Chapter 14

Space Radiation and its Biological Effects

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Chapter Contents

14.1 Introduction: Background and Driving Forces

Galactic cosmic rays (GCR) and solar cosmic rays (SCR) are the primary sources of the radiation field in space. GCR have their origin in previous cataclysmic astronomical events such as supernova explosions. They contain all particles from hydrogen to uranium, all fully ionized, with energies up to 10^{11} GeV and with low fluxes of around a few particles cm^{-2} s^{-1}. SCR are solar energetic particles (SEP) originating from solar flares or shock waves driven by a coronal mass ejections (CME), as well as in corotating interaction regions in the interplanetary medium. Of most concern for human spaceflight are Solar Proton Events (SPEs) a subgroup of SEP events. Such events consist mostly of protons, with a small percentage of heavy ions with energies up to several GeV. The duration of the events last from hours to days, in which fluences of up to 10^{11} particles cm^{-2} can be reached.

GCR expose biological systems and humans to quite low mean dose rates not leading to acute radiation effects, but the exposure causes an additional risk of carcinogenesis, degenerative tissue effects, damages to the central nervous system (CNS) and accelerated aging. Exposures to SPE also contribute to these listed risks, but in addition may cause acute effects, like performance degradation, acute radiation sickness or even death. To prevent exposures due to solar particles spacecraft can be equipped with shelters, but shielding is not effective against GCR. While effects of high doses are relatively well investigated and reasonably understood, the biological effects caused by heavy ions are poorly understood. Mitigation of the effects of heavy ions is one of the most important challenges to be solved for the exploration of the solar system. This chapter describes the space radiation field, its biological effects and measures that are necessary to limit the exposures in space missions to acceptable levels. Laser-driven ion acceleration can provide an advanced tool to study heavy ion effects in order to close gaps of knowledge.

Humans leaving the Earth to visit other planets of our solar system are therefore exposed to the full spectrum of GCR and SCR. Especially critical are exposures during interplanetary travel and during Extravehicular Activities (EVA), as well as during excursions on planetary surfaces. Habitats on planets can be constructed finally as thick shelters providing sufficient shielding thickness to reduce radiation levels to those on Earth. In interplanetary travel only limited shielding can be provided by the spacecraft structures; the same holds true for spacesuits. Since GCR consists of particles up to extremely high energies, their penetration ability ranges up to several hundred centimeters in aluminum. Penetrating the material, GCR loses energy by two ways, by the Coulomb interaction and by nuclear collisions. In Coulomb interaction most of the energy is transferred to the electrons of the target atoms. In nuclear collisions target and projectile fragments are produced. One particle can cause a whole cascade of secondary radiation. Having the same energy as the projectiles, projectile fragments penetrate even deeper. Excited target atoms may explode thereby producing low energy particles, mostly protons, neutrons and alpha particles, which deposit high amounts of energy in small volumes.

In contrast to GCR, short term exposures by SCR particles may become so high, that life threatening exposures become possible. The good message is that the energies of the particles are moderate and thus shelters can provide sufficient protection in interplanetary travel. Exposures especially during EVA and planetary excursions have to be prevented through adequate forecasting and mission planning.

Radiation effects to be taken into consideration are both, early and late effects. Early radiation effects, such as acute radiation sickness, manifest in minutes to days. They occur only through elevated exposures by SCR and may cause performance degradation, life span reduction or even inflight death. GCR cannot cause early effects due to the low fluence rates, but increases the risk

of late effects, from which carcinogenesis and damage to the CNS are of major concern. Late effects manifest within years or even decades.

While radiation effects at high doses are reasonably well understood, this is not the case for low doses of heavy ions. The exposure is not homogenous, since some cells in the human body are exposed and some are not. Heavy ions deposit a large amount of energy along their path with a core of about 50 nm around it followed by a very rapid decrease of the energy transfer with increasing distance from the path center due to so-called delta electrons. One ion hitting the nucleus of a cell may cause cell death [e.g. Bücker 1974, Reitz 1995].

The main target is the DNA in the cell nucleus, where a single heavy ion can cause complex damages consisting of single strand breaks (SSBs), base damages and double strand breaks (DSBs), while sparsely ionizing particles like protons mostly produce single strand breaks. Whereas SSBs can be repaired easily by the cell, DSBs are difficult to repair and are potentially mutagenic and lethal (see section 14.4.1). Although the flux of heavy ions is low, they represent the major contributor to radiation risk in space missions. Since the biological effects of heavy ions are poorly understood they represent the main source of uncertainties in risk estimates. Preparing a mission to Mars requires an extensive ground-based radiobiological program to achieve the reduction of uncertainties in radiation risk assessment and the development of appropriate countermeasures. The major facility is the NASA Space Radiation Laboratory (NSRL), established by NASA at the Brookhaven National Laboratory on Long Island (NY), followed by the Heavy Ion Medical Accelerator in Chiba (HIMAC), Japan. The NASA Space Radiation Health Program is by far the most intense undertaking towards mitigating the radiobiological risk in explorative missions (see website http://humanresearchroadmap.nasa.gov/). A strong collaboration between Europe and NASA

was envisaged in the IBER Program (see website https://www.gsi.de/work/forschung/biophysik/esa_iber.htm), the first European Accelerator-based Research Program (EARP) [Durante 2007] performed at GSI (GSI Helmholtzzentrum für Schwerionenforschung). Having supported the performance of 25 experiments the program was terminated due to the on-going construction of the new facility, **F**acility for **A**ntiproton and **I**ON **R**esearch (FAIR) at GSI. New beam times have become recently available as part of a "FAIR phase 0" transitional program allowing to implement a new IBER research program for the period of 2018 until 2022. After FAIR becomes available the IBER program will need to be continued and intensified having a facility which has the potential to become the leading facility worldwide for space radiobiology. A further facility, but only providing relatively low heavy ion energies up to 100 MeV/n is the Grand Accélérateur National de Ions Lourds (GANIL) in Caen, France, with its biological facility Laboratoire d' Accueil et de Recherche avec les Ions Accélérés (LARIA). More facilities around the world exist, but most of them suffer either providing the appropriate particles and energies or from the provision of the infrastructures, such as biological laboratories and animal facilities. The accelerators listed are heavily used in nuclear physics research and medical treatment, therefore only limited beam time can be provided to address all open issues present for explorative missions. Because in space all particles and energies are available, the simulation of the space radiation field at accelerators is a challenging time consuming task [Norbury 2015].

Laser-driven ion beams represent an excellent opportunity to increase the available beam time for studies of the biological effects of heavy ions of energies up to 100 MeV/n. Laser facilities additionally have the potential advantage of being physically much smaller than particle accelerators. The broad distribution of laser-driven ion species and their kinetic energies, if

properly controllable, could become a complementary feature to available accelerator sources. A detailed description of the needed research topics can be also found in the HUMEX study (see website, http://www.dlr.de/me/PortalData/25/Resources/dokumente/publikationen/humex-summary.pdf) and the THESEUS study (see website, http://www.esf.org/fileadmin/Public_documents/Publications /Cluster3_web.pdf). The following paragraphs will give a more detailed description of the radiation field in space and its specifics followed by a description of biological effects and the studies needed for the radiation risk reduction in explorative missions.

14.2 Radiation Fields in Space

The following description includes only radiation which is relevant to the radiation exposure of humans in space. Such types of radiation need energies that are sufficiently high to enter into the human body and the ability to ionize the atoms or molecules of the body. The radiation field inside the solar system is dominated by our sun and consists of a complex mixture of particles of solar and galactic origin. All particles and energies are present in the field [Wilson 1978]. Three main sources can be identified: GCR originated outside the solar system, SCR emitted from the solar surface and Trapped Radiation (TR) caused by interaction of GCR and SCR with planetary magnetic fields.

There are long term and short term temporal variations caused by the activity of the sun. Although different cycles have been already identified [Braun 2005], the most important for the radiation field modulation is the Schwabe cycle with a mean duration of approximately 11 years, in which the solar activity passes from one solar minimum activity period through a phase of maximum activity and back to the next minimum. One continuous measure since 1755

describing this activity is the Zürich sunspot number [Hathaway 2002].

The sun continuously emits particle radiation, primarily electrons and protons: the solar wind. Although the particle energies are so low that it would be absorbed within some micrometers of tissue, the solar wind is the major driver which determines the extent of the radiation exposure to GCR and TR. The solar wind fills out the complete solar system and carries a magnetic field which represents a heliocentric potential against which the GCR particles have to work when entering the heliosphere. During maximum solar activity the GCR exposure becomes lower, since the lower energy particles are no longer capable of entering the solar system. The solar modulation of GCR causes a shift of the energy for maximum intensity from solar minimum to solar maximum by about 500 MeV, with a strong attenuation of the flux during solar maximum below energies of about 30 GeV/nucleon [Badhwar 1997]. GCR are composed mainly of protons to about 85% and alpha particles to about 14% with the remainder of about 1% being heavier nuclei [Mewaldt 1988].

In addition, there are also episodes of extreme solar activity in which sudden releases of magnetic energy may occur in the corona previously stored in non-potential (stressed) fields, which result in Coronal Mass Ejections (CMEs) and Solar Flares. CMEs are huge clouds of magnetized plasma expelled from the solar corona into interplanetary space [Chen 2001]. Solar Flares manifest themselves as enhanced radiation across the whole electromagnetic spectrum due to heating and interaction of high-energetic particles with the solar atmosphere. Both, CMEs and solar flares, may be associated with SPEs which cause a radiation hazard to astronauts. Such extreme SPEs may last from hours to several days. The high magnetic fields embedded in such events lead to a reduction of GCR, the so-called Forbush decreases. On the other hand, a huge amount of particles, mostly protons with a small varying amount of heavy ions with energies up

to several GeV, can be released. There is no long term forecast for such events. In the case of solar flares where the ejected particles immediately spiral around the interplanetary magnetic field lines, the travel time to Earth may be in the order of 30 minutes to 1 day, whereas in case of CME's the particles may reach the Earth after 1-4 days. The onset of a SPE can be recorded by satellites, but neither the flux nor the energy spectra can be predicted. Energy spectra of candidate SPEs demonstrate an enormous variability of energy spectra as well as for the range of intensities observed [Wilson 1997].

The third radiation source is the radiation belt around the Earth. The radiation belt is a product of the interaction of GCR and SCR with the Earth's magnetic field and the atmosphere [Allkofer 1975]. The radiation belts extend over a region from 200 km to about 75000 km around the geomagnetic equator. The radiation belts consist of electrons and protons, and some heavier ions trapped in the magnetic field. Different processes contribute to the build-up of the radiation belts. The inner belt is mainly formed by protons and electrons as products from decaying neutrons, produced in interaction of cosmic particles with the atoms of the atmosphere. The outer belt is filled mainly by solar particles, which are injected during magnetic disturbances caused by particle events hitting the Earth. In each zone, the charged particles spiral around the geomagnetic field lines and are reflected back between the magnetic poles which act as mirrors. At the same time, because of their charge, electrons drift eastwards, while protons and heavy ions drift westwards. The electrons reach energies up to 7 MeV, the protons up to 700 MeV with a fluence maximum near 100 MeV. As with GCR, the trapped radiation (TR) is modulated by the solar activity. With increasing activity the proton flux decreases, while the electron flux increases. The proton flux decreases because the Earth's atmosphere expands leading to a loss of protons due to increased interaction with the molecules of the atmosphere. The electron

contribution increases because more electrons are fed into the radiation belts through enhanced solar activity. The electron fluxes in the outer zone show diurnal variations up to a factor of 16, but short term variations may raise the mean flux by two or three orders of magnitude. The flux in the center of the inner belt is quite stable. However, at the lower edge of the belt where the International Space Station (ISS) is operating electron and proton fluxes may vary by a factor of 5.

Charged particles from GCR and SCR have to penetrate the Earth's magnetic field to reach an orbiting spacecraft. For each point inside the magnetosphere there exists a cut-off rigidity which is proportional to the magnetic field component perpendicular to the direction of the particle motion. To reach this point the particle rigidity (particle momentum divided by its charge) must exceed the local geomagnetic rigidity cut-off. The rigidity is a function of the geomagnetic latitude and increases from high latitude towards the equator. At the poles the cut-off rigidity is zero, so particles of any energy can enter. As a result the GCR flux decreases from the poles to the equator.

14.3 Radiation Fields inside Spacecraft, on Planetary Surfaces and in the Human Body

The radiation field inside a spacecraft or on planetary surfaces differs significantly from the primary field in space. Penetrating spacecraft walls radiation is partly absorbed and secondary radiation is produced by scattering and nuclear interaction. Due to the non-homogenous distribution of the equipment inside spacecraft, the internal radiation field depends on the location inside the spacecraft. On planetary surfaces the field depends on the existence of a magnetic field, the thickness and the composition of the atmosphere and the surface material. This field is further modified when entering the human body. The analysis of the particle transport inside the body is a prerequisite when determining absorbed doses and the risk of early

and late effects.

Several radiation transport codes are in place to allow the calculation of particle fluxes and dose rates behind defined shielding. The Boltzmann transport equations for atomic and nuclear collisions may be solved by numerical and analytic techniques [Wilson 1993] or by Monte Carlo techniques [Ferrari 2001, Agostinelli 2003, Allison 2006, Townsend 2005, Waters 2002, Niita 2006]. Calculation of doses inside the human body additionally needs to employ computational phantoms, which represent the anatomy of the human bodies or parts of it [ICRP 2009, Yucker 1990, ICRP 2013].

The codes have to be validated by measurements with area monitors inside and outside spacecraft at well-selected locations with known shielding distributions and by individual measurements with personal dosimeters. Organ absorbed dose cannot be measured in the human body, therefore human phantoms equipped with radiation monitors are used to provide the essential confidence for radiation transport calculations [Reitz 2009].

Usually, the absorbed dose is the basic quantity to measure radiation exposure. The absorbed dose is the quotient of the energy deposited by ionizing radiation within an elemental volume to the mass of matter in that volume. The absorbed dose is measured in units of Gray (Gy) (1 Gy = 1 J/kg (= 100 rad)). Whereas different radiation qualities produce the same type of effect, the magnitude of the effect per unit of absorbed dose can be different. For radiation protection, the Quality factor (Q) was introduced in order to account for the different relative biological efficiencies (RBEs) of different types of ionizing radiation. This factor depends not only on appropriate biological data, but primarily it reflects a judgement concerning the importance of the biological endpoints. Q is defined in dependence of the linear energy transfer (LET). It is set to 1 for LET < 10 keV/µm, in the LET range from 10 - 100 keV/µm to 0.32 * LET - 2.2 keV/µm

and for LET > 100 keV/µm to 300 / $(LET)^{0.5}$ [ICRP 1991]. The dose equivalent at a point is defined as the product of absorbed dose and Q. The quantity effective dose equivalent [ICRP 2013] is the sum of all organ doses which can be calculated as product of Q and absorbed dose by additionally applying tissue weighting factors as defined in ICRP103 [ICRP 2007]. The effective dose equivalent is given in units of Sievert (Sv) (1 Sv = 1 J/kg (=100 rem)).

During space missions, astronauts are constantly exposed to GCR. This chronic whole body exposure with single energetic particles (electrons, protons, α-particles and heavy ions) results in an inhomogeneous dose distribution in the body. The flux is quite low and counts to about 4 protons, 0.4 Helium ions and 0.04 heavier particles per cm^{-2} s^{-1}. Therefore, the cells that are hit by a single energetic heavy ion are exposed to a high dose, and others that are not hit receive no dose at all. The traversing ions produce "ionization channels" in the hit cells and the biological effect depends on the extent of damage to sensitive biomolecules. Assuming an ionization channel of 10 µm in diameter for iron as example doses can be as high as 100 kGy. The damage of DNA DSBs has been visualized by immunofluorescence in a human skin fibroblast exposed to 2 Gy of ionizing radiation (iron ions); DNA DSBs are located along a particle trajectory [Durante 2006]. Therefore the radiation protection system which is based on mean absorbed dose is just an approximated surrogate and consequently providing the highest uncertainty in risk estimates.

In interplanetary missions, in addition to this chronic, in average low dose exposure at low dose rate, an acute whole body exposure to a high radiation dose at a high dose rate can occur during a SPE. For high doses the above mentioned radiation protection quantities should not be used, instead the RBE weighted mean absorbed dose in the organ or tissue should be applied which is given in Gray equivalents (Gy-Eq). The best estimates of RBE values for the different radiations

are given in in ICRP Publication 58 [ICRP 1989]. For protons > 2 MeV a RBE of 1.5 is recommended.

In Low Earth Orbit (LEO), where the ISS is operating, the SPE exposures are low to moderate due to a quite efficient geomagnetic shielding, while the contribution of the charged particles trapped in the Earth's magnetic field (Van Allen belts) to the total dose cannot be neglected [Facius 2006].

Radiation monitors were flown as part of all human missions and on numerous satellites. In the early times of spaceflight passive detectors which integrate dose and flux over time dominated. Later on active devices complemented the information on the radiation environment by adding temporal information. Good summaries of measurements can be found elsewhere [Badhwar 2002, Benton 2001, Reitz 2005, Reitz 2008, Casolino 2002, Dudkin 1995, Dudkin 1996]. A summary of effective dose equivalent rates for various missions, such as Apollo, Skylab and Shuttle missions, MIR and early ISS can be found in a compilation by Cucinotta, 2003. The Apollo deep space missions (to the Moon) show mean dose rates up to 3 mSv/day. In these missions the nuclei of the GCR dominate the exposure. Shuttle missions with inclination between 40 and 60 degrees show very nicely the influence of the solar cycle and maximum effective equivalent dose rates up to 1 mSv/day. Up to 4 mSv/day were observed in low inclination missions (around 28° inclination) above 600 km altitude whichare a result of the higher contribution of the protons from the radiation belt.. The ISS has been operating since 1998 at an altitude around 400 km and an inclination of about 51.5°; the first long-duration human stay was from November 2000 to March 2001. Environmental measurements on board

the ISS in June 2016 show equivalent dose rates up to 0.7 mSv/day. For comparison the mean exposure rate on Earth is about 0.0066 mSv /day. Measurements on the ISS are permanently done by a suite of instruments; results can be found on the web under http://wrmiss.org. Figure 14.1 shows particle count rates recently measured with a silicon detector of 6.93 cm^2 detection area on the ISS. The peaks represent proton counts when the ISS is passing through the South Atlantic Anomaly, a region where the radiation belt comes closer to the Earth surface. The other counts are GCR particles; the maximum flux is in the polar regions, the lowest at the equator.
A summary of the measurements of the Mars Science Lab Radiation Assessment Detector (MSL-RAD) is given in Table 14.1. The table presents the particle flux, dose and dose equivalent rates with which we are faced in interplanetary travel or on the surface of Mars.

Figure 14.1: Count rate measurements onboard the ISS of the two DOSTEL telescopes as part of the DOSIS experiment (Principal Investigator: Dr. Guenther Reitz (German Aerospace Center). The GCR count rates are due to the changing magnetic cut-off conditions during the ISS orbit with dependence of latitude; GCR count rates are at a minimum at the magnetic equator and a maximum at the highest latitude position; the spikes occur when the ISS is crossing the South Atlantic Anomaly of the radiation belt; the peaks are mainly due to protons. (DoY =Day of Year)

Table 14.1 Flux, dose and dose equivalent rate measurements of GCR during the cruise to and on the surface of Mars by the MSL-RAD

RAD Measurements	**Mars Surface**	**Cruise**	**Units**
Differential charged particle	0.26	0.64	Particles cm^{-2} s^{-1} sr^{-1}

flux density			
Dose Rate	0.21 ± 0.04	0.46 ± 0.06	mGy d^{-1}
Average Quality Factor <Q>	3.05 ± 0.26	3.82 ± 0.30	(dimensionless)
Dose Equivalent Rate	0.64 ± 0.06	1.84 ± 0.30	mSv d^{-1}

The dose equivalent rates during cruise, compared to that on ISS, are close to a factor of three higher. On the Mars surface we experience about the same exposure as on the ISS. On the Mars surface, the exposure is due to GCR only, as in the cruise, where on ISS the radiation field is a mixture of protons from the radiation belts and GCR.

The total number of particle hits per cell nucleus (diameter 11.3 μm, area 100 μm^2) in the human body at average skin depth while exposed during a stay on Mars at the mean surface level during one year based on measurements of the Martian Radiation Environment experiment (MARIE) arrived at about 40 protons, 1 Helium ion and 0.1 ions with charge greater than two [Saganti 2002].

Table 14.2 Calculation of dose equivalent for two NASA reference missions based on MSL-RAD measurements compared to calculation of effective dose equivalent taking into account a human body in a space suit on the Mars transfer vehicle and on Mars

Mission Phase	**Dose Equivalent/ Effective Dose Equivalent (Sv)**	**Notes**
Astronaut Career Limits*	**~ 0.60 - 1.20**	Depends on age, gender, etc.
Cruise to Mars (180 days)	~ 0.33 / 0.22	Near Solar Max

Mars Surface Mission (600 days)	~ 0.38 / 0.24	Thin habitat shielding
Mars Surface Mission (300 days)	~ 0.19 / 0.12	Thin habitat shielding
Return to Earth (180 days)	~ 0.33 / 0.22	Near Solar Max
Total Mission Dose Equivalent (300 days on Mars)	**~ 0.85 / 0.56**	
Total Mission Dose Equivalent (600 days on Mars)	**~ 1.04 / 0.68**	

*Lower and upper values for NASA career limits based on three percent excess risk of fatal cancer

Until now only doses of GCR including 'belt' protons in LEO are reported. The doses contributed by SPE in interplanetary space vary from zero to a couple of Gy depending on the fluence, the shape of the energy spectra and provided shielding thickness. Because the onset of the SPE can be monitored (no forecast of fluence or shape of energy spectra is possible), an inflight interplanetary crew can at least move to shelter. About 40 g/cm^2 of material (corresponding for example to 15 cm aluminum) is considered to be sufficient shielding. This shelter thickness allows the crew a safe cruise even at times of high solar activity. Excursions on planetary surfaces present of course a higher risk, especially on celestial bodies without atmospheres. The Mars atmosphere with a shielding thickness of 20 g/cm^2 of CO_2 provides already a complete protection against most SPEs. Housings adequately constructed with 2-3 m wall thickness of regolith or located deep enough in caves can guarantee exposure levels close to the exposure levels on the Earth surface.

Table 14.2 shows the calculation of dose equivalent and effective dose equivalent based on

MSL-RAD measurements compared with calculations of GEANT4 transport model with a human phantom implemented in the MSL mission.

14.4 Effects in Humans

Astronauts can "see" the exposure to GCR and trapped radiation in form of light flashes when they close their eyes [Pinsky 1975]. This phenomenon occurs after about a 15 minute dark adaptation and is explained by highly energetic heavy ions that interact directly or indirectly (via Cherenkov radiation in vitreous humour) with the retina [Bidoli 2002], or possibly with the optic nerve or the visual centers in the brain, producing a visual sensation.

The extent, type and onset of radiation effects observed in humans depend on the dose, the dose rate, the radiation quality and the individual sensitivity of the exposed human or animal (see Figure 14.2). Acute radiation effects in humans appear quite soon after exposure to a high dose in a short period of time (minutes to a few days). Late effects, such as cancer, can occur after years or decades in survivors of radiation exposure and have no threshold dose. Their probability for occurrence is proportional to the exposure level.

Figure 14.2: Acute, chronic and late effects of radiation exposure. Exposure to ionizing radiation produces DNA double strand breaks (pink foci) in the cell nucleus (blue) that can be visualized by immunofluorescence staining of the phosphorylated histone H2AX (γH2AX). The outcome depends on many influencing factors, including the microenvironment of the hit cells and a local or systemic immune response.

14.4.1 Basic Mechanisms: DNA Damage and Cellular Radiation Response

Ionizing radiation reacts with cellular macromolecules by direct ionization or indirectly via radiolysis of the cellular water. Thereby-generated oxygen radicals attack the DNA molecule and disrupt the ribose-phosphate backbone leading to single- and double-strand breaks, and induce base damage, loss of bases, or DNA-DNA and DNA-protein crosslinks. Such damage can disturb the information carried by the affected DNA molecule. DNA damage is regarded as the central element in cell killing by ionizing radiation, whereby DSB are considered to be the most cytotoxic damages [Jackson 2009]. These early events after radiation can pave the way to disease by activation of the cellular radiation response.

The cellular response to radiation is predominantly a DNA Damage Response (DDR) (see Figure 14.3) that detects lesions, signals their presence and promotes their repair [Jackson 2009]. This signal transduction pathway involves multiple sensors for different types of DNA lesions, transducer molecules and a variety of effector molecules and enzymes for repair. As radiation can simultaneously activate multiple pathways [Dent 2003], the DDR results in potentially cell-protective (cell cycle arrest, DNA repair, survival) or cell-altering (misdifferentiation, premature differentiation, senescence, mutations) or even destructive responses (different types of cell death) [Khanna 2001, NASA 2004, Ohnishi 2002].

Figure 14.3: The DNA damage response as central element of the biological reaction to ionizing radiation exposure and the different outcomes

14.4.2 Non-targeted Effects

In addition to the direct effects on DNA as the main biological target, non-targeted effects such

as the bystander effect and the adaptive response can influence the outcome after exposure to ionization radiation and are therefore important for space radiation risk assessment. Bystander cells are not directly exposed or traversed by radiation, but are in the neighborhood of a cell that had been hit or are incubated with medium from irradiated cells, and show responses [Mothersill 2004].

14.4.3 Acute Effects

SPE events pose the risk of acute high doses and high dose rate exposures. A large SPE such as the one that occurred in August 1972 might result in absorbed dose rates as high as 1.4 Gy/h Parsons 2000]. Exposure to an acute single dose elicits the acute radiation syndrome (**Fehler! Verweisquelle konnte nicht gefunden werden.**14.3), also known as radiation sickness, with symptoms depending on absorbed total radiation dose, type of radiation, the dose distribution in the body and the individual radiation sensitivity [Cronkite 1964, Drouet 2010]. A rapid onset of nausea, vomiting, and malaise (absorbed dose > 0.5 Gy) characterizes the prodromal stage, which is followed by a nearly symptom-free latent phase of weeks to days, depending on dose. The prodromal stage can be life threatening, if vomiting occurs while the astronaut performs an EVA in a space suit.

The acute radiation syndrome affects the tissues with rapid turnover in the first place. Cellular fate is determined by decision between cell death and survival. Accordingly, the effects on the individual result from depletion of already differentiated cells by cell death mechanisms, and from failing replacement by stem cells due to cell cycle block and cell death. Only cells overcoming the cell cycle block are able to replace radiation-damaged tissue to regain its normal function.

The bone marrow is one of the most radiosensitive organs in the body. In the manifest phase of

radiation sickness, depression of its function (bone marrow or hematopoietic syndrome) appears in humans exposed to doses of 0.7 - 4 Gy. These doses are lower compared to those eliciting the gastrointestinal tract syndrome (5- 12 Gy) or the CNS syndrome (> 20 Gy). The lethal dose for 50% of the exposed human individuals within 30 days was estimated to be 3-4 Gy ($LD_{50/30}$). Recent studies suggest that in all three sub-syndromes, exacerbated innate immune responses play a major role in pathogenesis [Drouet 2010, Jacob 2010, Van der Meeren 2005]. Epithelial and endothelial cells are suggested as sources of the pro-inflammatory cytokines in the acute radiation syndrome [Van der Meeren 2005]. Immune suppression is the predominant feature of the bone marrow syndrome. Due to the longer lifespan of erythrocytes, anemia develops later (within 2-6 weeks) than the lymphopenia. Death usually occurs from sepsis at 30-60 days after radiation exposure, if the patient cannot be carried through the critical period of the possibly reversible aplastic state of the bone marrow [Cronkite 1964]. Cytological abnormalities (multipolar mitosis, micronuclei, mitotic bridges, binucleated cells) and a reduced mitotic index were observed in human bone marrow cells (e.g. erythroblasts) during the first days after accidental sublethal whole body γ-radiation exposure, and cytological abnormalities persist at a lower frequency for years after the accident [Fliedner1964].

The gastrointestinal tract syndrome appears after a short latent period after whole-body irradiation with 5 - 12 Gy. It is due to loss of the intestinal epithelium after massive cell death and lack of mitotic success in the intestinal epithelium crypts, and injury to the fine vasculature of the submucosa. Invading bacteria produce local and systemic inflammation and sepsis with multiple organ failure [Drouet 2010]. Enhanced by the concomitant immunosuppression, death occurs between three and ten days post-exposure. If some crypt cells survive, they will regenerate functional crypts and repopulate the villi.

The onset of the CNS syndrome occurs after a very short latent period of several hours to days after exposure to very high acute doses (> 20 Gy in humans). Cells with highest differentiation status and lowest reproductive capacity, the neurons, are affected. The prognosis is fatal.

In spaceflight, exposure to mostly protons during a large SPE could result in the acute radiation syndrome. Experiments with mice have shown, that 2 Gy of protons delivered within 36 hours induce anemia and immunosuppression with decreased numbers of erythrocytes, lymphocytes, monocytes and granulocytes, and a decreased relative spleen mass [Gridley 2008]. In mice exposed to 3 Gy of protons, a strong immune depression was observed already 12 hours after exposure, with the nadir on day 4 [Kajioka 2000]. Increased susceptibility to infections, cancer induction by promotion of initiated cells, and disorders of the immune system such as autoimmunity or hypersensitivity are possible consequences of the immunosuppression.

Table 14.3 The Acute Radiation Syndrome

Dose range (Gy)	**Sub-syndrome or stage**	**Affected cells / tissues**	**Symptoms**	**Therapeutic approach**	**Refer-ences**
> 0.5	Prodromal stage	Neurons in the CNS, e.g. in the caudal medulla, Nervus vagus	Rapid onset of nausea, vomiting, and malaise	Antiemetics	[Makale 1993, Tofilon 2000, Marquette 2003]
0.5-4	Hematopoietic	Bone marrow stem cells including megakary-oblasts	Progressive lymphopenia, immune system suppression, susceptibility to infections, thrombocytopenia with increased bleeding tendency, early granulocytosis followed by progressive granulocytopenia, anemia	Antibiotics, antifungal drugs, isolation, electrolyte & platelet or blood transfusions, Granulocyte Colony-Stimulating Factor (G-CSF), allogenic bone marrow transplantation	[Cronkite 1964, Dainiak 2003, Chao 2007, Drouet 2010]
5-12	Gastrointestinal	Differentia-ting cell compartment – stem cells in crypts; endothelial cells, activation of the innate immune system	Diarrhoea, sepsis, multiple organ failure; > 10-12 Gy: 100% lethality		[Drouet 2010, Jacob 2010, Gaugler 2005, Singer 2004,Gourlemon 2005]
> 20-30	Neuro vascular	Mature functioning cells: neurons and endothelial tissue	Loss of coordination, confusion, convulsions, eventually coma, and signs of the bone marrow and gastrointestinal syndromes, vomiting, dehydration, cerebral	none	[Jacob 2010]

	edema, injuries to the nerves, death occurs within few days or hours

Therapeutic approaches for the acute radiation syndrome were tested in non-human primates; dogs, mice, rats and pigs [McVittie 2005, Donnadieu-Claraz 1999] and in accidently irradiated humans. The efficacy of other growth factors, such as Keratinocyte Growth Factor (KGF) and combinations of different growth factors (Stem Cell Factor - SCF, Nerve Growth Factor - NGF, erythropoietin, pegylated growth factors), antioxidants (e.g. N-acetyl cysteine) and anti-inflammatory approaches (e.g. inhibitors of cyclooxygenase-2- COX-2-, anti-IL-antibodies, curcumin, Ghrelin) are currently under investigation [Drouet 2010, Jacob 2010, Neal 2003].
In case of high dose SPEs astronauts have to be protected by a warning system allowing movement to a radiation shelter.

14.4.4 Chronic and Late Effects

Delayed or chronic effects of radiation exposure include cancer and non-cancer effects such as degenerative diseases. Cancer induction is a highly relevant and life threatening late effect of radiation exposure by radiation accidents, in atomic bomb survivors, for human spaceflight or radiotherapy. Ionizing radiation can definitively provoke tumor initiation, due to its DNA damaging effects. The role of radiation in tumor promotion and progression is less clear.
In radiotherapy, induction of secondary tumors by low radiation doses to the tumor-surrounding tissue occurs stochastically. The probability of tumor induction in the dose range below 1 Gy was derived from the cancer incidence (solid tumors, leukemia) in atomic bomb survivors who

were exposed at high dose rates [Pierce 1996, Pierce 2000]. With increasing survival times of patients after cancer radiotherapy, there is growing concern for the risk of secondary cancer, especially in children who are inherently more radiosensitive [Baskar 2010]. These epidemiological data were derived almost entirely from low-LET radiation exposures. Human data for cancer risk by GCR, especially high-LET heavy ions, are absent, and radiobiological data are limited. Currently, the quality factor (Q) for biological weighting of the GCR dose is governed by results derived from experiments with mice revealing a very high RBE for induction of tumors of the Harderian gland by heavy ions (LET > 100 keV/µm) [Fry 1983, Alpen 1994]. During a long-term space exploration mission, astronauts accumulate high exposures to GCR. A causal relationship between the frequency of chromosomal aberrations in peripheral blood lymphocytes and cancer allows estimation of cancer risk by appropriate analysis of the aberration frequency [Durante 2001]. A significant increase in chromosomal aberrations was observed in astronauts after long duration flights [George 2001]; data on cancer in astronauts are limited and lack statistical confidence, due to small group size [Longnecker 2004]. By the chromosomal aberration risk assessment technique, the cancer risk after a long-term mission on the former Russian space station Mir was estimated to be increased by 20 – 30% compared to a control group [Durante 2001]. For a Mars mission the uncertainties in cancer risk projections were estimated to be 400-600% [Cucinotta 2001a]. The latter projection involved many biological and physical factors, each adding a different range of uncertainty attributed to limited data and knowledge to the overall uncertainty. Several factors contribute to the overall uncertainty from which radiation quality is the major contributor followed by dose rate effects, others are risk transfer across populations, dosimetry, errors in human data and microgravity [Durante 2008].

Different organs can be affected by radiation-induced degenerative disease, e.g. the eye lens, and the central nervous, digestive, respiratory, endocrine, immune system or cardiovascular system. The eye lens is a quite radiosensitive tissue, as it has no mechanism for removal of dead or damaged cells and is not connected to the blood stream. During life, lens epithelial cells are continuously produced by mitosis in the germination zone of the lens and they differentiate into transparent lens fibers. Cataracts are detectable changes in the normally transparent lens of the eye; for example, resulting from disturbed differentiation into lens fibers. The threshold for cataract formation after protracted radiation exposure was as low as 2 Gy for sparsely ionizing radiation. Other investigators suggest even a threshold of 100-300 mGy for cataract formation, or dismiss any threshold [Worgul 1999]. Concluding from studies with rabbits exposed to neon or argon ions, Lett supposed that astronauts could experience late radiation effects one or more decades after a long-term space mission beyond LEO [Lett 1980]. In mice and rats exposed to energetic heavy ions, it was shown that high LET ionizing radiation is especially effective in cataract formation, even at doses below 2 Gy [Worgul 1989, & 1993, Hall 2006]. A lower threshold for cataracts of about 100 mGy was published recently by Blakely et al. [Blakely 2010]. Late cataractogenesis in Rhesus monkeys (Macaca mulatta with median life span near 24 years) was observed about 20 years after the exposure to protons of different energies, and in rabbits after exposure to energetic iron ions [Cox 1992, Lett 1991]. Besides animal experiments, data from radiotherapy patients are used for space radiation risk assessment concerning cataract formation or cancer induction in astronauts [Lett 1994, Wu 1994, Blakely 1994]. Up to now, lens opacities are the only proven space radiation late effect in astronauts [Cucinotta 2001b, Rastegar 2002] and they occur with higher frequency in astronauts exposed to higher proportions of high LET-radiation [Cucinotta 2001b]. As cataract surgery can restore the vision, it is not warranted

to consider cataractogenesis as a major critical health risk in short to medium-term spaceflight, in view of an overall mission death risk of a few percent. During long-term missions that can occur over several years, the expression time for cataracts has to be considered. During such missions, a cataract might develop before return to Earth and thereby it represents a mission risk.

During an interplanetary mission, astronauts can accumulate a considerable number of hits at critical sites of the brain [Craven 1994, Curtis 1998]. This gives rise to concern about CNS effects that could reduce the neurocognitive performance of the crew during the mission. Possible mechanisms are induction of DNA damage and cell death in neurons and neural precursor cells, disturbance of neurogenesis, electrophysiological activity, synaptic plasticity and neurotransmitters, neuroinflammation and oxidative stress [Rola 2005, Limoli 2007, Rola 2008, Vlkolinsky 2007,Machida 2010, Tseng 2014, Rivera 2013, DeCarolis 2014, Baulch 2015]. Animal experiments revealed learning, memory and executive function deficits after heavy ion exposure [Rabin 2000, Rabin 2005, Britten2012, Lonart 2012].

In cancer therapy patients, an elevated risk for cardiovascular disease has been known for decades. Recent epidemiological data show that also low dose exposure can result in cardiovascular effects [Bhattacharya 2015] and has to be considered in space radiation risk assessment [Boerma 2015]. Ionization radiation can affect e.g. endothelial cells or cardiomyocytes [Soucy 2011, Colemann 2015].

14.5 Ground-based Research

The limited knowledge of the biological effects from exposure to heavy charged particles is an ongoing concern in human spaceflight [Cucinotta 2011]. Open questions in space radiation biology are the difference in mechanisms for high vs. low LET radiation, the extent of the dose rate effect and the radiation quality dependence, the extrapolation of cell culture and animal data

to humans, and the individual radiation sensitivity (radio sensitivity syndromes represent the extremes; polymorphisms) all contributing to the radiation risk assessment. The atomic bomb survivor data serve as main reference for radiation risk estimates of space radiation, but the exposure conditions for the survivors and astronauts are quite different (Table 14.4). The exposure profile in space differs quite substantially from those which usually apply for reference experiments or data sources on Earth; especially where fluence rates and time scales are concerned.

Limited data are available for non-cancer late effects, e.g. cataracts and cardiovascular diseases. A quantitative risk assessment of CNS effects is completely missing [Cucinotta 2013].

Table 14.4 Differences in exposure conditions of the atomic bomb survivors (reference for radiation risks) and astronauts in space

Exposure Parameters	**Atomic Bomb Exposure** [§]	**Space Exposure**
Dose rate, duration	Instantaneous/acute, seconds	GCR: chronic/protracted, months – years; SPE: acute, hours-days
Radiation quality	Low LET gamma rays	Most complex mixture of disparate radiation qualities conceivable
Body distribution	Essentially homogeneous	Depending on external shielding, inner organs largely homogeneous
Exposed population	Common age, gender, health	Selected for physical/ psychic

	status distribution of a city population	prowess, age, and health
Environmental conditions	Normal terrestrial	Microgravity, confined ecological system, artificial/technical components dominating

§: Data Base: atomic bomb survivor epidemiology

Understanding acute effects requires data for whole body and partial body irradiation. Accidental exposures to SPEs result in inhomogeneous irradiation of the body, depending on the slope of energy spectra and exposure situations. There are no data on dose rate dependency for acute effects. Modification of the radiation response through the spaceflight environment is totally neglected in all agency radiation protection programs.

Experimental data on molecular and cellular mechanisms in cell, tissue and organ cultures are needed, and animal studies are required for studies on cancerogenesis, degenerative diseases and countermeasure testing. It needs to be proven whether or not the prodromal syndromes are different in humans and animal systems. As astronauts in a space suit or in a planetary habitat live in an atmosphere different of that on Earth, effects of altered oxygen and carbon dioxide concentrations, leading to hypoxia or hyperoxia or hyperkapnia certainly cannot be neglected. Furthermore countermeasures have to be provided, such as shielding and biomedical approaches (diet and radioprotectors). Effective biomedical countermeasures beyond amifostine and antioxidants have to be developed by ground-based research with appropriate models. Most recently it was found that CDDO-Me (bardoxolone methyl) showed a dose reduction factor

(DRF) of almost 2, which is very promising. Clinical tests indicate that it shows minimal toxicity in animal studies [Eskiocak 2010]. Ion sources are also needed for detector development and characterization to allow for ground and space borne intercomparisons. Improved detectors are needed to provide field dosimetry.

14.6 Summary

This chapter is intended to provide the major dosimetric features that are needed to draw a picture of which particle types, fluences and doses are required to perform reliable space radiation simulation. Because this picture is far from being complete, please refer for more detailed information to cited literature. The chapter also lists major biological questions that must be solved in order to reduce the uncertainties of risk estimates. The simulation of the radiation field in space is rather difficult due to the mixture of particles needed and by the rather long exposure times required to accumulate significant dose in the human body or the cell system under investigation. A recent paper describes in detail the needs for a GCR simulation [Norbury 2016]. The state of laser-driven heavy ion beams is currently far from providing all particle energies that are present in space. However, it is valuable to employ such laboratory sources providing a range of particles and kinetic energies for space research. The laser-driven case for energetic electron and ion production is in an early stage of development and we can expect useful advancements of this technology. We envisage protons and heavy ions with kinetic energies up to 100 MeV/n for this new laser-driven technique. (see chapters 2, 4 and 5 (Part I) for electron and ion acceleration status with high power lasers). For example many biological investigations require high LET, which means that energies of 20-50 MeV/n (with carbon for example) can be efficient for acquiring missing radiobiological data. Although laser-driven

particle fluences can be very high and therefore suited to provide high doses in short time, space reference systems typically require low particle fluences continuously distributed over an extended period. Therefore it can be a challenging task to reduce flux levels using collimator optics. A notable advantage of laser-driven ion sources is there emission characteristics, i.e. the broad angular divergence which reduces fluence quickly over a certain distance from the source and enables large field irradiation in a potentially compact setup. A second key advantage might be the intrinsically broad energy distributions of laser-driven ion sources – so, one can consider irradiating samples with a broad energy spectrum which comes closer to the space environment than an ion beam of well-defined energy at a conventional accelerator. A third key advantage might be the intrinsic capability of the laser-driver to generate multiple synchronous beams with different particles, again better simulating the real space environment if properly controllable. Those potential advantages usher optimism that laser-driven particle sources can expand the experimental toolbox for radiation biological studies. In particular, they can help to close the current gap for facility beam time for radiation biologists to answer the open questions and to reduce the extraordinarily large uncertainties in radiation biology for explorative missions.

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