moon in the near future, and a first manned mission to Mars. These endeavors call for a harmonization of the different risk models and dose limits for international exploratory missions in both LEO

and BLEO (beyond-low Earth orbit), where currently no recommendations have been issued yet. The lack of an international space radiological protection strategy will lead to the paradoxical situation that some astronauts would be forced to leave the mission before others depending on the dose limits set by their space agency. The success of international missions, especially for interplanetary scenarios, depends on the development of a unified strategy, which is now a high priority.

The mentioned limits and this unified strategy must rely also on a space radiation risk model based on transport codes, radiobiological modeling, risk assessment, and uncertainty analysis, to provide both cancer and non-cancer radiation hazards. The following ingredients have been identified as critical for the development and optimization of a risk model:

i) Improving the characterization of ionizing radiation in space taking advantage of measurements, environmental models, transport codes, and track structure models;
ii) Increasing the direct knowledge about the potential detrimental health effects of space radiation exposure by means of fundamental biology works as well as international occupational cohort studies;
iii) Potential improvements in the health risk assessment for astronauts, including both considerations underlying the development of the European contribution to the risk model as well as the main uncertainties that need to be taken into account in the development of such a model.

In general, it is accepted that detailed physics characteristics (charge, energy) of the impinging radiation will be needed for any advanced risk model.

7 Countermeasures

7.1 Passive shielding

Shielding is the main countermeasure for the exposure to cosmic radiation during interplanetary exploratory missions. However, the mitigating effects of shielding of cosmic rays, both of galactic or solar origin, are limited because of the high energy of the charged particles involved and the nuclear fragmentation occurring in shielding materials. As mentioned, this is especially valid for GCR due to their higher energy. Although computational codes can predict the shielding performances in space, there is still the need for further biological and physical measurements to benchmark the codes. All calculations and measurements show that light, highly hydrogenated materials (such as polyethylene) are ideal materials for space radiation shielding [184, 185].

New materials are unlikely to provide significant improvement for passive shielding because the shielding limit, represented by liquid hydrogen [3], is not far from the one provided by highly hydrogenated shields already developed. However, in a perspective of an integrated view of the shielding problem, the search for materials that beside providing good radiation shielding, work well in other space relevant areas (for example resistance to impacts) may become relevant and drive further technological developments.

For what concerns the biological effects of space radiation, risks of acute effects in deep space or on planets are limited to the event of a large SPE, especially if occurring during an EVA phase. A storm shelter will be able to spare the crew members from most deterministic effects, notwithstanding a residual risk of late stochastic effects [186]. However, very energetic events ($E > 1$ GeV/n) would be much more difficult to shield efficiently, but fortunately they are unlikely.

As to the chronic exposure to GCR, the knowledge of stochastic effects of heavy ions is still insufficient to provide accurate risk estimates for interplanetary missions [187, 188]. So, biological experiments aiming to measure the RBE of heavy ions with shielding are urgently needed to benchmark the current models [189]. In fact, the results in Brookhaven and at the Heavy Ion Medical Accelerator (HIMAC) show that the biological response is a complex function of the dose and of the radiation quality behind the shields [190, 191].

Finally, the classical conception of permanent habitat shielding could be complemented with ad hoc approaches to face emergency situations. Possibilities to be further investigated include the relocation of elements already present in the habitat to create new shelter area: This has the advantage of optimizing the use of onboard resources, and the best relocation scheme could be suggested by smart system analyzing in real time the radiation environment characteristics. Also, personal shielding devices can provide additional protection, e.g., garments to be worn during the occurrence of a SPE [32]. Personal shielding vests are being studied and tested also for full-time use and protection [192].

7.2 Active shielding

Mitigation of the radiation impact on the crew can also be performed by deflecting the radiation using a magnetic or electric field, mimicking the shield provided by the Earth magnetic field. Many recent projects worked on this idea, proposing, for example, superconducting magnets and several possible field configurations to maximize the particle trajectory deflections while minimizing the magnetic field lines and its effects inside the habitat. Use of a combination of electric and magnetic shield has also been studied 193. The strategy looks quite impressive, and possibly a winning one, especially if in conjunction with the other radiation countermeasures as well as with promising applications in space research, such as the possible use of high-temperature superconducting (HTS) (see, e.g., [194] for a reference technological development of HTS magnets for space applications). However, the budgets (mass, power)

and the possible danger (huge superconducting currents) still require several technological breakthroughs to be accepted [195, 196]. Similar comments can be made about electric field active shielding [197, 198].

7.3 Pharmacological countermeasures

Few studies have evaluated pharmacological agents for their ability to prevent or limit radiation toxicity or to act as rescue therapy, able to reduce post-radiation exposure morbidity or mortality. Most of the studies are too preliminary or performed only at the in vitro or ex vivo level; some of them included unpurified plant extracts containing a mixture of molecules that theoretical may inhibit, supplement, or may be responsible for the observed data. A very few compounds have been studied in humans, and fewer molecules are approved for clinical use.

There are several strategies for pharmacological prevention of radiation exposure toxicity. Some agents may act in a prophylactic manner by acting to prevent or limit radiation-induced cellular damage by making tissue more resistant to radiation exposure. Others may act as a rescue therapy, limiting post-radiation morbidity and mortality by augmenting cellular, tissue, and organ system recovery. The ideal compound(s) will have a long shelf life at room temperature, a high degree of bioavailability, low toxicity at required doses, a low-side-effect profile, and preferably be efficacious through oral, subcutaneous, or intramuscular administration.

On the molecular and cellular levels, their classification may include: (1) direct scavengers of ROS and other free radicals, (2) antioxidant agents that induce/alter endogenous levels of ROS-detoxifying enzymes such as MnSOD, (3) agents that enhance or modulate DNA damage signaling and repair, and (4) agents that prevent execution of death pathways in radiation-damaged cells. According to several recent studies, these mechanisms are not mutually exclusive; one radioprotective agent could exert its biological activity through one or more pathways.

Some of the agents proposed are: amifostine approved for the treatment of radiation toxicity, Beta Glucan as a prophylactic radioprotectant, polyhydroxylated fullerenes, vitamins E, A, and C, trace metals, calcium channel blockers and many antioxidant plant extracts or purified polyphenols [199]. Recently, the use of Aspirin and Warfarin as potential anticancer preventive drugs was also proposed and the integration of their use in risks models strongly encouraged [200].

The development of new biotechnological countermeasures is based on the discovery of a subset of miRNAs (miR-125, miR-16, and let-7a) able to regulate vascular damage caused by simulated deep space radiation. The physiological relevance of these spaceflight-associated miRNAs was demonstrated by the inhibition of their expression enabling to rescue in vitro simulated deep space radiation-mediated damage using human 3D vascular constructs [62].

The ideal radioprotectors and radiomitigators, e.g., having high efficacy, low side effects, wide window of protection against all types of toxicity, easy and comfortable administration, and long-term stability (storage), reasonable cost-effectiveness, are still lacking besides decades of research [201]. Repurposing of FDA-approved drugs can accelerate development of space radiation countermeasure [202]. A more balance diet for astronauts is a promising strategy as preventive countermeasure. Plants are a rich source of bioactive compounds and could be cultivated onboard or used to produce nutraceuticals, as reported below.

Finally, RNA therapy and vaccine represent new routes toward the development of more efficient and less toxic countermeasures [203]. Personalized medicine, nutrigenetics, and nutrigenomics are novel approaches for developing effective countermeasures for space radiation-induced damages [204].

It should be emphasized that the efficacy of radiation countermeasures needs to be carefully evaluated through ground-based radiation sources enabling the simulation of the space radiation environment.

7.4 Nutritional countermeasures

As mentioned above, dysregulation of immune system during spaceflight has been clearly demonstrated along with its tight correlation to psychological and physical stressors as well as alterations of the redox homeostasis. Similarly, an altered dietary intake, nutrient absorption and metabolism negatively impact the host immune responses and resistance to infection [205, 206]. These considerations motivated the research on the development of dietary countermeasures.

In general, the ISS food system is rather dominated by meat and meat products and is low in fruits and vegetables. Astronauts are adequately supplied with vitamins E, A, C and D even if their effectiveness in boosting immune function needs further investigation, on Earth and in space.

Nucleotide-based supplements, e.g., uracil/uridine, revealed immunoprotective effects on immune function and were proposed as potential countermeasures for the observed immune dysfunction associated with space travel. Polyphenols, omega-3 fatty acids, and glutathione are efficient antioxidants and could be provided as nutraceutical formulations.

The integration of astronauts' diet also with fresh food produced onboard can be based on the cultivation of species and plant systems which are nutrient-dense functional food, to promote optimal health and reduce the risk of disease, thus being used as nutritional countermeasures. The correct choice of species and cultivars, rich in vitamins and antioxidant compounds, can help strengthen the physiological defenses of the stressed astronauts' body. Moreover, there might be a possible radiation-induced dose-dependent enrichment of edible plant organs with functional compounds (i.e., polyphenols, carotenoids, ascorbic acid) useful to increase human physiological defenses when the body is exposed to factors promoting degenerative oxidative processes [167].

More recently, algae cultivation in space opens new routes toward nutritional countermeasures. In addition to their role in CO_2 absorption, O_2 production, and waste recycling, microalgae are a rich source of proteins and antioxidants [207, 208]. Actually, microalgae cultivation is happening onboard ISS in a Chlorella-powered photobioreactor, which in a near future would supply nutritious food during long-permanence space missions[1] [180].

7.5 Microorganisms as radiation countermeasures

Radiation-resistant extremophiles provide limitless opportunities in human therapeutics, pharmaceuticals, biotechnology, and biodegradation of toxic and radioactive compounds. In particular, fungal biotechnology can be harnessed such that space stations are self-sustaining with respect to food, pharmaceuticals, waste recycling, and plastic degradation for long-term missions [209].

Because of the ability of extremophiles to survive in high radiation, the various metabolites and enzymes they produce can be manufactured and used for human therapeutics as well as bioremediation of radioactive compounds in nuclear waste fields. Exposure to radiation needs to be considered particularly when thinking of long-duration missions into deep space (out of Earth's magnetic field), as it is the case for a mission to Mars. This is because radiation-induced mutations can lead to functional changes, particularly in microbial species onboard, due to their short generation lifetime [210, 211]. For instance, a study conducted aboard the Mir space station demonstrated a 2–3 times higher mutation rate for the bacterial gene (repsL) cloned in the yeast *S. cerevisiae* during spaceflight compared to ground-based experiments [212]. On the ISS EXPOSE-E facility experiment PROTECT, *Bacillus spp.* spores were shown to have mutation rates four times higher after exposure to outer space conditions for 1.5 years. At low shielding, an average dose rate of 400 μGy d^{-1} was measured, with a total exposure dose of 215 mGy [213].

The identification of radio-tolerant microorganisms and the mechanistic understanding underlying tolerant phenotypes are of outmost relevance for future space missions as well as for possible countermeasure development. During the same EXPOSE-E mission, it was shown that some cyanobacteria and green algae survived the same length of direct exposure [214, 215]. Onboard the ISS-JEM exposed facility, in the Tanpopo experiment, dehydrated *D. radiodurans* bacterial cells survived exposure to the low Earth orbit for 1 year, even if with decreased survival rates compared to ground controls, thanks to the activation of molecular strategies including the accumulation of outer-membrane-associated vesicles (for nutrient uptake, cellular waste removal, distribution of solute, and trafficking of potential signaling molecules) DNA repair and activation of enzymatic and not enzymatic antioxidant responses [216].

7.6 Physiological countermeasures (synthetic hibernation)

In recent years, there has been increasing discussion about synthetic hibernation or synthetic torpor. Several European space agencies are investing in this new physiological countermeasure.

In the framework of the Hybe project, ESA is dedicated to investigating the possibility of using synthetic hibernation for astronauts in long-duration space missions. If projected onto humans, hibernation has several features that could solve significant problems related to human space exploration.

Hibernation is an energy-saving strategy. It is a biological condition and a natural physiological process used by several mammals (endotherms) to protect themselves in critical life conditions. During their inactive state, hibernators reduce heart and breath rate and their vital functions to a minimum [217]. Metabolism is drastically reduced [217].

Hibernation is an active process. During hibernation, the significant decrease in body temperature is caused by a reduced metabolic rate due to decreasing the homeostatic compensatory system [218, 219].

The first studies on hibernation date back to the 1960s, coinciding with the onset of the space race and the Apollo missions, which culminated in the first manned Moon landing in 1969.

The concept arose from the notion that hibernation could serve as a valuable tool for enduring prolonged interplanetary voyages, such as missions to Mars and beyond [220–222].

By inducing a physiological state similar to hibernation, known as synthetic hibernation, in astronauts, it would become possible to significantly reduce the size of the spacecraft, leading to drastic cost reductions. Eliminating crew quarters could reduce the spacecraft mass by up to a third, resulting in substantial fuel savings equivalent to several tons.

Hibernating astronauts would not require food or water. Throughout the journey, the vehicle's temperature could be maintained at a lower level, reducing energy consumption. Additionally, besides being inactive, astronauts would be less susceptible to cabin fever, characterized by stress and aggression due to prolonged confinement in tight spaces. Moreover, they would not experience the issues associated with weightlessness, such as muscle or bone wastage, commonly observed in astronauts living in microgravity [223]. Studies suggest that hibernation could mitigate these concerns [224].

Hibernation could also aid in solving the issue of exceeding dose and risk limits for long missions like the one to Mars: Initially, astronauts in torpor could spend most of their time in hibernation pods, providing the opportunity to implement proper shielding around them, such as water containers. Furthermore, during the inactive state, hibernators become more resistant to radiation [225].

[1] https://www.space.com/space-station-algae-experiment-fresh-air.html

Despite these very promising space-related countermeasures, about a decade after the first experiments and after the Moon's conquest by Neil Armstrong, interest in hibernation tends to wane. In 2004, a fascinating discovery brought hibernation back into vogue: The first primate able to undergo hibernation, the fat-tailed dwarf lemur *Cheirogaleus medius*, was discovered by a German research group [226].

These latest discoveries have brought to light that hibernators' distribution is widespread in the mammals' family, and they suggest that the gene set necessary to survive the process is probably common. In contrast, at some point in evolution, the regulatory mechanisms may have been lost in non-hibernators, including humans [227, 228].

There are reported cases of humans surviving an accident in situations where their whole-body temperature fell to 13.7 °C without severe damage [229, 230].

A recent fossils discovery of humans, dating back 400.000 years, from bones dug up from an ancient mass grave in northern Spain suggests that our ancestors may have dealt with extreme cold a thousand years ago. These hominids could have survived to it strategically by slowing down their metabolism using hibernation through the winter. Those fossils show months of interrupted bone growth [231].

A hibernation-like phenotype is now possible in not-naturally hibernators, like rats [220–222, 225, 228].

Perfecting synthetic hibernation with new drugs and/or procedures and understanding the mechanisms behind synthetic hibernation could bring enormous benefits to future human space missions by greatly reducing the risks of cosmic radiation, microgravity on astronauts and reducing costs.

7.7 Individual susceptibility (crew selection)

Individual radiation susceptibility refers to radiation-induced cancer or any related stochastic prior feature such as cell transformation [232, 233]. Radiation-induced carcinogenesis may be the most significant consequence of exposure to space radiation and identifying individuals with increased radio-susceptibility may conceivably be important for the selection of astronauts.

There are well-known genetic conditions or diseases that result in extreme hypersensitivity to sparsely ionizing radiations. Besides the Ataxia Telangectasia (AT) syndrome, or the Gorlin's syndrome, other examples of hypersensitivities to radiation-induced cancers revealed from the incidence of second cancers following radiotherapy include patients with retinoblastoma, neurofibromatosis type 1, and Li–Fraumeni syndrome [234].

Knowledge of genes affecting radiation sensitivity has led to the study of associations between polymorphisms for such genes and increased susceptibility to radiation-induced cancer for subsets of individuals in human populations. Recently, with improved technologies, it has become possible to examine a broad spectrum of polymorphic variants in what are known as genome-wide association studies [109, 233, 235].

Genetic and epigenetic profile changes associated with individual radiation sensitivity are well documented and have led to enhanced understanding of the mechanisms of the radiation-induced DDR. DDR pathways are potential targets for transcriptional biomarkers of cancer susceptibility and radiation exposure. Deficiencies in genes involved in the ATM/chk2/p53 pathway, particularly in the ATM gene, lead to phenotypic elevated radiosensitivity observed in clinical cancer-prone conditions such as AT and AT-like disorders (ATLD).

Further transcriptomic analyses have shown that micro-RNAs (miR), potentially regulating DDR pathways, are promising biomarkers of radiation oncology ([109] and references therein, [236]).

This research is in continuous development and many issues are open. Most of the data have been obtained for low-LET radiation, and there are no human data that address risk from extended exposure to complex radiation fields that will occur during space travel. However, several insights have emerged from carcinogenesis studies using rodent models. Two of the more important ones are that differences in genetic susceptibility to radiation carcinogenesis observed in low-LET exposures extend to HZE ion exposures and that the proportion of malignant tumors induced may be greater for HZE ions than γ-rays. Research to determine whether the same genetic polymorphisms that determine susceptibility to spontaneous or γ-ray-induced tumors also determine susceptibility to HZE ion-induced tumors is ongoing ([237] and references therein).

A robust predictive assay able of identifying radiation hypersensitive or cancer-prone individuals could be very useful in crew selection for long-term spaceflights [238]. The search for tests that can recognize genetically predisposed subgroups of the general population is moving forward. At the same time, it is questionable whether such tests fall within the norms of society in most countries at the moment. However, for a high-risk and high-cost endeavor such as a mission to Mars, screening prospective astronauts for increased resistance to space radiation may be entirely appropriate in order to reduce both risk and cost associated with the missions.

7.8 Operations

In perspective, operations should use crew members according to the "radiation" history and susceptibility of each individual. In this frame, the development and set in use of centralized system to manage radiation data become even more important: data on the dose received from a possible CRC would go automatically into the "health book" of each astronaut for future fast consultations and use, together with the astronaut's "health history," to support decisions about duties during normal and emergency situations. Changes in the mission plan could also be foreseen to mitigate the overall crew radiation risk.

8 Tools and infrastructure

8.1 Concept of fidelity of analogs

The only high-fidelity radiation analogs are the space ones, where rates, intensities directions, and composition mimic or even "are" the deep space ones. This includes the ISS (the only analog of this kind currently available) and will eventually include LEO habitats or planetary/Moon bases, including future commercial LEO platforms. We must note also that a LEO analog, such as the ISS, currently provides its fidelity at higher accessibility (lower costs, easier logistics) than any other deep space platforms. Also, an altered gravity condition as a possible co-stressor is naturally present for experiments performed in space.

Ground accelerators are of easier access and more controlled use, and they must be used to study the biological effects of radiation. The need of analogs for these studies demands to reduce the requirements for high fidelity for now. As mentioned, the issues to be considered for understanding the impact of these "not complete fidelity" of the particle accelerators are the rate, intensities, direction, and composition (as well as the absence of co-stressors, but options are available to perform combined radiation and microgravity studies, see later).

8.2 Ground based

8.2.1 Irradiation infrastructures (accelerators)

Together with particle anisotropy, the radiation field composition (i.e., the particles abundances and energies) is one of key elements to estimate the dose received by the astronauts. Uncertainties on the field composition, particle rate, particles anisotropy, and dose will all impact the prediction accuracy of the health risk related to a specific mission.

As mentioned, space-based experiments represent the ideal approach to tackle this problem, because they provide a characterization of the actual radiation field experienced by astronauts. Several measurement campaigns have been carried out to obtain the radiation environment in the Earth orbits, and the recent unmanned missions to Mars have provided additional information for deep space as well as the planet surface. Measurements taken in space, however, present several downsides, such as the lack of advanced equipment, the cost, the limited manpower, the extremely limited statistics, as well as the fact that the irradiation parameters (e.g., dose, dose rate, radiation field composition) are not controllable. These factors can limit the feasibility of both physics and biological experiments, which aim at investigating the basics of the radiation interaction with living matter.

Ground-based facilities can provide a variety of beam species in a broad energy range and thus can mimic the single radiation components found in space. The easier accessibility and extremely lower costs of ground-based tests compared to space-based experiments allow to carry out a diversity of studies, ranging from basics physics to biology and engineering, which can eventually help improving the health safety of space travels.

As we have seen above, two of the main limitations for ground-based experiments are: i) the different radiation field from the real space environment in composition, rate, and direction, and ii) the typical particle/dose rates in space (excluding high-fluxes SPEs), which cannot be reproduced as (if technically feasible) would require extremely long irradiation/exposure time.

Technological advances in accelerator facilities will help with point i). The latest upgrades at the NSRL of Brookhaven National Laboratory (US) have led to the development of advanced irradiation modes, which can reproduce both SPE and GCR spectra. The SPE simulator delivers protons with an energy between 50 and 150 MeV (from the SPE events occurred in 1972 and 1989). The GCR simulator is designed to deliver a mixed radiation field of different ions, from protons to Iron, at energies ranging from 100 to 1500 MeV/n (2500 MeV for protons) to reproduce the composition of cosmic rays. The ion species and energies can be varied from pulse to pulse, with a switch time below 1 min [18, 239]. An additional GCR simulator just started operating at GSI (Germany) (Schuy et al., 2020). It is based on a passive approach, where the mixed radiation field is generated by the interaction of ion beams with modulated fragmentators.

The particle dose rates observed in space are extremely difficult to achieve on ground. The main unfeasibility is to deliver prolonged exposures (days or weeks). This limitation mostly affects biological experiments, where the outcomes can be highly dependent on the dose rate.

An overview of the European accelerator facilities of interest for space application is reported in Table 2. Facilities fully dedicated to clinical applications as well as radiation facilities that deliver only gammas, electrons, and low-energy neutrons have not been taken into consideration in this table. Furthermore, in order to meet the requirements for space radiation research, facilities offering only low-energy ion beams, useful for the study of basic radiobiological mechanisms, have been excluded from the list.

8.2.2 Other useful sources (gamma, neutron, electron, and alpha)

As mentioned above, the space radiation environment is challenging to be reproduced on Earth because it involves chronic, prolonged exposure to mixed fields of ionizing radiation at dose rates lower than 1.8 mSv/day [7.5 10^{-2} mSv/h] [14]. It can be estimated that during a mission direct cellular damage from heavy ions results from about one-track traversal in any given cell and relatively few cells will have any track traversals at all.

Table 2 Summary of ions and energies available at European accelerator facilities. These data were collected within the project ERFNet (European Radiation Facilities Network) funded by ESA [240]

Particle	Maximum energy	Facility name Location/country
Neutron	800 MeV	**ISIS** (ChipIR) Oxfordshire/United Kingdom
Protons (Z = 1)	33 MeV	**GANIL** Caen/France
	80 MeV	**LNS—INFN** Catania/Italy
	190 MeV	**AGOR** **KVI-CART** Groningen/the Netherlands
	220 MeV	**HIT** Heidelberg/Germany
	225 MeV	**MIT** Marburg/Germany
	228 MeV	**Trento Proton Therapy Center—TIFPA** Trento/Italy
	230 MeV	**CNAO** Pavia/Italy
	230 MeV	**PTC** Dresden/Germany
	250 MeV	**PSI** Villigen/Switzerland
	800 MeV	**MedAustron** Wiener Neustadt/Austria
	1000 MeV	**GSI** (SIS18) Darmstadt/Germany
3-Helium (Z = 2)	120 MeV/u	**AGOR** **KVI-CART** Groningen/the Netherlands
	1000 MeV/u	**GSI** (SIS18) Darmstadt/Germany
4-Helium (Z = 2)	20 MeV/u	**GANIL** Caen/France
	80 MeV/u	**LNS—INFN** Catania/Italy
	90 MeV/u	**AGOR** **KVI-CART** Groningen/the Netherlands
	220 MeV/u	**HIT** Heidelberg/Germany
	1000 MeV/u	**GSI** (SIS18) Darmstadt/Germany
12-Carbon (Z = 6)	80 MeV/u	**LNS—INFN** Catania/Italy
	90 MeV/u	**AGOR** **KVI-CART** Groningen/the Netherlands
	95 MeV/u	**GANIL** Caen/France
	400 MeV/u	**CNAO** Pavia/Italy

Table 2 continued

Particle	Maximum energy	Facility name Location/country
	430 MeV/u	**HIT** Heidelberg/Germany
	430 MeV/u	**MIT** Marburg/Germany
	1000 MeV/u	**GSI** (SIS18) Darmstadt/Germany
16-Oxygen (Z = 8)	80 MeV/u	**LNS—INFN** Catania/Italy
	90 MeV/u	**AGOR** **KVI-CART** Groningen/the Netherlands
	95 MeV/u	**GANIL** Caen/France
	551 MeV/u	**HIT** Heidelberg/Germany
	1000 MeV/u	**GSI** (SIS18) Darmstadt/Germany
56-Iron (Z = 26)	1000 MeV/u	**GSI** (SIS18) Darmstadt/Germany
Other ions	https://www.lns.infn.it/it/acceleratori/fasci-disponibili.html	**LNS—INFN** Catania/Italy
	Full list available at https://www.ganil-spiral2.eu/scientists/ganil-spiral-2-facilities/accelerators/	**GANIL** Caen/France
	Full list available at http://www.rug.nl/kvi-cart/	**AGOR** **KVI-CART** Groningen/the Netherlands
	Full list available at https://www.gsi.de/en	**GSI** (SIS18) Darmstadt/Germany

In ground-based experiments, most of the HZE studies have been carried out under relatively high-dose-rate conditions where more than one track per cell is very probable. This issue, combined with other reasons related to the maximum total doses that an astronaut is likely to receive, raised the question whether experiments should be confined to the low-dose range where an average of one track per cell, or preferably much fewer, would apply. From an experimental design point of view, this requirement could add severe limitations to the measurements due to the difficulty in achieving the statistical resolution necessary to establish any dose effect relationships at all, even for fairly sensitive biological response systems. This issue might be mitigated only in part by carrying out experiments at sufficiently low dose rates or by sufficient dose fractionation, where full damage development leading to any effect from one track would be completed before a subsequent track occurs [235].

Long-term fractioned exposures are possible at NSRL, which has thus far demonstrated the capability of delivering several fractions per week for up to thirty days. This is an important advance, but the instantaneous dose rate per fraction, as well as the integrated dose rate compiled during the complete number of fractions, is still too high compared to what would be expected in space.

The same holds for the facilities listed in Table 3 which cannot currently offer dose rates low enough to mimic the actual environment in space.

Several facilities, although providing non-space relevant radiation, may be of some indirect interest for basic radiobiological studies when exploring low rate effects that cannot be studied with other means. These facilities use radioactive sources to grossly mimic the quality of high- or low-LET space radiation.

A ^{252}Cf neutron facility has been developed at the Colorado State University (CSU) to provide data for health risks resulting from exposures to high-LET radiation at dose rates and durations relevant for missions currently being envisioned by NASA. Neutrons from ^{252}Cf are not an analog to GCR generated neutrons (in the habitats), being of much lower energies; however, they do have a high-LET contribution that may mimic the distribution of LET from HZE in space. The CSU ^{252}Cf facility offers the advantage of

Table 3 Selected list of European low-dose/low-dose-rate facilities (in order of increasing dose rate). Most of them have been described in CONCERT Air[2] bullettins (https://cordis.europa.eu/project/id/662287/reporting)

Facility (AIR[2])	Location	Radiation source	Dose rate (mGy/h)	Biological samples
Libis	ISS Rome, Italy	Cs-137 (3 different sources)	$2{\cdot}10^{-3}$–$2{\cdot}10^{1}$	Cells and small animals (e.g., *Drosophila melanogaster*)
Micado'lab	IRSN Saint Paul Lez Durance, France	Cs-137	$5{\cdot}10^{-3}$–10^{2}	Model organisms in ecotoxicology (nematode, daphnid, zebrafish, plants)
Low-dose-rate facility	PHE London, UK	Cs-137	$5{\cdot}10^{-2}$–10^{2} (with lead shielding)	Cells, animals
Figaro	CERAD, NMBU Norway	Co-60	$4{\cdot}10^{-1}$ – $3{\cdot}10^{3}$	Cells, animals (small rodent, fish, amphibians, plants, GMO*)
SCRS-GIG	Główny Instytut Górnictwa Katowice, Poland	Photons (Cs-137; X-rays) Neutrons (Am-Be) Beta (Sr-90) Radon	γ-rays (collimated): $1{\cdot}10^{-3}$—$1.87{\cdot}10^{2}$ γ-rays (panoramic): $1.5{\cdot}10^{-1}$—1.7 X-rays (collimated:) up to $4{\cdot}10^{4}$ Neutrons (panoramic): $3{\cdot}10^{-2}$ Beta (collimated): 50—$3{\cdot}10^{3}$ Radon in air up to 10 kBq/m^3	Easily adaptable to expose living organisms (cell culture and small animals, plants) to different radiation types
Alpha particle irradiators	ISS Rome, Italy	Am-241; Cm-244	~$1.3{\cdot}10^{-1}$–$2{\cdot}10^{4}$	Cell monolayers

**GMO* genetically modified organisms

continuous, protracted, daily exposures to hundreds of animals at low dose rates (e.g., 1 mGy per day) for periods exceeding one year [241].

A number of low-dose-rate facilities are presently available in Europe to irradiate biological samples at dose rates below 10^{-1} mGy/h, a value that can be considered the maximum relevant for space. As shown in Table 3, most of them are based on gamma sources. The alpha particle irradiators can only be used for irradiating cell monolayers, due to their short range; the low-rate neutron source may permit high-LET in vivo and in vitro investigations.

Although it is clear that gamma rays, alpha or neutrons from radioactive sources have different track structures than GCR, they represent today the best compromise for ground-based radiobiological mechanistic studies at dose rates comparable to those present in space for low- and high-LET radiation.

Even if not directly related to studies on the mitigation of space radiation, it is nevertheless interesting to consider also underground facilities, such as the one at the INFN—Gran Sasso National Laboratories, Assergi, Italy (Air[2], Issue 3, December 2015). Other underground facilities in the world are mentioned in [242]. In such extreme environments, the dose rate contribution by directly ionizing cosmic rays and neutrons is negligible. Underground biology studies are not only relevant for challenging the linear no-threshold model currently assumed in radiation protection, but can also be useful for astrobiology and for mechanistic studies aimed to untangle the contribution of the two stressors: microgravity and radiation.

8.2.3 Studying combined radiation and microgravity effects

As given in Introduction, the space environment includes different hazards for human exploration (radiation, confinement, distance, microgravity, and hostile/closed environments), which have health risks and negative effects in multiple organ systems. Both microgravity and space radiation have been shown to provide various influences on human health, and these two factors might become a major issue for manned explorations.

To study these combined effects on ground, there are two major challenges related to the availability simulators for low dose rate and the possibility to combine during exposure, and not subsequently, space radiation and microgravity simulation with particular reference to partial gravity environments such as on Moon and Mars surfaces (1/3 g and 3/8 g).

Advanced ground-based systems for simulating gravity alterations have made it possible to study the response of living beings to altered gravity to prepare for experiments in space. Although a ballistic rocket, parabolic flight, or drop tower can produce a μg environment for free fall on the Earth, the disadvantages of these approaches are the limited time of exposing to μg, the additional hypergravity, and the lack of possibility to combine with radiation sources.

Table 4 Radiation measurements in relevant sites for human exploration

Location	Detector/mission	year	Dose equivalent rate (mSv/day)	References
ISS	Dostel	2016	0.647	[12]
ISS	Dostel	2019	0.731	[246]
ISS	ALTEA (*)	2012	0.55*	[29, 30, 247, 248]
Moon transit	HERA M42	2022	0.96–1.24	[192]
Moon surface	LND	2019	1.37 ± 0.25	[249]
Mars transit	MSL RAD	2012	1.84 ± 0.33	[14]
Mars surface	MSL RAD	2012/13	0.64 ± 0.12	[13]

(*) average over the three ISS directions, corrected for the proton efficiency.

To simulate μg on ground, the use of rotating devices such as the rotating wall vessel bioreactor (RWV: Synthecone, Houston, Texas, USA) and the random positioning machine (RPM: Dutch Space, the Netherlands) is commonly accepted as validating systems. These devices revolve the sample in an uninterrupted manner, opposing and balancing the direction of gravity and diminishing its impact, simulating reduced gravity; they might be used for cellular systems, plants, aquatic animals, or invertebrates. The major limitation in the use of this well-validated microgravity simulators is related to the need of interrupting revolutions amid irradiation, because the sample is susceptible to irradiation outside the incubator after or before rotation, or the dose flatness in the irradiation area is non-uniform if the sample is irradiated from outside a device such as an RPM. To deal with these limitations, researchers from Japan recently developed for in vitro experiments a simulator of the environments on the Moon and Mars with neutron irradiation and gravity change (SwiNG) using disposable closed cell culture chambers. The device simulates partial gravity using a centrifuge in a three-dimensional clinostat. Six samples are exposed at once to neutrons at a low dose rate (1 mGy/day) using Californium-252 in the center of the centrifuge [243, 244]. The need of complex animal models or mammalians imposes the use of whole-body simulation studies such as mice subjected to prolonged hindlimb unloading or tail suspended, with concurred acute or chronic radiation exposures that might affect different organ and systems such as the immune function [245].

8.3 Space analogs (ISS, DSH, Moon, etc.)

Today the only space analogs are the LEO Stations, such as the International Space Station (ISS). In the near future we might have, with severe limitations about use and logistics, also orbiting lunar habitats, and eventually the Moon base. Recent radiation measurements in these sites are reported in Table 4.

These values are measured in specific periods of the solar cycle, which modulate the integrated dose rate up to about a factor 2 [246]. The maximum of the solar activity (corresponding to a minimum GCR dose contribution) has been reached around 2014–2015, while the minima were at about 2009–2010 and 2020–2021. We just left the new maximum (2024).

8.4 Databases and computational framework

8.4.1 Standardized reference databases

The characterization of the space radiation environment and perspective risk assessment largely benefit from the availability of standardized computational platforms and reference databases that are routinely used for these purposes.

SPENVIS (Space Environment Information System) (https://www.spenvis.oma.be/ see, e.g., [250, 251]) allows users to work with a mission-oriented interface that integrates several environmental models, shield transport solvers, and dose estimation tools for preliminary design studies.

OLTARIS (https://oltaris.nasa.gov/), the NASA On-Line Tool for the Assessment of Radiation in Space [252] allows users to work within a detailed physics and geometry framework, combining state-of-the-art radiation transport codes with parametric or CAD-based vehicle representations to compute organ-level dose and risk metrics consistent with NASA standards.

8.4.2 GeneLab

Within NASA OSDR (Open Science Data Repository) initiative, NASA GeneLab (https://visualization.genelab.nasa.gov/data/) is an open platform to facilitate the study of biological responses to the space environment through multiomics datasets [253]. It hosts and curates genomics, transcriptomics, proteomics, and metabolomics data from experiments conducted on cells, model organisms, and human samples in spaceflight and ground-based analogs. The GeneLab Data System (GLDS) provides standardized, high-quality datasets, while the GeneLab Analysis Platform offers tools for integrative computational analyses, enabling researchers to explore the effects of microgravity, space radiation, and other environmental stressors on biological systems. By linking exposure information to molecular responses, GeneLab complements environmental tools (such as SPENVIS and OLTARIS), supporting the development of predictive models for astronaut health and space biology research.

8.4.3 RadLab

RadLab is an open radiation data repository and analysis platform within the same NASA OSDR (https://visualization.osdr.nasa.gov/radlab/gui/overview/). Developed in 2023 and online since 2024, it features a database with a user-friendly data retrieval system, along with a visualization and analysis toolkit. Its graphical user interface (GUI) allows for fast dataset browsing, while an application programming interface (API) enables users to write custom code for advanced and specialized analyses.

RadLab provides open, centralized access to radiation data relevant to human spaceflight. It includes data from numerous detectors aboard the ISS, as well as from detectors in orbit around the Moon, Mars, and the Sun. New data is regularly added to the database. The platform facilitates easy intercomparison between datasets from different detectors, improving our understanding of the radiation environment and supporting space radiobiologists in utilizing space radiation data more effectively [254].

9 Selected relevant research programs

The following highlights e few broad research programs that address many of the issues discussed in this paper. While being by no means exhaustive, this selection illustrates ongoing international collaborative efforts aimed at enabling human exploration of deep space.

9.1 European research activity programs: IBER

The European Space Agency has a wide scientific program named "Science in Space Environment" (SciSpacE) that includes scientific activities on research platforms such as ground-based space analogs (e.g., bedrest studies, research on Antarctic stations, radiation facilities, drop tower, sounding rockets, parabolic flights), as well as a research program onboard the ISS. In this framework, ESA started in 2008 the IBER (Investigating the Biological Effect of space Radiation) scientific program to foster investigations into biological effects of space radiation using the accelerator facilities. As mentioned, ground-based experiments at accelerators can contribute to improve risk assessments or study countermeasures on cells or animals to allow a safe and stable human exploration of, e.g., the Moon or Mars with acceptable risk from exposure to space radiation. Four major themes for relevant research have been identified within the IBER program: (i) prediction of risk for late effects: carcinogenesis, tissue degenerative effects, hereditary effects, (ii) prediction of risk for acute effects: prodromal syndrome, bone marrow, intestinal epithelium, skin, (iii) combined effects of cosmic radiation and other stressors in the deep space and planetary environments, and (iv) countermeasures. Such a scientific program can be nicely mapped on some of activities discussed in this paper.

The IBER program includes the implementation of experiments through two different access to beam time. The first option goes through dedicated Announcements of Opportunity at the GSI laboratory, three of which has been announced and exploited since 2009 to 2019. A second modality for the IBER program was open since 2018: Beam time can also be requested via a Continuously Open Research Announcement (CORA-IBER) at the following facilities: GANIL (Caen, FR), AGOR KVI-CART (Groningen, NL), HIT (Heidelberg, DE), UPTD (Dresden, DE), and Trento Proton Therapy Center—TIFPA (Trento, IT).

The IBER beam time assignment goes through a Program Advisory Committee (PAC) that not only evaluates the experiment proposals before granting the beam time, but also review the obtained results.

In principle, any future wide scientific program for space exploration, as that one we want to depict in this paper, can benefit from a close synergy with the IBER program. In particular, the facilities that are already participating to IBER could be easily included in a coordinated effort.

9.2 ISS4Mars as a synergic opportunity

Recently a program to strategically use the ISS to prepare for human mission to Mars, has been discussed among the ISS international partnership. The fundamental question that was addressed is *what research approaches would be beneficial on ISS but were not being proposed because they did not fit in the current utilization boundaries?* The ISS4Mars concept and name has been first presented in 2015 at the "Human in Space" symposium in Prague [255] and recently accepted worldwide through a 1-year-long virtual workshop that discussed in detail how this ISS utilization could enhance and exploit the works on critical hazards and countermeasures focusing on all the 5 hazards (see Introduction) for spaceflight. The workshop brought together participants from nine international space agencies, research managers, discipline experts, technology developers. A brief account of the workshop and a full description of the ISS4Mars initiative can be found in [256, 257].

Now the coordination of the implementation planning for ISS4Mars has been transitioned to the Multilateral Human Research Panel for Exploration (MHRPE), which already works on coordinating human research on the International Space Station. *ISS4Mars activities will be coordinated with international, science, engineering, ops, crew, transportation providers, and safety stakeholders and will be scheduled so that they are compatible with ISS operations (e.g., visiting vehicle, EVAs, other research activities,* etc.*)* (from [256]).

All issues discussed in this document fit well into the ISS4Mars envelope. The continuous proactive participation of space agencies is envisioned in order to exploit this new and exciting opportunity.

10 Concluding remarks

The effects of space radiation on astronauts' health are considered among the main risks for human space exploration. The pervasive interactions between ionizing radiation and all facets of human spaceflight, spanning from cells, tissues, and organs to life support systems, and microbial habitats highlight the complexity and significance of its impact. These effects, both direct and indirect, pose a substantial threat to astronaut health and may threaten the success of long-duration or deep space missions.

Characterizing the radiation environment where astronauts live and understanding the effects of radiation on their health are critical steps toward developing effective countermeasures to reduce radiation-related risks. Efforts in radiation measurements, modeling, radiobiology, and space physiology must be strategically aligned to enhance the performance and reliability of these protective strategies. We examined the unique aspects of space radiation and the current state of knowledge of its effects on humans and life support systems. We also discussed the effectiveness of existing countermeasures and proposed directions for future development, from specific research topics to a broader debate about available approaches and tools. The success of these efforts lies in the extent to which these efforts improve the effectiveness of radiation countermeasures, which must be rigorously evaluated within a quantitative risk assessment model.

Physical passive countermeasures have approached near-optimal performance. Commonly used space materials such as polyethylene, considered a benchmark for shielding, achieve effectiveness within a factor of 2 of the theoretical maximum. Other materials have shown comparable shielding performance while offering additional benefits (e.g., impact resistance), albeit with some usability drawbacks. Active countermeasure approaches still require technological breakthroughs to be viable for space exploration. These are promising, and we ask for further research. Most importantly, we emphasize a synergistic approach, combining physical passive and active countermeasures with pharmaceutical, dietary, physiological, and operational strategies. This approach should be tailored to each astronaut's mission profile, possibly also including genetic information. Recent rapid and relevant advances in technologies often referred to as "AI" may provide the tools needed to make this personalized, integrated countermeasure strategy feasible.

A more detailed understanding of radiation-induced damage and dysfunction within the human body, an area that still requires significant advancement, is essential for developing targeted countermeasures. These must go beyond simply reducing absorbed or biologically weighted doses, as is the case with conventional physical shielding, and lead to targeted countermeasures. Pharmacological interventions and specialized diets that synergize with the body's natural defense mechanisms to enhance radiation resilience are currently under development and warrant further advancement. Hibernation appears to be a particularly promising technique, especially for long-duration missions. Comprehensive studies assessing radiation risk reduction during hibernation and the feasibility of its extension to humans are essential, as positive findings will permit to include hibernation in the AI-managed synergistic "countermeasure package" mentioned earlier.

Plants radiation resilience is of interest too, also due to their multiple roles in food production and resource regeneration systems. However, their full radiation response profile must still be investigated, as relevant non-monotonic behaviors could be significant for the most effective use of plants during deep space missions.

Finally, two general considerations. With the astronaut population now exceeding 800 individuals, early "PARA-epidemiological" studies are emerging. These show no current evidence of space radiation-induced illnesses (excluding cataracts). However, this finding has by no means any statistical significance ("PARA" is here intentionally emphasized), and furthermore, except for a small cohort who traveled to the Moon, astronauts have all remained within Earth's magnetic shield protection. This last consideration is strongly mitigated by the similarity in dose equivalents measured in low Earth orbit (LEO) and on the Mars surface, and by the small difference with deep space (less than a factor of three). This makes LEO a good platform for building an epidemiological oriented database for galactic cosmic rays (GCR). This is however not true for solar particle events (SPEs), where the protective effect of Earth's magnetic field increases to 1–3 orders of magnitude. Thus, we remain largely unaware of how SPEs affect humans in deep space, especially when factoring in possible interactions with microgravity. This specific problem must also be addressed.

The second point relates to the ongoing effort to define dose limits for astronauts, thresholds that must be respected using proper radiation countermeasures. Despite differences among space agencies and changing limits over decades, these limits are primarily being defined in the context of Mars missions. As future deep space missions envision prolonged human presence in space, the ultimate goal of radiation protection should be to adopt an integrated approach to place astronauts in the best possible conditions to develop resilience to space radiation. This strategy should combine countermeasures for habitat design and operations, with biological countermeasures, including pharmaceutical, dietary, and physiological interventions, potentially tailored through personalized approaches that incorporate genetic information. Given the substantial room for advancement in these latter, we envisage and encourage a greater emphasis on their development in future research efforts.

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