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Opinion/Position paper

Research plans in Europe for radiation health hazard assessment in exploratory space missions

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ABSTRACT

The European Space Agency (ESA) is currently expanding its efforts in identifying requirements and promoting research towards optimizing radiation protection of astronauts. Space agencies use common limits for tissue (deterministic) effects on the International Space Station. However, the agencies have in place different career radiation exposure limits (for stochastic effects) for astronauts in low-Earth orbit missions. Moreover, no specific limits for interplanetary missions are issued. Harmonization of risk models and dose limits for exploratory-class missions are now operational priorities, in view of the short-term plans for international exploratory-class human missions. The purpose of this paper is to report on the activity of the ESA Topical Team on space radiation research, whose task was to identify the most pertinent research requirements for improved space radiation protection and to develop a European space radiation risk model, to contribute to the efforts to reach international consensus on dose limits for deep space. The Topical Team recommended ESA to promote the development of a space radiation risk model based on European-specific expertise in: transport codes, radiobiological modelling, risk assessment, and uncertainty analysis. The model should provide cancer and non-cancer radiation risks for crews implementing exploratory missions. ESA should then support the International Commission on Radiological Protection to harmonize international models and dose limits in deep space, and guarantee continuous support in Europe for accelerator-based research configured to improve the models and develop risk mitigation strategies.

1. Introduction

Space radiation is generally recognized as a major health risk for astronauts (Chancellor et al., 2014). With the impending Deep Space Gateway and plans for moon and Mars exploration involving international crews (ISECG, 2013), an international space radiological protection strategy has now a high priority.

For the International Space Station (ISS) that operates since 1998 in Low Earth Orbit (LEO), all participating partner agencies (NASA for USA, FSA for the Russian Federation, CSA for Canada, ESA for Europe and JAXA for Japan) work on the basis of a common radiation protection framework mutually agreed upon for all ISS Crew (Multilateral Medical Operations Panel, 2016). Each planned exposure is executed in adherence to the As Low As Reasonably Achievable (ALARA) principle of radiological protection (ICRP, 2007). Exposures to ionizing radiation are managed by a combination of exposure limitation and optimization practices that minimize risks. Despite the uniform limits to prevent from tissue (deterministic) effects (Straube et al.,

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Table 1
Career effective dose limits (in Sv) for astronauts in LEO recommended by different National Space Agency. Values for NASA and JAXA refer to a 1 year mission, and are based on a 3% maximum REID caused by cancer within 95% confidence limits. Values from McKenna-Lawlor et al. (2014).

Space agency	Age at exposure (years)				
	Gender	30	40	50	60
NASA	M	0.78	0.88	1.00	1.17
	F	0.60	0.70	0.82	0.98
JAXA	M	0.60	1.00	1.20	1.20
	F	0.60	0.90	1.10	1.10
ESA	M/F	1.00	1.00	1.00	1.00
RSA	M/F	1.00	1.00	1.00	1.00
CSA	M/F	1.00	1.00	1.00	1.00

2010), not every agency did adopt and express limits for the entire career (targeting stochastic effects) of its astronauts identically (Table 1). In fact, ESA and CSA use a single career dose limit of 1 Sv for all gender and ages, based on a recommendation from the International Commission on Radiological Protection (ICRP) (ICRP, 1991). The Russian Space Agency (RSA) use a specific model (Petrov, 2002; Petrov et al., 1981; Shafirkin et al., 2002) that takes into account the whole space environment, but the acceptable risk in the model also corresponds to a career dose limit of 1 Sv in LEO. NASA (National Research Council, 2012) and JAXA apply different limits based on their national space radiation risk assessment models (McKenna-Lawlor et al., 2014). For any mission, NASA calculates the acceptable number of safe days in deep space as the maximum number of days resulting in a 3% risk of exposure-induced death (REID) at the upper 95% confidence interval (Cucinotta et al., 2013a). REID is limited to fatal cancers. NASA policy only allows missions which do not lead to exceeding the number of safe days in space. The requirement of a 95% confidence level depends on the scientific data, and may be modified according to new results coming from research. Cumulative exposures of ISS crewmembers to all sources of ionizing radiation are limited as a consensus dose limit over 30 day and 1-year time intervals in order to prevent unacceptable deterministic effects to the blood-forming organs (BFO). The “blood-forming organs” refers to bone marrow, spleen, and lymphatic tissues. Active (red) bone marrow is a surrogate for BFO (Multilateral Medical Operations Panel, 2016). No agency has issued any specific recommendation for limits in Beyond Low Earth Orbit (BLEO) missions (McKenna-Lawlor, 2016; NCRP, 2006).

ESA is currently strengthening its initiatives in identifying requirements and promoting research towards optimizing radiation protection for astronauts. ESA supports the development of common risk limits and risk estimations or, in the absence of consensus, the development of ESA methodologies for the purpose of human exploration of space. In support of the above, ESA put in place a Topical Team (TT) to provide expert advice on relevant research to be undertaken. This TT, supported by the Radiation Protection Initiative (RPI) of the Directorate of Human and Robotic Exploration, forms a forum for ESA and non-ESA experts from space-science, biology, epidemiology, medicine and physics to identify the most pertinent research requirements for improved space radiation protection. As part of this initiative, the TT performed a detailed survey on available “Ground-based facilities and models for space radiation research” (Durante et al., 2017) which contribute to research on risk assessment for exploration-class missions. Similarly, the RPI conducted a multilateral summit (see Section 2) on Ionizing Radiation and Human Health Risks in the frame of its medical and operational charge. The purpose of this paper is to report in detail on future European research directions, required efforts and recommendation for optimizing a space radiological protection that were identified by the TT.

The research requirements identified by the TT broadly fall into three main research areas, namely: improving characterizations of ionizing radiation in space; increasing knowledge on the potential detrimental health effects of space radiation exposure; and better characterizing the associated risks to astronauts. The relatively short term aim of providing an optimized approach to guide the occupational radiation health risk assessment for astronauts, in terms of cancer and non-cancer health effects, will enable improvements in effective risk communication between space agency medical operations and astronauts and aid decision-making relevant to human space missions. The TT, therefore recommended ESA to promote the development of a European Space Radiation Risk Model (ESRRM) based on innovations in risk assessment and uncertainty analysis. Further longer-term improvements to the new ESRRM could be based on developments of innovative radiation transport codes, refined RBE models and results from nanodosimetry experiments. The ESRRM should be developed to provide cancer and non-cancer radiation risks for crews in realistic BLEO missions. A further important TT recommendation was for ESA to support ICRP in future efforts to harmonize international models and dose limits in BLEO in line with RPI and the International Systems Maturation Team – Radiation (ISMT-RAD). The next section describes the ESA initiatives in optimizing radiation protection of astronauts and the subsequent three main sections describe in detail the research requirements in each of these ESA identified main research areas.

2. The current initiatives of ESA in optimizing radiation protection for astronauts

ESA's initiatives are partly carried out in collaboration with the ISMT-RAD, which is a coordinated activity of ESA with other partner national space agencies (NASA, RSA, JAXA, CSA) to provide radiation protection for their crewmembers (Straube et al., 2010). The ISMT-RAD experts have agreed to compare risk estimation methods of the different agencies to reach a consensus on dose limits for multilateral human space exploration. In December 2017, the ISMT-RAD convened at the European Astronaut Centre in Cologne (Germany), to discuss the possibility of adopting an international consensus framework for human-risk modelling and limits on astronaut exposures to ionizing radiation for exploration-class space missions. Examples of such missions include a cis-lunar (e.g., Deep Space Gateway), long-duration presence in a “free-space”, habitat located outside the influence of the Earth's geomagnetic field, or a mission to a planetary surface such as Mars. The outcome of this meeting was that ISMT-RAD group contacted the ICRP explicitly to request direct recommendations and guidance from the ICRP on the following critical topics identified at the meeting:

Non-cancer tissue effects of radiation. These include potential radiation effects on the central nervous system (CNS) during spaceflight (Jandial et al., 2018; Roberts et al., 2017), such as performance decrement or behavioral responses that may impact crew health and mission success. A review (including the NASA CNS limits) of available evidence and recommendations on additional research are required and currently under way from the National Council of Radiological Protection (NCRP) (NCRP, 2016).

1. Inclusion of cardiovascular disease. Recent evidence points to a substantial late radiation-induced risk, but the existence of a threshold, although possible, is not proven (Hughson et al., 2017). Recommendations for the inclusion of cardiovascular disease as a detrimental health outcome are required.
2. Lens opacification (Chylack et al., 2012). Recommendations on the occurrence and latency of lens opacification during a long duration exploration-class mission that extends up to 3-years are required.
3. A common risk assessment framework and exposure limits. Recommendations for establishing a common risk assessment framework and exposure limits for cancer risks for exploration-class human spaceflight missions are required. Significant contributors to uncertainty include radiation quality factors, low dose and dose rate effects and transfer of risk from cell and animal studies and exposed

human populations such as the atomic bomb survivors (Cucinotta, 2015; Durante and Cucinotta, 2008).

4. Risk-model evaluation. An evaluation of results from a selection of space agency-provided risk models for defined reference missions is required (ISMT-RAD may also provide an independent evaluation).

The ISMT-RAD identified a substantial overlap between their needs for safe space exploration and the following stated ICRP research priorities:

- Effects of protracted exposures and low dose rates
- Mechanisms of low-dose effects and dose-response models that take account of them
- Organ-specific, and age and gender differences in, sensitivity to cancer induction
- The role of genetic differences in determining individual sensitivity
- Effects other than cancer and genetic effects and their contribution to health detriment
- Relating exposures, doses, and effects on population viability for nonhuman biota
- Reliability of dose assessments
- Dosimetry and protection methods in medicine
- Ethical and social dimensions of the system of radiological protection
- Mechanisms for interaction with stakeholders

ESA supports the development of common ISMT-RAD risk limits and risk estimations or, in the absence of international consensus, the development of ESA methodologies for the purpose of human exploration of space.

3. Improving characterizations of ionizing radiation in space

3.1. Measurements

There is a need for continued measurements of the energy, particle and energy deposit spectra using spectrometers on satellites, the International Space Station (ISS) and arctic high latitude balloons. These inputs are needed to validate and update models. With a benchmarked model it becomes possible to adequately calibrate the dosimeters and use the data properly. Throughout cross calibrations among different detectors (Berger et al., 2017; Narici et al., 2017a,b) is needed to improve model validations. Furthermore, measuring the radiation environment inside space habitats (i.e. the ISS (Narici et al., 2017a,b; Zeitlin et al., 2019)) helps to improve understanding of the variability of a radiation field due to complex and possibly rapidly changing shielding, proper for the inside of a habitat. It has been envisaged that to properly fulfil these tasks, novel detectors, able to provide detailed information on the radiation quality in increasingly smaller packages, will be needed.

3.2. Environmental models

Galactic Cosmic ray (GCR) environmental models are developed to provide a reliable input for radiation transport models. GCR models currently in use are the Badhwar O'Neill 2014 (O'Neill et al., 2015), DLR (Matthiä et al., 2013), and Nymmik (Nymmik et al., 1996) models. These models are validated by measurements from balloon and satellite measurements, such as measurements from ACE/CHRIS. Model uncertainties are currently in the range of 20% and will be propagated into effective dose calculation behind shielding. A further source of uncertainty arises from the requirement to convert the effective doses into the organ doses that are required for input into the health risk assessment models. Therefore, continued measurements of the spectra of the cosmic ray components are necessary to benchmark these models and improve their reliability.

3.3. Transport codes

Any space radiation risk model, based on fundamental physics and radiobiology, must start with the primary ionizing events in the human cells. To estimate the biological damage caused by the ionizing events, information about the ionization density along the particle tracks must be known. Accurate estimations of the radicals, produced by primary space radiation, must also be available. To achieve this information, we first need to be able to calculate fluence, angular and energy deposition distributions of both primary and secondary particles, including projectile and target fragments, neutrons, etc., produced when the primary cosmic ray particles react with the spacecraft and the human body (ICRP, 2013). To be able to estimate the radiation risks to humans inside complex geometries, nuclear reaction models and space radiation transport codes are therefore needed (Sihver, 2008). In all particle and heavy ion transport codes, the probability function that a projectile particle will collide with a nucleus within a certain distance x in the medium depends on the total reaction cross sections, which also scale the calculated partial fragmentation cross sections (Norbury et al., 2012). It is therefore crucial that accurate total reaction cross section models are used in the transport calculations. Most transport codes use different semi-empirical total reaction models which are not sufficiently benchmarked for all systems of importance for space radiation due to a lack of experimental data (Sihver et al., 2012).

A transport code which uses a simplified, numerically integral, version of Boltzmann's transport equation, is called a deterministic code. The Boltzmann equation calculates the mean number of particles as a function of the phase-space coordinates. Different deterministic computer codes are based on different approximations to the full Boltzmann equation and/or on different models for the quantities which are considered to be relevant for the transport calculation (Durante and Cucinotta, 2011). Deterministic codes are fast since the coefficients used in the Boltzmann equation represent very simple one-particle quantities, and all correlations are neglected. Therefore, the deterministic formulation does not elaborate a large amount of information as in the Monte Carlo (MC) based event generators described below. One dimensional (1D) deterministic ray tracing models are very fast, but do not consider out-off beam scattering or lateral leakage. The calculated results can therefore be misleading. An example of a deterministic space radiation code is HZETRN (Wilson et al., 1997), used by NASA. HZETRN employs numerical solutions to the time-independent, linear Boltzmann equation. It utilizes the continuous slowing down approximation and a semi-inclusive/semi-empirical abrasion-ablation model for the nuclear fragmentation cross sections. HZETRN was originally 1D, but has been expanded to three dimensions (3D) (Wilson et al., 2014). In Europe, the deterministic code TRiP98 is used for heavy ion therapy in clinics (Krämer and Durante, 2010), and would be the best candidate to become a European deterministic code for fast dose estimation. Another approach is to calculate probability density functions by using stochastic MC techniques (Truscott et al., 2000), which would preserve information concerning correlations between different particles. However, with most of the MC codes one can only obtain the mean value of one-body observables in phase space, e.g., heat, flux, and dose.

In Table 2, some major 3D MC radiation transport codes are tabulated. The first dynamic step of the nuclear reaction, leading to the fragmentation cross sections of importance for space radiation, are most often calculated with different versions of exclusive Intranuclear-Cascade (INC) and Quantum Molecular Dynamics (QMD) models in MC codes (Durante and Cucinotta, 2011). The QMD model can treat a nuclear reaction in a semi-classical many-body framework and describe all correlations among the ejects. On the other hand, the INC models describe a nuclear reaction by sequential two-body collisions between nucleons in a fixed target mean field. The second, statistical, de-excitation step of the reaction, is calculated using different evaporation models. In Europe, GEANT4 (Agostinelli et al., 2003), FLUKA

Table 2
Examples of some of the major MC particle transport codes.

Name	Developer	Application	Language	Features
MCNP (X,5,6)	LANL	Nuc. Energy, Nuc. Physics	FORTRAN	World standard of nuclear energy High reliability, Criticality
GEANT4	CERN etc.	High En. Physics, Radiology, Astronomy	*C++*	Object-oriented, Platform to integrate models and tools developed all over the world, applied in magnetic and mass shielding calculations (see eg. Planetocosmos), space science
FLUKA	CERN, INFN	High En. Physics, Accelerator, Radiology, Astronomy	FORTRAN	Applied to accelerator shielding design, radio therapy, space science
EGS	KEK, SLAC	Radiology	FORTRAN	EM cascade code Applied to mainly radiology
SuperMC	FDS	Fusion, Radiology	*C++*	Developed for ITER High CAD-affinity, Visualization
PHITS	JAEA, RIST, KEK	Accelerator, Radiology, Astronomy	FORTRAN	Easy start-up Applied to accelerator design, radiology, space science
SHIELD-HIT	INR	Accelerator, Radiology, Astronomy	FORTRAN	Applied to accelerator design, radiology, space science

(Battistoni, 2008), and PHITS (Sato et al., 2018) are the three major multi-purpose three-dimensional Monte Carlo particle and heavy ion transport codes. Since the heavier ions in the GCR will break up to form lighter particles when penetrating the shielding of a spacecraft, and the human body, the production cross sections for light target and projectile fragments are of great importance. However, when comparing the simulated results from different transport codes, it has been shown that there are still large uncertainties in their cross sections (Giraudo et al., 2018; Matthiä et al., 2016). All models share a deficiency in the knowledge of the fundamental light fragment and neutron production cross sections that are critical to understanding the consequences of GCR transmission through matter (shielding, spacecraft components, and human tissue). There is in addition the need to identify the largest uncertainties associated with calculating the transport of space radiation through thick shielding as is the case in space mission applications.

To be able to correctly calculate the first physical and chemical steps in the event chain leading to DNA and cell damage, in a space radiation risk model, calculations of particle track structure and energy deposition distributions in 3D are needed (Bernal et al., 2013). This requires 3D MC simulations with conservation of energy and momentum event-by-event, or analytical functions based on event-by-event calculations. Monte Carlo codes provide a detailed treatment of the three-dimensional transport of neutral particles and ions, simulating the continuous distribution of energies and angles of scattered particles from available double-differential scattering cross sections.

3.4. Track structure models

Determination of the cancer risk incurred from the exposure of space radiation is an important requirement for the success of long-term space missions. After the various components of space radiation have been determined, they have to be properly weighted according to their contribution to cancer induction relative to the induction rates from low ionizing radiation. Currently, quality factors or relative biological effectiveness factors (RBE) for cancer induction are used for the different radiation qualities (ICRP, 2007, 2003). Typically, these quality factors are defined by national and international commissions based on existing radiobiological data and presumed knowledge of the ionization density distribution of the radiation field at a given point of interest.

The set of RBE values used in the NASA model (Cucinotta et al., 2013a,b) is different from the values recommended by ICRP (ICRP, 2007), and they are tumor-specific, owing to the experimental observation that the RBE changes for different tumor types (Weil et al., 2009). The RBE values are used in an amorphous track structure model (Katz et al., 1996), where the radial dose for different heavy ions is calculated and average values are used. Amorphous track structure models are also used in Europe for heavy ion therapy (Grün et al., 2012), where the primary endpoint is cell killing. Extension of the local effect model (LEM) to other endpoints, such as cancer (Eley et al., 2016), is possible and may result in a European approach to the RBE calculation for space radiation.

3.5. Micro- and nano-dosimetry

Another option for evaluating and monitoring quality factors for space radiation exposure is the use of very compact microdosimeters to monitor space radiation quality. From the spectra recorded by the microdosimeters, the mean dose weighted lineal energy and average quality factor can be determined using the protocol outlined in ICRU report 36 (Booz et al., 1983). Microdosimetry records stochastic energy deposition events in micrometer volumes and one assigns quality factors to components of the lineal energy spectrum. However, a quality factor based on the frequency of critical DNA damage events at the nm-scale would be more realistic. Therefore, nanodosimetry, which records individual ionizations occurring in simulated DNA segments, can be used to indirectly quantify DNA damage relevant to late effects. This approach may be more directly related to cancer initiating events. However, additional radiobiological research correlating nanodosimetry data with biological end-points such as mutations and cancer induction will be needed to confirm this view. In fact, radiation seems to play an important role in promoting carcinogenesis especially in adults, and this inflammation-mediated mechanism is quite distinct form that of DNA damage alone (Cucinotta and Durante, 2006; Shuryak et al., 2010).

Several approaches have demonstrated the usefulness of nanodosimetry detectors (Grosswendt, 2005). However, the current technology has its limitations, foremost its lack of portability due to the need of sophisticated pumping and gas systems and its slow data acquisition time when sampling from a single sensitive volume. If the realm of nanodosimetry is to be investigated further, in particular for applications in space radiation protection and monitoring, an improved nanodosimeter is required that can be deployed on spacecraft. For this, the basic concept of the configuration of current nanodosimetry apparatus may need to be revisited (Schulte et al., 2008).

The approach of nanodosimetry based quality factors has also other limitations. For example, it is not clear which nanodosimetric quantities shall be used to quantify DNA double strand breaks (DSBs). Current nanodosimeters do not give any information on the regional association of complex DSBs. It could be that a realistic quality factor can be only obtained by a combination of a nanodosimetric quantity with a model describing chromosomal radiation interaction (Schneider et al., 2018).

In summary, nanodosimetric data yield meaningful quality factors for space radiation protection, which are based on a biological endpoint, namely the number of complex DSBs. The advantage of nanodosimetry is that it does not require the identification of individual particles in a complex radiation field at the same time as it provides information about the ionization density on a DNA scale along the particle tracks. The practical application of nanodosimetry in space

radiation protection requires further technical development, in particular, of compact nanodosimeters and of biological verification studies (Schulte et al., 2008).

4. Increasing direct knowledge about the potential detrimental health effects of space radiation exposure

4.1. Missing biology for risk assessment

It has been pointed out many times that the main contributor to uncertainty in space radiation risk comes from the biological effects of cosmic radiation (Durante and Cucinotta, 2008). 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 (Durante and Kronenberg, 2005). NASA has recognized long ago the necessity of funding research in this direction, and this commitment led to the construction of the NASA Space Radiation Laboratory (NSRL) (La Tessa et al., 2016) at the Brookhaven National Laboratory in Upton (NY) and to fund independent US research groups to perform space-relevant radiobiological research at NSRL (Schimmerling, 2016, 2003).

ESA has followed the same direction, first funding a preliminary study on Investigation of Biological Effects of radiation (IBER) in 2008 (Durante et al., 2007) and then implementing a research program at the SIS18 accelerator of the GSI Helmholtz Center in Darmstadt (Durante et al., 2010). ESA also supported a TT on space radiation to provide recommendations on space radiation research. Recently the TT has re-evaluated the IBER report (Durante et al., 2017), also considering the EU THESEUS roadmap (THESEUS, 2014) published in 2014 and the 2016 ESA roadmap (ESA, 2016) for future research. The TT review encompassed the previous IBER activity with the ESA and THESEUS roadmap, as well as with the NASA Human Research Roadmap (NASA, 2015) and the MELODI (EU Multidisciplinary Low Dose Initiative, 2018; Kreuzer et al., 2017) low-dose initiative in Europe to identify the main issues that would most benefit European team expertise and funded projects. In Table 3 the IBER research priorities are shown in correspondence with NASA's roadmap gaps. While the US will support the Space Radiation Health Program at NSRL, ESA will continue supporting IBER at GSI and the five European heavy-ion infrastructures via a continuously-open research announcement (CORA) for ground-based facilities (GBF). The new facility FAIR (Durante et al., 2019), currently under construction in Darmstadt, will start operations in 2025 with a strong program in applied nuclear sciences (Durante et al., 2019a,b). According to an ESA study led by the Fraunhofer Institute (Metzger et al., 2016), FAIR will become the leading GCR simulator worldwide because of the very high energy (around 10 GeV/n) achievable for heavy ions. ESA has signed in March 2018 a Memorandum of Understanding with FAIR for future applications of FAIR in space radiation research.

4.2. Considerations required for developing an international occupational cohort study

Long-term health risk assessment (HRA) approaches include building an international occupational cohort study of astronauts. This would involve preparing the European epidemiological data in a form that is suitable for eventually combining into such a study. There are already many radiation-epidemiological studies available from occupational groups e.g., airline pilots (Hammer et al., 2012) and uranium miners (Walsh et al., 2015), that have provided very useful quantifications of the occupational radiation risks arising from many detrimental health effects such as cancer. Cohort studies (Grimes and Schulz, 2002) are usually considered to be the gold-standard amongst the various types of studies possible. Some statistics pertinent to the potential development of an international astronaut cohort are as follows (data from www.worldspaceflight.com). World-wide, approximately 560 astronauts have flown to date. The total time in space has been currently estimated at 141 person-years. Assuming an average age at exposure of 40 years and epidemiological follow-up to age 80 years, the estimated person-years at risk for the currently exposed astronauts would be 22,400 (i.e., 560 (80–40)). The major contributors of data to such an international cohort study would be the USA, Russia and Europe with 348, 116 and 46 flown astronauts respectively. A potential first-step in international cohort development would be for the non-USA space agencies, including ESA, to already start to ensure that their archives for health effects and exposure history data (for flown, ground and in-training astronauts) are stored in a way that is compatible with the largest NASA databank.

The IBER research program aims at filling the gaps in knowledge concerning the effects of space radiation on astronauts. A major issue is the effectiveness of GCR at low doses for causing carcinogenesis and late tissue degenerative effects (especially to the CNS and the cardiovascular system). Another point is the current lack of information on the dependency for acute effects of particle charge and energy and dose rate. Do low dose effects follow the same biological pathways known to be involved in disease progression for high doses? Knowledge of the health risks associated with exposures to ionizing radiation above 100 mGy is quite well established, while lower dose risks are inferred from higher level exposure information (ICRP, 2007). Uncertainties regarding these health risks need to be clarified with the help of mechanistic studies. The EU-funded network of excellence DOREMI (2010–2016) has shown that low dose and low dose-rate effects are the result of complex network responses including: genetic, epigenetic, metabolic and immunological regulation. Evidence is available for the existence of nonlinear biological responses in the low and medium dose range as well as effects other than that of classical DNA damage (Averbeck et al., 2018). It should be also noted that there is a lack of information concerning longer-term outcomes in the area of adverse behavioral health (NCRP, 2016) and cardiovascular events (Hughson et al., 2017). Interaction across risk domains is the biggest challenge at all.

5. Potential improvements in the health risk assessment for astronauts

This section first gives details of the main considerations required for developing a European risk model in terms of which time integrated risk measures may be suitable. Then the main uncertainties that need to be considered in the development of a European risk model are illustrated, based on calculations carried out for one particular choice of time integrated risk measure.

5.1. Main considerations underlying the development of a European risk model

Short-term approaches include the development of an ESRRM for predicting the radiation related risk of detrimental health effects. Development of an ESRRM requires: the adoption of suitable time integrated risk measures (e.g., Lifetime Attributable Risk (LAR)) which are based on risk results from radiation epidemiology cohorts (e.g., Excess Relative or Absolute Risk (ERR or EAR); pertinent assumptions (e.g., for smoking and medical-screening status, dose and dose rate effectiveness (DDREF), the shape of the risk to dose response (e.g., linear-no-threshold (LNT)), the neutron relative biological effectiveness (RBE); and input data (e.g., for population based age specific mortality & cancer rates). All potentially suitable currently available risk assessment measures build on ERR or EAR risks per unit radiation dose (e.g., from the Life Span Study of survivors of the WWII atomic bombings in Hiroshima and Nagasaki (Grant et al., 2017)).

One measure of risk obtained retrospectively, directly from ERR and EAR, once a cancer has occurred, is the probability of causation (PoC) – as recently implemented for industrial compensation claims in

Table 3
Comparison of the NASA priorities with the proposed IBER priorities.

NASA identified gap Risk of radiation carcinogenesis	IBER priorities
Cancer 01: How can experimental models of tumor development for the major tissues (lung, colon, stomach, breast, liver, and leukemias) be developed to represent the major processes in radiation carcinogenesis and extrapolated to human risk and clinical outcome projections?	To explore the role of specific target cells for radiation-induced late developing health effects
Cancer 02: How can experimental models of tumor development for the other tissues (bladder, ovary, brain, esophagus, skin, etc.) be developed to represent the major processes in radiation carcinogenesis and extrapolated to human risk and clinical outcome projections?	To explore the role of specific target cells for radiation-induced late developing health effects
Cancer 03: How can experimental models of carcinogenesis be applied to reduce the uncertainties in radiation quality effects from SPE's and GCR, including effects on tumor spectrum, burden, latency and progression (e.g., tumor aggression and metastatic potential)?	To understand the health effects of inhomogeneous dose distributions, radiation quality
Cancer 04: How can models of cancer risk be applied to reduce the uncertainties in dose-rate dependence of risks from SPE's and GCR?	To explore the shape of the dose-response relationship for radiation-induced health effects
Cancer 05: How can models of cancer risk be applied to reduce the uncertainties in individual radiation sensitivity including genetic and epigenetic factors from SPE and GCR?	To understand the potential impact of individual susceptibility on radiation-induced health effects To explore and define the role of epigenetic modifications in radiation-induced health effects
Cancer 06: How can models of cancer risk be applied to reduce the uncertainties in the age and sex dependence of cancer risks from SPE's and GCR?	
Cancer 07: How can systems biology approaches be used to integrate research on the molecular, cellular, and tissue mechanisms of radiation damage to improve the prediction of the risk of cancer and to evaluate the effectiveness of countermeasures? How can epidemiology data and scaling factors support this approach?	To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer disease
Cancer 08: What are the most effective biomedical or dietary countermeasures to mitigate cancer risks from exposure to SPE and GCR? What side effects should be tolerated versus mission risks?	
Cancer 09: Are there significant effects from other spaceflight factors (e.g. altered gravity (μ-gravity), stress, altered immune function, altered circadian rhythms, depressed nutritional status, or other) that modify the carcinogenic risk from space radiation?	Identify potential effects of microgravity and radiation on the immune system by studying well defined model systems using e.g. clinostats and random positioning machines during heavy ion exposures
Cancer 10: Are space validation experiments needed for verifying knowledge of carcinogenic or other risks prior to long-term deep space missions, and if so what experiments should be undertaken?	
Cancer 11: What are the most effective shielding approaches to mitigate cancer risks?	Optimize shielding materials and methods for GCR and SEP to mitigate radiation effects
Cancer 12: What quantitative models, numerical methods, and experimental data are needed to accurately describe the primary space radiation environment and transport through spacecraft materials and tissue to evaluate dose composition in critical organs for mission relevant radiation environments (ISS, Free-space, Lunar, or Mars)?	
Cancer 13: What are the most effective approaches to integrate radiation shielding analysis codes with collaborative engineering design environments used by spacecraft and planetary habitat design efforts?	
Cancer 14: What biodosimetry methods are required for exploration missions and how can biomarker approaches be used for outcome prediction and surveillance?	To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer disease
Cancer 15: Given that the majority of astronauts are never smokers, are there research approaches that can elucidate the potential confounding effects of tobacco use inherent in population-based epidemiology data on space radiation cancer risk estimates?	
RISK of acute (In-flight) and late central nervous system effects from radiation exposure	
CNS - 1: Are there significant adverse changes in CNS performance in the context and time scale of spaceflight operations? If so, how is significance defined, and which neuropsychological domains are affected? Is there a significant probability that space radiation exposure would result in adverse changes? What are the pathways and mechanisms of change?	To explore the role of specific target cells for radiation-induced late developing health effects

(*continued on next page*)

Table 3 (*continued*)

RISK of acute (In-flight) and late central nervous system effects from radiation exposure	
CNS - 2: Does space radiation exposure elicit key events in adverse outcome pathways associated with neurological diseases? What are the key events or hallmarks, their time sequence and their associated biomarkers (in-flight or post-flight)?	To explore the role of specific target cells for radiation-induced late developing health effects
CNS - 3: How does individual susceptibility including hereditary pre-disposition (e.g. Alzheimer's, Parkinson's, apoE allele) and prior CNS injury (e.g. concussion, chronic inflammation or other) alter significant CNS risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?	To understand the potential impact of individual susceptibility on radiation-induced health effects
CNS - 4: What are the most effective biomedical or dietary countermeasures to mitigate CNS risks? By what mechanisms are the countermeasures likely to work?	
CNS - 5: How can new knowledge and data from molecular, cellular, tissue and animal models of acute CNS adverse changes or clinical human data, including altered motor and cognitive function and behavioral changes be used to estimate acute CNS risks to astronauts from GCR and SPE?	To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer disease
CNS - 6: How can new knowledge and data from molecular, cellular, tissue and animal models of late CNS risks or clinical human data be used to estimate late CNS risks to astronauts from GCR and SPE?	To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer disease
CNS - 7: What are the best shielding approaches to protect against CNS risks, and are shielding approaches for CNS and cancer risks synergistic?	To identify most efficient shielding material and methods involving human phantoms to mitigate risk
CNS - 8: Are there significant CNS risks from combined space radiation and other physiological or space flight factors, e.g., psychological (isolation and confinement), altered gravity (micro-gravity), stress, sleep deficiency, altered circadian rhythms, hypercapnea, altered immune, endocrine and metabolic function, or other?	
RISK of acute radiation syndromes due to Solar Particle Events (SPEs)	
Acute - 1: Determine the dose response for acute effects (focusing on effects that are evident at space-relevant doses) induced by SPE-like radiation, including synergistic effects arising from other spaceflight factors (e.g. altered gravity (microgravity), stress, altered immune function, or other) that modify and/or enhance the biological response.	To explore the role of specific target cells for radiation-induced late developing health effects To explore the shape of the dose-response relationship for radiation-induced health effects. To understand particle and dose rate dependency of the prodormal syndrome and other acute tissue effects. The impact on acute radiosensitivity through other spaceflight factors, e.g. immune status, high oxygen concentrations, altered body fluid distribution etc.
Acute - 2: What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict acute radiation risks in astronauts? How can human epidemiology data best support these procedures or models?	To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer disease
Acute - 4: What are the probabilities of hereditary, fertility, and sterility effects from space radiation?	To understand the potential impact of individual susceptibility on radiation-induced health effect. Germline mutation rates and transgenerational instability as well as effects of spermatogenesis and oogenesis should be investigated applying heavy ion beams
Acute - 7: What are the most effective biomedical or dietary countermeasures to mitigate acute radiation risks?	To understand the potential impact of individual susceptibility on radiation-induced health effects
Acute - 8: How can Probabilistic risk assessment be applied to SPE risk evaluations for EVA, and combined EVA + IVA exposures ?	To understand the potential impact of individual susceptibility on radiation-induced health effects
RISK of cardiovascular disease and other degenerative tissue effects from radiation exposure	
Degen - 1: How can tissue specific experimental models be developed for the major degenerative tissue risks, including cardiovascular, lens, and other tissue systems (e.g. immune, endocrine, respiratory and/or digestive) in order to estimate space radiation risks for degenerative diseases?	To explore the role of specific target cells for radiation-induced late developing health effects
Degen - 2: What are the mechanisms of degenerative tissues changes in the cardiovascular, lens, digestive, endocrine, and other tissue systems? What surrogate endpoints do they suggest?	To explore the role of specific target cells for radiation-induced late developing health effects
Degen - 3: What are the progression rates and latency periods for radiation-induced degenerative diseases, and how do progression rates depend on age, sex, radiation type, or other physiological or environmental factors?	
Degen - 4: How does individual susceptibility, including hereditary predisposition, alter radiation-induced degenerative disease processes and risk estimates? Does individual susceptibility modify possible threshold doses for these processes in a significant way?	To understand the potential impact of individual susceptibility on radiation-induced health effects
Degen - 5: What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict degenerative tissue risks in astronauts? How can human epidemiology data best support these procedures or models?	To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer disease.
Degen - 6: What are the most effective biomedical or dietary countermeasures to mitigate degenerative tissue risks? By what mechanisms are these countermeasures likely to work? Are these countermeasures additive, synergistic, or antagonistic to other risks?	To understand the potential impact of individual susceptibility on radiation-induced health effects
Degen - 7: Are there synergistic effects from other spaceflight factors (e.g. altered gravity (μ-gravity), stress, altered immune function, altered circadian rhythms, or other) that modify space radiation-induced degenerative diseases in a clinically significant manner?	
Degen - 8: Are there research approaches using simulated space radiation that can elucidate the potential confounding effects of tobacco use on space radiation circulatory disease risk estimates?	

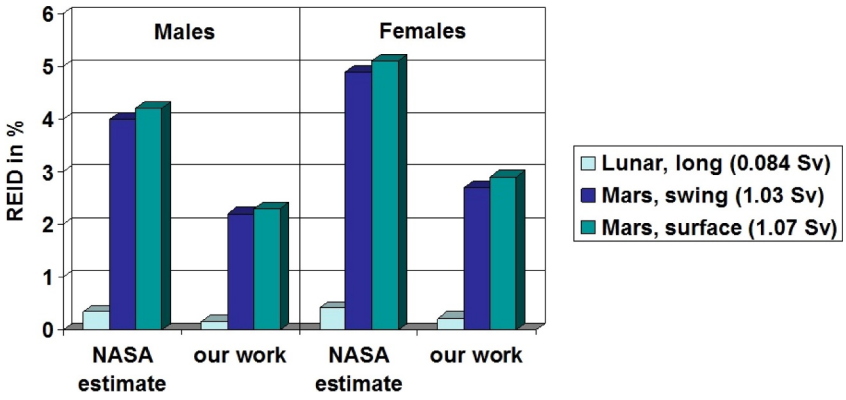

Fig. 1. REID in% for solid cancer mortality for solar minimum and 5 g/cm^2 aluminum shielding for variable RBE, a linear-exponential model and age at exposure 40 years. The figure shows a comparison between the NASA calculations and first estimates of potential new risk factors.

Germany (ProZES: www.bfs.de). Other measures often used in radiation epidemiology for predictive risk assessment, include Lifetime Attributable Risk (LAR), Risk of Exposure Induced Death (REID) and Excess Lifetime Risk (ELR) (Kellerer et al., 2001) but all have some distinct disadvantages for astronaut HRA. One such disadvantage is that conventionally applied time-integrated risks are based on current population and health statistical data that are not well suited for risk estimates for Astronauts who are not readily represented by the general population due to distinctly different levels of life-style factors such as smoking and fitness and different levels of post-mission cancer screening. A second disadvantage is that conventionally applied risks are not optimal for risk projections decades into the future due to large uncertainties in developments of future secular trends in the population-specific disease rates. Novel approaches may be more suitable for application to astronauts, such as a risk representation with the Radiation Attributed Decrease in Survival (RADS) which is only based on the radiation-attributed hazard, is insensitive to competing risks and eminently suitable for risk projections for highly atypical groups of exposed persons, such as astronauts (Ulanowski et al., 2019). RADS represents a cumulative radiation risk conditional on survival until a certain age and is known in general statistical literature as “cumulative risk”.

Decisions to be made in connection with developing a European risk model for astronaut HRA include: should the outcome of detrimental health effects (incidence or mortality) be considered?; which outcomes should be considered (e.g., the most radiation sensitive cancer sites comprising the thyroid, female breast; leukemia, plus all other solid cancers, as in the Fukushima HRA (Walsh et al., 2014))?; which risk measures should be applied (ERR, EAR, PoC, LAR, REID or a novel approach such as RADS)?; and which uncertainties should be considered? (see the next section). With a series of well justified choices, it should be possible to build a European risk model that accounts for the major uncertainties, the atypical nature of astronauts and is optimally applicable at the potentially high doses that may be relevant beyond low earth orbit.

5.2. The main uncertainties that need to be considered in the development of a European risk model

Analyses of the epidemiological data on the Japanese A-bomb survivors (Grant et al., 2017), who were exposed to γ-rays and neutrons, provide detailed information on the dose-response of radiation-induced cancer and form the main basis for current space radiation risk models. Since the dose range of main interest for radiation protection purposes is of the order of a few tens to a few hundred mGy, the analysis of the A-bomb survivors often focuses on this range. However, estimates of cancer risk for larger doses are becoming more important for long-term human space missions. Therefore, future space solid cancer and leukemia mortality/incidence radiation risk models should apply risk estimates valid at doses that include one Gy and above. It is possible to extend current analyses of the A-bomb survivors’ data to include some high-dose categories.

Usually colon dose, as supplied with publicly available A-bomb survivor datasets, is used to obtain risk factors for all solid cancers. However, it is known that the use of colon dose underestimates the average dose to all organs (Walsh et al., 2004). Thus, a newly developed space radiation risk model should include organ-averaged weighted doses instead of the colon weighted dose.

A neutron RBE of 10 is traditionally applied in the analyses of the A-bomb survivor data. However, there are some reported indications of a high neutron dose contribution (Kellerer et al., 2006). Therefore, the impact of neutron RBE on space radiation protection should be analyzed by using three different values for the relative biological effectiveness of neutrons (10, 35 and 100). In addition, the impact of a dose dependent RBE for neutrons determined by Sasaki et al. (2006) should be investigated.

Further improvement of the risk model can be achieved by fitting the data using a linear and a linear-exponential dose-response relationship using a variation in the dose and dose-rate effectiveness factor (DDREF). Combined analyses of the A-bomb survivor data with data from radiotherapy patient cohorts (Newhauser and Durante, 2011; Schneider and Walsh, 2008) can also be used to further improve risk models, in particular the risk dependence on age at exposure and attained age (Schneider and Walsh, 2015).

First estimates imply that the use of organ-averaged dose instead of colon dose would reduce risk by around 30%. A dose-dependent neutron RBE could lower risk by about 15–20% (Schneider and Walsh, 2009). The bending-over of the dose-response relationship for radiation induced cancer could result in a reduction of radiation risk by around 5% for dose levels typical for human space missions. In Fig. 1 the impact of these first estimates is shown by a comparison to the results of the NASA risk model (Cucinotta et al., 2013a) in terms of risk of exposure induced cancer death (REID). The comparison was done for solar minimum and 5 g/cm^2 aluminum shielding for a variable RBE, a linear-exponential model and an astronaut age of 40 years at exposure to 0.084 Sv for a long lunar mission, or approximately 1 Sv for a Mars mission (see Fig. 1 for details). Clearly it is seen that a re-evaluation of the risk factors could impact radiation risk estimates for space crews on long-term mission above 500 days potentially exposed to doses up to 1 Sv or even higher.

6. Conclusions

Long-term, crewed international space missions will become a reality in the 21st century (ISECG, 2013). Space radiation risk is generally considered as the main potential showstopper for safe exploration of the

Solar system (Chancellor et al., 2014), but until now the space agencies use different models to calculate the maximum permissible radiation dose for the crew, thereby resulting in different dose limits (McKenna-Lawlor et al., 2014). For BLEO there are no risk limits defined, but models can be applied (Cucinotta et al., 2017). Ethical considerations support the concept that the dose limits should be based on acceptable risk for astronauts. Attempts to dismiss all the limits and resort to e.g. informed consent have been criticized according to the ALARA principle (Kahn et al., 2014; Shuchman, 2014). Because the dose for a mission to Mars is estimated to amount to roughly 1 Sv (Zeitlin et al., 2013), and is therefore close to the dose limit for all agencies, at the moment there is a paradoxical situation that an international exploration mission would be essentially impossible, since some astronauts would be forced to leave the mission before others depending on the dose limit set by their space agency. The TT recommended ESA to promote the development of a new ESRRM based on innovation and European-specific expertise in transport codes, radiobiological modelling, risk assessment and uncertainty analysis. Finally, the ESRRM could also be used in the European Radiation Facilities Network (ERFNet, ESA project at feasibility stage), an infrastructures network managed by a smart system that aims at optimizing space habitat designs to mitigate radiation risk.

A further important TT recommendation was for ESA to support ICRP in future efforts to harmonize international models and dose limits for BLEO among the different agencies. Finally, the TT recommended to continue to increase the investment in radiobiology and physics research at accelerators in Europe (IBER).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lssr.2019.04.002.

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