

RADIATION PROTECTION FOR SPACE ACTIVITIES: SUPPLEMENT TO PREVIOUS RECOMMENDATIONS



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November 3, 2014

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[For detailed information on the availability of this and other NCRP commentaries see page 87.]

Preface

As a result of recent discussions with the National Aeronautics and Space Administration (NASA), the National Council on Radiation Protection and Measurements (NCRP) is providing this Commentary to supplement the previous recommendations from NCRP provided in the following reports:

- Report No. 98, *Guidance on Radiation Received in Space Activities* (NCRP, 1989);
- Report No. 132, *Radiation Protection Guidance for Activities in Low-Earth Orbit* (NCRP, 2000);
- Report No. 142, *Operational Radiation Safety Program for Astronauts in Low-Earth Orbit: A Basic Framework* (NCRP, 2002);
- Report No. 153, *Information Needed to Make Radiation Protection Recommendations for Space Missions Beyond Low-Earth Orbit* (NCRP, 2006); and
- Report No. 167, *Potential Impact of Individual Genetic Susceptibility and Previous Radiation Exposure on Radiation Risks for Astronauts* (NCRP, 2010).

NCRP also published the proceedings of a symposium held in 1996 entitled *Acceptability of Risk from Radiation – Application to Human Space Flight* (NCRP, 1997a).

This Commentary takes into account the most current information on early and late radiation health effects from space radiation, for both cancer and noncancer outcomes [*i.e.*, cardiovascular disease, central nervous system (CNS) dysfunction or disease], and the associated uncertainties.

In particular, this Commentary addresses the following specific issues:

- use of the existing NASA standard for current low-Earth orbit (LEO) activities of 3 % risk of exposure-induced death (REID) from cancer alone for extended LEO and exploratory missions;
- use by NASA of the 95 % confidence level to account for the uncertainties in cancer risk projection calculations;
- potential for inclusion of recent scientific knowledge on cardiovascular disease and CNS dysfunction or disease in radiation protection for NASA space missions; and
- highest priority research to address uncertainties in the estimation of radiation risk for NASA space missions, including the biological effectiveness of high atomic number and high-energy particles.

In addition, a discussion of ethics considerations and ethical principles that may bear on the application of NCRP advice on these scientific and radiation protection issues is included.

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John D. Boice, Jr.

President

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Executive Summary

The National Council on Radiation Protection and Measurements (NCRP) has provided guidance to the National Aeronautics and Space Administration (NASA) on radiation risks from space activities and protection guidelines through a series of reports spanning some 20 y (NCRP, 1989; 2000; 2002; 2006; 2010). As a result of recent discussions between NASA and NCRP, it was agreed that it would be timely for NCRP to develop a commentary that would supplement the previous recommendations from NCRP and that would take account of the most current information on the cancer and noncancer risks from exposure to radiation and their associated uncertainties. This approach would lead to considerations of the NASA guidelines for radiation protection for space activities.

NASA has established standards to protect the health and safety of flight crew members who take part in NASA human space flight programs (crew members). For exposure to space radiation, protection standards for missions in low-Earth orbit (LEO) were first approved by NASA in 2007 and the most recent revision of these standards was approved by NASA in 2014. NASA recently developed a revised cancer risk projection model. This revised model requires consideration in the context of the existing recommendations together with how the current uncertainties can impact radiation protection guidelines. These protection standards have been applied to past and current missions on the International Space Station (ISS), which have been of relatively short duration of up to six months. There is now the possibility of longer-duration missions on the ISS and additionally the need for design and planning of potential future exploratory missions, which involve travel beyond LEO. This Commentary discusses the implications of these expanded missions in a general manner. However, these scenarios also will require a substantially expanded consideration of the application of the current protection standards, an issue that is beyond the scope of this Commentary. The following paragraphs are a summary of the issues addressed by NCRP and its conclusions and attendant recommendations to meet the aims of the Commentary.

Application of the existing NASA standard used for current LEO missions to extended LEO missions.

Based on the current state of knowledge, it is reasonable that the radiation protection standard of 3 % risk of exposure-induced death (REID) for cancer, originally developed for crew members in LEO on shorter-term missions, should be used for longer-term (more than six months) missions in LEO with the additional precautions that have been stipulated by the NASA Chief Health and Medical Officer (Williams, 2012). Furthermore, the application by the standard of the 95 % confidence level to the 3 % REID for cancer is prudent and appropriate, given the current uncertainty in knowledge about the biological effects of galactic cosmic radiation for causation of carcinogenesis. Potential implications of uncertainties that are not evaluated in the current NASA risk projection model (Cucinotta *et al.*, 2013a), such as possible increased lethality of high atomic number, high-energy (HZE)-induced cancers (Cucinotta, 2014), should be borne in mind.

Application of the existing NASA standard used for current LEO missions to exploratory missions.

The issue of radiation protection limits for exploratory missions is more complex given the likelihood that radiation exposures will be increased in magnitude and biological

effectiveness, and as a consequence of different mission scenarios. The current NASA standard states that Exploration Class Mission radiation exposure limits shall be defined by NASA based on NCRP recommendations. However, NCRP has not previously provided advice on limits beyond LEO. At this time NCRP suggests that the present 3 % limit on REID for cancer, evaluated at the 95 % confidence level of the risk probability distribution function (PDF), while possibly not conservative enough, should be regarded as the least restrictive criterion that can be accepted for limiting risk from exploratory missions. However, NCRP notes that the calculation of the limiting radiation exposure (“safe days in space”) derived from this current limit is based on existing projection models and incomplete biological information. Thus, the use of the current limit may not necessarily lead to conservative conclusions. A research program that provides additional scientific and technical data may lead to the need for further definition of acceptable levels of radiation risk, for example to take into account additional health effects and the difference in mission scenarios, resulting in more restrictive mission limits. At this time, NCRP does not recommend any specific radiation protection limit for exploratory missions.

The potential for inclusion of recent scientific knowledge on cardiovascular disease and central nervous system (CNS) dysfunction or disease in radiation protection for NASA space missions.

At this time, the knowledge base on the potential risks from radiation exposure to cardiovascular tissues and the CNS, and particularly the potential for a greater effectiveness with exposure to HZE particles, is too limited to make recommendations on whether such risks should be included in the evaluation of REID. However, this is an area of rapid increase in knowledge, and NASA may, in the future, need to consider including risk of noncancer effects (particularly for the cardiovascular system and CNS) in the evaluation of REID. This is an area in great need of biological research as indicated below.

What is the highest priority research to address uncertainties in the estimation of radiation risk for NASA space missions?

Within the *Human Research Program Integrated Research Plan* (NASA, 2012), NASA has developed broad-based interdisciplinary research activities primarily aimed at addressing several uncertainties in the cancer risk projection model. The goal is to both reduce uncertainties in the parameters that enter the model and to test the correctness of the assumptions on which the model is based. To achieve this, the research has been designed and implemented with a strategy of central coordination and integration of experimental results and theoretical and analytical work from extramural and intramural projects. NCRP endorses this focus and recommends that close coordination, integration and continuity remain important features of the strategy, especially in view of the necessarily wide range of study topics within the plan. In addition, interagency cooperation is encouraged for addressing basic questions of common interest.

Because the largest contributor, by far, to the uncertainty in REID is the lack of adequate information regarding the biological effectiveness of HZE particles and high-energy neutrons, further research should continue to emphasize the understanding of the biological mechanisms and determination of relative biological effectiveness (RBE) for cancer induction by these particles, particularly at low fluences; this is clearly essential to facilitate continued development of enhanced risk models. NCRP recommends that such a program should continue to develop research with the most appropriate and relevant laboratory animal models and *in vitro* cellular and tissue systems from these animal models and from human sources.

The NASA research program also includes studies on potential risks from noncancer effects of space radiation. These studies should include an emphasis on developing a mechanistic understanding of the induction of the effects. Given the present state of knowledge, it is prudent to encourage new research that will address specific questions on charged-particle effects on the cardiovascular system and the CNS. Again, research should involve the use of laboratory animal models and *in vitro* cell and tissue systems from both animal models and human sources and be conducted with a strategy of close coordination, integrations and continuity. A discussion of the recommended research priorities and approaches is provided in the Commentary.

The continued availability of the NASA Space Radiation Laboratory (NSRL) is essential for the conduct of the recommended research. The research should be carried out in a timely fashion because planning of future missions and design of spacecraft and support systems for exploratory missions might be impacted by the research findings. NASA should take into consideration that accelerator facilities tend to have a finite lifetime and that these resources will not be available forever. For that reason, maintaining a robust research effort at NSRL is required to obtain results in a timely manner and to avoid compromising this research by attempting to defer it to the future. Continued availability of NSRL is especially supported because the cost is largely mitigated by leverage of Brookhaven National Laboratory resources.

Ethics considerations and ethical principles that may bear on the application of NCRP advice on radiation protection for space activities.

A number of ethical considerations accompany any worker protection program and this is certainly the case for the current situation for NASA for LEO missions, as has been discussed by NCRP and others. However, both NASA and crew members face an enhanced range of ethical concerns as they move forward in preparing for extended LEO and exploratory missions. Section 6 of this Commentary is intended to assist all parties in understanding the different ethical principles that they will need to consider in their various interactions. It identifies the major points for concern and potential solutions without defining a set of recommendations. The principles discussed are: provide a good (beneficence), prevent a harm (non-maleficence), respect one's autonomy (autonomy), and act fairly (justice). NCRP continues to support the view in NCRP (2010) that suggests a normative model in which NASA administrators and crew members come together in dialogue to develop common approaches and resolve any differences that might arise.

These conclusions and recommendations are based on the current state of knowledge and experiences related to the possible health effects of space radiations. It is anticipated that additional research, along the lines proposed in this Commentary, together with enhanced technology, will lead to further enhancement of the cancer risk projection model and refinement in the evaluation of REID for cancer as well as consideration of CNS and cardiovascular effects.

1. Introduction

1.1 Objectives of the Commentary

The National Aeronautics and Space Administration (NASA) has established standards to protect the health and safety of flight crew members who take part in NASA human space flight programs (referred to as crew members in the rest of this Commentary). For exposure to space radiation, protection standards for missions in low-Earth orbit (LEO) were first approved by NASA in 2007 and the most recent revision was approved by NASA in 2014.¹ These standards are partially based on recommendations from the National Council on Radiation Protection and Measurements (NCRP) for missions in LEO. Increases in knowledge over subsequent years have led to advances in the way the standards are evaluated for practical application, but the basic standards have remained unchanged. These standards have been applied to past and current missions on the International Space Station (ISS), which have been of relatively short duration of up to six months. There is now the possibility of longer-duration missions on the ISS and additionally the need for design and planning of potential future exploratory missions, which involve travel beyond LEO. NASA has agreed that NCRP provide this Commentary that addresses the basic principles of radiation protection for crew members of space missions, incorporating the latest scientific data on radiation biology and the current understanding of radiation health effects.

This Commentary considers the use of the existing NASA standard for LEO activities, particularly the career limit based on the risk of exposure-induced death (REID) for cancer, for application to extended LEO and exploratory missions. Consideration includes the use of the 95 % confidence level to account for uncertainties in risk projection. Recent developments in the NASA cancer risk projection model are discussed, including the contribution to this of the NASA research program. The current approach of short-term dose limits to protect against noncancer effects is evaluated and the potential is discussed for inclusion of recent scientific knowledge on cardiovascular disease and central nervous system (CNS) dysfunction or disease. Recommendations are made for the highest priority research that could address uncertainties in estimation of radiation risk for space missions. In addition, a discussion is included of ethics considerations and ethical principles that may bear on the application of the NCRP advice in this Commentary.

1.2 Space Radiation Environment

Crew members in space are exposed to a unique and complex radiation environment having three major components: galactic cosmic radiation (GCR), solar particle events (SPEs), and trapped radiation belts [reviewed in numerous publications (*e.g.*, Cucinotta *et al.*, 2013a; Kronenberg and Cucinotta, 2012; NCRP, 2006)]. Trapped radiation belts are not considered further here because they make no contribution beyond LEO, make only a small contribution

¹NCRP had essentially completed this Commentary when it learned of the most recent revision (dated July 30, 2014) by NASA of these standards (NASA, 2014a). While the 2014 revision did not impact the conclusions or recommendations of the completed Commentary in any way, some of the language and details in the 2014 revision differ from the 2007 version (NASA, 2007). In order to be most current and avoid confusion, this Commentary reflects the language and details as contained in the 2014 revision.

to organ doses on the ISS with existing shielding approaches and flight rules (Cucinotta *et al.*, 2008), and are associated with smaller uncertainties than those of heavy ions.

GCR is isotropic and composed of particles that are mostly highly energetic, consisting of protons (85 %), helium ions (14 %), and high atomic number, high-energy (HZE) particles (remaining 1 %) (Zeitlin *et al.*, 2013). Ions of all naturally-occurring elements are present in the GCR; however, the ions of primary concern have an atomic number up to 28 and energies from less than $\sim 1 \text{ MeV n}^{-1}$ (n^{-1} is per nucleon) to more than $\sim 10 \text{ GeV n}^{-1}$. GCR is relatively constant over time, although the GCR fluence rate for ions with energies $< 2 \text{ GeV n}^{-1}$ varies with the 11 y solar cycle, being about two times higher at solar minimum than at solar maximum. SPEs consist primarily of protons, generally of energies from $\sim 1 \text{ MeV}$ to several hundred megaelectron volts. In contrast to the relatively constant GCR, SPEs occur sporadically, their frequency varies with the solar cycle, and averages 5 to 10 events per year as observed from LEO, with most occurring during solar maximum. A library of SPEs for solar cycles 19 through 23 identified 13 events, during nearly 60 y of observation, that had protons with energies $> 30 \text{ MeV}$ and with fluences exceeding $10^9 \text{ protons cm}^{-2}$ (Cucinotta *et al.*, 2013a). While most SPEs are low dose rate, rare SPEs (*e.g.*, the August 1972 event) would have been capable of delivering to crew members of interplanetary missions dose rates over several hours that exceed the International Commission on Radiological Protection (ICRP) criterion for low dose rate (namely, $< 0.1 \text{ Gy h}^{-1}$) (Parsons and Townsend, 2000).

Crew members will be exposed in the interior of vehicles or habitats in space, except during extravehicular activities when their only protection will be a space suit. The particles in GCR are highly penetrating and cannot readily be stopped by shielding in space; additionally, nuclear reaction products with velocities similar to the velocity of the incident particle will emerge from material in the path, slowed down by energy loss in the material. SPE protons with energies $< 30 \text{ MeV}$ will be unable to penetrate spacecraft or extravehicular activity suits, although higher energy protons from all sources will contribute to radiation exposure in space.

Depending on their charge and energy, the particles in GCR have high linear-energy transfer (LET) compared to the low-LET of sparsely ionizing gamma rays and x rays. As high-LET HZE particles traverse matter, a large fraction of their total energy is deposited as secondary electrons produced along the particle track. The particle track structure depends on the particle type and its energy, with the track width reflecting the distance traversed by the ejected secondary electrons of maximum energy. Secondary electrons with sufficient energy (delta rays) can exit radially from the particle core of tight ionizations and traverse many cell widths in tissues (Blakely, 2012; Katz *et al.*, 1971). Because of the high ionization density along the tracks, the HZE particles, depending on their atomic number and energy, produce clustered damage in deoxyribonucleic acid (DNA) (Cucinotta *et al.*, 2000; Goodhead, 1994; Hada and Sutherland, 2006; Nikjoo *et al.*, 1999) and also more distant spatially correlated damage by single tracks (Rydberg, 1996). Such types of damage are more difficult for a cell to repair accurately and this is likely to account for the high relative biological effectiveness (RBE) of HZE particles for causing biological damage including cell death, mutations, chromosome aberrations, and carcinogenesis (Held, 2009). It should be appreciated that RBE values depend on many factors (*e.g.*, particle type and energy, cells or tissues irradiated, dose and dose rate, as well as on the biological endpoint studied). Because RBE is the ratio of absorbed doses required to produce identical biological effects, it is not entirely appropriate to use RBE in situations where there are qualitative differences between the types of damages caused by high- and low-LET radiations. The parameter Z^{*2}/β^2 , where Z^* is particle effective charge number and β is particle velocity, describes the density of ionizations in the particle track with less ambiguity than does LET and is used by NASA (Cucinotta *et al.*, 2011a; 2013a). Protons are generally considered to be low-LET (with small values of Z^{*2}/β^2), and thus low RBE, except at the last fraction of a millimeter of their tracks where the LET increases.

Although radiation exposures from GCR and SPEs can result in significant cumulative doses to crew members during long-duration flights outside LEO, exposures generally occur at low fluences and fluence rates, with the exception of rare SPEs (Blakely, 2000; Blakely and Kronenberg, 1998; NCRP, 2006). For example, GCR fluence rates during solar maximum have been estimated as: 4 protons $\text{cm}^{-2} \text{s}^{-1}$, 0.4 helium ions $\text{cm}^{-2} \text{s}^{-1}$, and 0.04 HZE particles $\text{cm}^{-2} \text{s}^{-1}$ with energies of a few hundred MeV n^{-1} to several GeV n^{-1} (Curtis and Letaw, 1989). Based on these fluence rates, it has been predicted that in deep space, for a typical cell nucleus of $100 \mu\text{m}^2$ cross-sectional area, each nucleus in a crew member's body would receive a proton traversal every 3 d, helium traversal once a month, and an HZE particle traversal once per year (Curtis and Letaw, 1989). However, the traversal of a cell nucleus would usually be accompanied by essentially simultaneous traversal of very large numbers of additional cell nuclei in the tissue along the track of the same particle. Recent measurements taken aboard the Mars Science Laboratory spacecraft during most of the 253 d transit to Mars have led to the estimate that the dose equivalent from the GCR alone for a possible 180 d mission to Mars (with a return-trip of similar duration, but not including time spent on Mars) scheduled at a similar time in the solar cycle and performed with current propulsion systems and comparable shielding is 0.66 Sv (Zeitlin *et al.*, 2013), consistent with the fluences quoted above. SPEs during such a mission would be expected to increase the dose equivalent, with the amount dependent on their frequency, duration, and energy spectra. Total dose-equivalent estimates for most human mission analyses for a 600 or 900 d mission have been between 1 and 2 Sv. From GCR in deep space, the NASA dose-equivalent rate averaged over organs of relevance to solid cancer is estimated to be $\sim 0.5 \text{ Sv y}^{-1}$ with realistic spacecraft shielding and it is about half this value on the Martian surface (Cucinotta *et al.*, 2013b). By comparison, on the ISS in LEO the corresponding quantity from GCR and trapped protons is ~ 0.1 to 0.2 Sv y^{-1} , depending on the stage of the solar cycle (Cucinotta, 2014; Cucinotta *et al.*, 2013b).

1.3 Radiation Protection in Space Activities

The current NASA standards that have to be met to maintain the health of space crews inflight are contained in *NASA Space Flight Human System Standard, Volume 1, Revision A: Crew Health* (NASA, 2014a). The standards provide a declaration of acceptable medical risk from deleterious health and performance effects of space flight and help target and prioritize biomedical research and technology development efforts, providing target parameters for products and deliverables that support the health maintenance of crews during space missions. They also promote operational and vehicle design requirements, and aid in medical decision making during space missions. For ionizing radiation, the standard is specified as the space permissible exposure limits (SPELs)² for space flight radiation exposure, which has the primary functions of preventing inflight risks that jeopardize mission success and of limiting chronic risks to acceptable levels based on legal, ethical or moral, and financial considerations. As stated in the rationale for space flight health standards for human performance, “Both short-term and career exposure limits are applied using assessments of the uncertainties in projection models with the space radiation environment defined by the program” (NASA, 2014a). Uncertainties are related to gaps in knowledge of biological effects of GCR, heavy ions, and the nature of SPEs. The SPEL standard states also that Exploration Class Mission radiation exposure limits shall be defined by NASA based in part on NCRP recommendations.

In NASA (2014a), planned career exposure for radiation shall not exceed 3 % REID for cancer mortality, adjusted for age and sex. The risk limit must be met at a 95 % confidence level.

²In some literature and common usage the radiation SPEL is often referred to as radiation “PEL (permissible exposure limit),” with no apparent change in meaning.

Additionally in the standard, for planned radiation exposure, career and short-term dose limits are imposed to prevent clinically-significant noncancer health effects including performance degradation, sickness, or death in flight. In addition to the risk limits, as an operating practice, the “as low as reasonably achievable” (ALARA) principle, a basic tenet in radiation protection, is a recognized NASA requirement. Further discussion of the ALARA principle in the context of space activities is presented in Section 6.2.2 and Appendix A.

Recent discussions regarding the possibility of extending the duration of ISS crew increments to 1 y have led the office of the NASA Chief Health and Medical Officer to examine the implications of such a decision on the implementation of the crew health standards, most notably the radiation exposure standard (Williams, 2012). As a result, the office:

“determined that for one-year ISS increments, a specific evaluation of each potential crewmember will be conducted to determine if the *projected* point estimate of the risk of exposure-induced death (REID) exceeds 1%. This evaluation will be performed using the latest 2012 radiation assessment model that includes a reduction in uncertainty analysis. Based on this evaluation, any crewmember exceeding 1% REID will have a complete uncertainty analysis performed which shall consider the individual’s complete radiation exposure and medical history and all other operational and mission risks. Based on these assessments, my office will make the appropriate recommendations for assignment on a case-by-case basis.”

In developing approaches to acceptable risk levels and approaches to quantify and mitigate radiation risks, NASA has for many years sought and received external guidance from NCRP and several bodies at the National Academies/National Research Council (NA/NRC), including the Institute of Medicine and the Space Science Board. Key recommendations are summarized briefly below, firstly, with respect to acceptable risk levels and, secondly, with respect to approaches to manage uncertainty in risk estimates and exposure limits.

Regarding acceptable levels of space radiation risk, NCRP (1989) recommended that NASA should use a 3 % lifetime fatality risk as the basis for dose limits. The level of 3 % was based on comparisons of space radiation risks with lifetime risks corresponding to limits of exposure of radiation workers on the ground and with risks of fatal accidents in “safe,” “less safe,” and “hazardous” other occupations, the middle group of these being preferred because crew members have other additional high risks apart from radiation. NCRP (1989) considered epidemiologic-based models to estimate age at exposure and sex-specific dose limits for crew members working in LEO. NASA implemented the NCRP recommended sex- and age-specific dose limits in 1990.

NCRP (1989) and NCRP (2000) reviewed the literature on lifetime risks associated with radiation and concluded that women had a higher risk than men for the same level of exposure. NASA subsequently incorporated this difference in sex-specific response to radiation into their protection guidance for crew members. The operational outcome was that female crew members would have less time in space than their male counterparts.

The data available for NCRP (1989; 2000) derived mainly from the studies of the atomic-bomb survivors and these data have now been reinforced with additional years of follow-up of this exposed population. The reasons for the increased lifetime risk for women compared with men are related in part to the differences in radiation sensitivity to cancer induction of the organs unique to each sex: the female breast and ovary are highly sensitive to the cancer producing effects of ionizing radiation whereas the male testes and prostate are notably insensitive. In addition there are a few other tissues where females have increased cancer rates compared with men, most notably the esophagus, stomach and lung. Table 1.1 is based on the latest mortality analyses from the atomic-bomb survivors and indicates the continuing sex-specific differences in the radiation risk estimates for major cancers.

TABLE 1.1—Sex-specific differences in the excess relative risk (ERR) per gray for major cancers (adapted from Ozasa *et al.*, 2012).

Cancer Type	ERR Gy ⁻¹ (averaged over both sexes) ^a	Female to Male Ratio (sex-specific ERR Gy ⁻¹ estimates)
All solid cancers	0.42	2.1 ^b
Esophagus	0.60	4.3
Stomach	0.33	3.7
Colon	0.34	1.4
Liver	0.38	1.6
Gallbladder	0.48	0.43
Lung	0.75	2.7
Bladder	1.19	1.7
Cancer Type (sex-specific organs)	ERR Gy ⁻¹ (age averaged)	Not Applicable
Female breast	1.5	
Ovary	0.79	
Prostate	Little evidence for an association with radiation (UNSCEAR, 2008)	
Testicular	Little evidence for an association with radiation (UNSCEAR, 2008)	

^aThe sex-averaged ERR Gy⁻¹ is shown for subjects at the attained age of 70 y after exposure at age 30 y.

^bA ratio of 2.1 can be interpreted as females having a risk of radiation-induced cancer death that is 2.1 times that of males. These patterns generally hold when estimates are based on excess absolute risk per gray and for cancer incidence data as well (Preston *et al.*, 2007).

NCRP (2000) noted that the comparison with “less safe” industries no longer supports a 3 % fatality risk as a basis for radiation dose limits because of improvements in safety in ground-based occupations. However, the primary approach of comparison with occupational risks to radiation workers on Earth remained essentially unchanged. Hence, NCRP (2000) stated that it:

“now considers the comparison with lifetime risks associated with the occupational exposure limits recommended for workers on the ground to be the most direct and the most valid. Consequently, NCRP recommends that the excess lifetime fatal cancer risk due to the radiation exposure of space workers for missions in LEO be limited to three percent excess mortality and that this be the basis of career limits.”

NA/NRC (2001), in relation to future long-duration space travel, noted:

“Until the radiation hazards to astronauts can be controlled or otherwise mitigated by physical shielding, a 1998 National Research Council report states, long-duration space travel should be postponed [NA/NRC, 1998]. Even if an effective physical radiation shield

is developed, it in no way diminishes the need for clinical study, including monitoring of crewmembers' exposures, long-term medical follow-up, and the development of preventive medical treatments to make astronauts more resistant to deep space-induced radiation damage."

In evaluating the radiation shielding requirements for potential lunar missions, NA/NRC (2008) wrote:

"The committee recommends that all elements of Project Constellation employ the radiation protection and risk management limits necessary to meet the NASA radiation protection standards presented to the committee."³

These standards are the SPELs described in NASA (2014a). NA/NRC (2008) also states:

"The committee strongly recommends that the permissible exposure limits specified in current NASA radiation protection standards not be violated in order to meet engineering resources available at a particular level of funding."

Regarding approaches to manage the uncertainties in estimating risks and dose limits for space missions, this issue also has been recognized in several reports from NA/NRC and NCRP. The uncertainty is largely due to the lack of information on the radiobiology of HZE particles from GCR that produce differences in biological effects from the typical types of radiation that humans are exposed to on Earth, and for which no human data are available. The uncertainty led NCRP (2000) to recommend that methods used for LEO radiation risk assessment are not of sufficient accuracy for deep space missions and also led to NCRP (2006) advising NASA on the information needed for accurate estimation of risks and setting exposure limits. Similar recommendations are made by NA/NRC (1996; 2008).

Faced with large radiobiological uncertainties while needing to support current missions, NASA developed a method to estimate subjective confidence intervals in cancer risk estimates using an approach to uncertainties developed by NCRP (1997b; 2000) that was extended to space exposures. NASA's approach to uncertainties as well as to acceptable risk formed the basis for the current NASA (2014a) SPELs; the approach was initially approved by the Aerospace Medical Policy Board in 2005. NASA's approach was reviewed by NA/NRC (2008). A recent update to NASA's computational model for space radiation cancer risk projections and uncertainties was reviewed by NA/NRC (2012) and was revised (Cucinotta *et al.*, 2013a) to address the NA/NRC recommendations.

NCRP (2000) noted, referring first to the earlier NCRP (1989):

"some have assumed that the guidance on dose limits in that report applied not only to missions in LEO but to all space missions. That was not the intention since the guidance provided was limited to exposures in LEO. In this Report, the guidance is also only intended to be applied for radiation exposures incurred during missions in LEO. Future NCRP reports will deal with other space situations."

³The NA/NRC (2008) report was written within the context that "NASA recently embarked on Project Constellation to implement the Vision for Space Exploration—a program announced by President George W. Bush in 2004 with the goal of returning humans to the Moon and eventually transporting them to Mars." The report stated that "Based on NASA's current progress in mission planning, this report focuses on exploration of the Moon and touches only on general aspects of Mars exploration." Project Constellation was subsequently replaced by the U.S. National Space Policy of President Obama's administration.

The reason for this statement is the large uncertainties in the risks from HZE particles. NCRP (2006) subsequently considered what information is needed to make radiation protection recommendations for missions beyond LEO. NCRP (2006) gives a thorough review of past studies of space radiation effects and radiobiology and provides an extensive list of recommendations for research. NCRP (2006) stated:

“The acceptable levels of risk for space exploration beyond LEO have not been defined at this time and need to be dealt with before sending manned missions to colonize the moon or to deep space such as a mission to Mars.”

1.4 Occupational Exposure to Crew Members

In its previous reports on radiation protection in space activities, NCRP treated the exposure received from the space radiation environment (Section 1.2) as occupational exposure (NCRP, 1989; 2000; 2002, 2006) and derived its recommendations for radiation protection in space activities with that consideration in mind. NCRP (2002) recommended that the sources of exposure included in the radiation protection limits for crew members:

“... should include the cumulative dose from space flight, the dose associated with mission-related aviation activities (excluding commercial flights), the dose from biomedical research conducted as part of the astronaut’s mission duties, and any other occupational doses including any received prior to work as an astronaut.”

Consistent with occupational exposure situations on Earth, these limits do not include radiation dose received on Earth from any diagnostic and therapeutic medical procedures conducted on the individual or from natural background radiation (ICRP, 2007; NCRP, 1993). In addition, previous radiation doses from such diagnostic and therapeutic procedures are assumed to have provided the individual a greater benefit than the risk associated with the doses and should not be used in determining qualifications for future missions in space. However, radiation exposure is only one of the risks that NASA management considers in its wider concern with the need to limit health risks to crew members and the impact of the health risks on qualification for flight.

2. NASA Radiation Protection Standards for Space Radiation

Under the National Aeronautics and Space Act (NASA, 1958), the U.S. Congress gave the National Aeronautics and Space Administration (NASA) the authority to establish regulations for its own operations. This includes establishing radiation dose limits for crew members in space flights. The process for establishing those dose limits, and the dose limits themselves, have evolved with time and have reflected advice over the years from NA/NRC (1996; 1998; 2008) and NCRP (1989; 2000). NASA's health and medical standards are established by the Office of the Chief Health and Medical Officer and are currently set-out in the *NASA Space Flight Human System Standard. Volume 1, Revision A: Crew Health* (NASA, 2014a), which establishes SPELs at a level that will:

“optimize crew health and performance, thus contributing to overall mission success, and to prevent negative long-term health consequences due to space flight.”

From NASA (2014a), the SPELs for space flight radiation exposure are:

- Planned career exposure to ionizing radiation shall not exceed 3 % REID for cancer mortality at a 95 % confidence level to limit the cumulative effective dose (expressed in sievert) received by a crew member throughout his or her career.
- Planned radiation dose shall not exceed career and short-term limits for noncancer effects as defined in Table 1 of the standard (see Table 2.2 of this Commentary).
- Lifetime fatality risks for noncancer circulatory and CNS diseases shall be limited as defined by career dose limits in Table 1 of the standard (Table 2.2 of this Commentary).
- Exploration Class Mission radiation exposure limits shall be defined by NASA based on NASA-requested recommendations from the National Academy of Sciences, the Institute of Medicine, and NCRP.
- Inflight radiation exposures shall be maintained using the ALARA principle.

The radiation protection limits for U.S. crew members participating in space flight are discussed in more detail in Section 2.1 (cancer) and Section 2.2 (noncancer effects).

2.1 Risk of Exposure-Induced Death from Cancer

2.1.1 Use of Risk of Exposure-Induced Death from Cancer

NASA currently uses a career limit of 3 % REID for cancer. The 3 % risk limit is based on NCRP (1989; 2000) recommended limits of *effective dose* that correspond to a career limit of 3 % excess lifetime cancer risk from occupational exposures to radiation for crew members in LEO missions. NASA radiation limits differ uniquely from radiation limits used for radiation workers on Earth. The NASA radiation limits are not dose limits; they are risk limits. Radiation limits set for terrestrial radiation workers, usually with low-LET radiations, are based on an implied calculation of risk, usually the probability of cancer, as a function of dose, which usually can be reasonably well estimated. However, the complex nature of HZE radiation in space means that equal absorbed doses for HZE radiation do not have the same biological effects (*i.e.*,

do not have the same risk). By establishing a career risk limit for REID for cancer, rather than a dose criterion, NASA may readily modify the corresponding dose limits as scientific knowledge about the relationship between risk and dose evolves. Furthermore, use of REID allows for adjustments for competing risk as well as for cancer deaths moved earlier in time by radiation exposure. Operationally, NASA sets career limits for any given crew member at the 95 % confidence level on the 3 % REID to allow for uncertainties in the risk projections.

NASA uses radiation risk projection models to set the age- and sex-specific exposure-to-risk conversion factors needed to define dose limits, project mission risks, and evaluate the effectiveness of shielding and other countermeasures. NASA's radiation cancer risk projection model developed in 2005 was based largely on NCRP (2000), but in 2010 NASA released a revised methodology for evaluating space radiation cancer risks for application to exploration mission trade studies⁴ and for evaluating crew risks for missions on ISS (Cucinotta *et al.*, 2011a). The revision accounted for more recent human radiation epidemiologic data and analysis, new research results from the NASA Space Radiation Laboratory (NSRL), particularly laboratory animal data indicating that quality factors differ for leukemia and solid cancers, and improved theoretical considerations based on concepts of radiation track structure rather than using quality factors based on LET. The Cucinotta *et al.* (2011a) model was reviewed by NA/NRC (2012), and subsequent updates of the model resulted in the current model, designated NASA Space Cancer Risk (NSCR) Model-2012 (NSCR-2012) (Cucinotta *et al.*, 2013a). From the current model, NASA calculates age- and sex-specific REID values for mission-specific and crew member-specific risks.

2.1.2 Use of the 95 % Confidence Level

NASA's risk projection model provides a probability distribution function (PDF) describing the uncertainty in REID. The central value (median) of this PDF is used as a point estimate; its width is given by the uncertainties associated with the calculation of REID (Cucinotta *et al.*, 2013a). At present, the only risk used in the calculation of REID is cancer lethality, but risk attributable to other endpoints may be incorporated into future calculations if warranted. The uncertainties in some factors that enter into the risk calculations, particularly radiobiological uncertainties, are large. For a given mission, the most probable value of REID and the associated PDF is determined, taking into account the mission trajectory, the material surrounding the crew, and other inflight factors. The REID value for the mission is set using the 95 % confidence level of the PDF. This value of the REID translates into "safe days in space," the number of days a crew member is exposed during that mission without exceeding the most probable REID value, within a margin of error given by the 95 % confidence level. In practice this means that as a consequence of ensuring that the career limit of 3 % REID for a crew member is not exceeded at the 95 % confidence level, the total number of career "safe days in space" may be based on a cumulative REID for all missions as low as 1 % or less. This takes into account the REID values for any new missions plus the crew member's cumulative REID from previous missions.

Some of the uncertainties are the same as with low-LET radiations, including extrapolation of cancer effects data from high to low doses and dose rates (NA/NRC, 2006; NCRP, 1997b), transfer of risks across populations and errors in epidemiologic data including dosimetry, selection bias, diagnostic inaccuracy, and surveillance bias. The largest uncertainty for space radiation is the value of the quality factor (Cucinotta *et al.*, 2011a). This is due to the limited understanding of heavy-ion radiobiology that can be attributed to two major factors:

⁴Trade studies are decision-making activities used to identify the most acceptable technical solution among a set of proposed solutions. By nature, all decisions are subjective and involve risks. Trade studies provide an effective means for addressing this by documenting the decision-making process to enable traceability and repeatability.

- paucity of data available from studies with relevant model systems performed at ground-based accelerators; and
- observation that HZE particles can produce biological effects that are, at least in part, different from those produced by terrestrial radiations such as gamma and x rays.

Furthermore, no human data are available on the effects of HZE radiation, although some data are available using human-derived cell or tissue models. Other uncertainties include knowledge of the space radiation environment and transport models and application of track structure information. Because of the important role of the 95 % confidence level, careful quantification of uncertainties is needed (EPA, 1999). Additionally, improving knowledge of the biological effects of space radiations is critical to narrowing the confidence interval and thus increasing the number of “safe days in space,” as well as providing a scientific basis for evaluating shielding approaches and medical countermeasures in adherence to the ALARA principle.

The REID computation and its 95 % confidence level are based upon the risk estimates from the Japanese atomic-bomb survivor study of ~51,250 adults exposed in 1945. The population survived a nuclear detonation, lived in a war-torn country, and was confronted with malnutrition, deprivation, infection, and other overriding health and psychosocial concerns. The exposure occurred in less than a second. The population and the exposure circumstance in Japan are not comparable to the crew members or space radiation and thus uncertainty factors are assumed to compute the 95 % confidence interval about the REID. In concert with other federal agencies, NASA has supported the Million U.S. Radiation Worker and Veteran Study (Boice 2012; 2014; Bouville *et al.*, 2015). This epidemiologic study of healthy American workers exposed gradually over time is considered more representative (*e.g.*, similar with respect to health, ethnicity and lifestyle factors) of the crew-member population than the Japanese atomic-bomb survivors. The study population is 20 times larger than the adult Japanese study population (Ozasa *et al.*, 2012) and has more individuals with cumulative doses >100 mSv (various evaluated quantities reflecting their exposure histories) (Bouville *et al.*, 2015). Thus it has the potential to improve the estimates of radiation risk (*e.g.*, by being more precise) and reduce the uncertainties in the REID and its 95 % confidence level (*e.g.*, by removing the need to adjust for differences between a Japanese population and a western population and by minimizing or reducing the need for a DDREF adjustment).

2.1.3 Comments on Use in Extended Low-Earth Orbit and Exploratory Missions

NASA's current SPEL for stochastic effects from space flight radiation exposure have been developed by NASA using previous NCRP advice on acceptable risk for cancer-induced death and related dose limits, as outlined in Section 1.3. To date, NCRP advice on limits has been only for missions in LEO; exploratory missions have been explicitly excluded because of uncertainties in risk projection (NCRP, 2000) and because the acceptable levels of risk beyond LEO have not yet been defined (NCRP, 2006).

In view of the possibility of extending the duration of ISS crew increments to 1 y, the NASA Chief Health and Medical Officer has put in place appropriate procedures for individual assessment of crew to protect against accrual of excessive risk during the extended flight (Williams, 2012). These precautionary procedures fall reasonably within the scope of previous NCRP advice for LEO, the current SPEL for REID (cancer), and the NASA risk projection model for cancer, including its 95 % confidence level. As a note of caution, however, it should be recognized that not all uncertainties in fatal cancer risk projection are included in the NASA risk projection model (Cucinotta *et al.*, 2013a). For example, the uncertainty analysis of the model does not include the possibility that HZE-induced cancers may have qualitative differences, including increased lethality, compared to other cancers.

It should be noted in this context that risks from noncancer diseases are highly uncertain at this time (Section 4) and their inclusion (particularly cardiovascular disease) could substantially increase REID for all diseases to values well above the values of REID for fatal cancer alone, on which the current SPEL for REID is based. These additional concerns suggest that the NASA policy to protect against the 95 % confidence level for fatal cancer risk may not be conservative for overall risk of radiation-induced death.

For exploratory missions, beyond LEO, the situation is very different in a number of important respects. The nature of the radiation field is substantially different, with increased dose rate, increased contribution from GCR, and increased threat from SPEs. Uncertainties in the biological effects of GCR become more prominent not only for cancer risk, but also for acute or delayed risks from noncancer effects such as to the CNS or the circulatory system. In addition, depending on the nature and duration of the planned mission beyond LEO, there may also be little or no prospect of withdrawing crew members who unexpectedly approach their risk or dose limit or who show signs of adverse effects of radiation already during the mission.

According to current knowledge of the radiation environment in deep space and the current NASA risk projection model, it has been calculated that the current SPEL, based on the 3 % REID for cancer would be exceeded by a large margin on a manned Mars mission (Cucinotta *et al.*, 2013b). Different mission scenarios were considered, including a 1 y ISS mission, a 1 y mission to an asteroid, and three different Mars missions. As an example, for a 940 d Mars conjunction mission at solar minimum, Table 2.1 (Cucinotta *et al.*, 2013b) shows that, for a 45 y old space crew member, the upper 95 % confidence limit for projected values of REID from cancer alone are more than twofold greater than the NASA SPEL, even in the case of nonsmoking male crew. In this most recent assessment, NASA also presented a second quantity, risk of exposure-induced cancer incidence (REIC), which is also referred to in Table 2.1. The quantity REIC is not presently used by NASA for radiation protection purposes.

NASA (2014a) states that Exploration Class Mission radiation exposure limits shall be defined by NASA based in part on NCRP recommendations. Such limits have not yet been defined and NCRP has not previously provided advice on limits beyond LEO. NCRP (2006) has, however, advised on the information needed to make recommendations for radiation protection for space missions beyond LEO, including research needs aimed at decreasing uncertainties in the risk projections. In addition to scientific and technical needs, acceptable levels of radiation risk for exploratory missions would need to be defined. Pending future NCRP advice, the current SPEL of 3 % REID at the 95 % confidence level, while possibly not conservative enough, should be regarded as the least restrictive criterion that can be accepted for limiting risk from exploratory missions. However, the number of safe days in space calculated using current knowledge may need to be reduced further due to incomplete knowledge.

2.2 Current Dose Limits for Noncancer Effects

The *NASA Space Flight Human System Standard* (NASA, 20014a) also defines short-term and career dose limits for noncancer effects (Table 2.2). The short-term limits are intended to prevent clinically-significant noncancer health effects including performance degradation, sickness, or death inflight. The short-term dose limits for the lens of the eye, the skin, and blood-forming organs are set at levels to prevent early and late health effects, and are adopted from NCRP (2000). Lifetime limits for the eye, circulatory system, and CNS are set to limit or prevent risks of cataracts and of degenerative tissue diseases such as stroke and heart disease. These limits are set independent of age and sex. It should be noted that the approach at this time uses an estimate of threshold doses for circulatory system and cataract risk, which is different from the probabilistic risk projection approach used for cancer limits. Recent limited data suggest that at least some degenerative effects (*e.g.*, cataracts) may not have thresholds,

TABLE 2.1—Lifetime risks (and 95 % confidence intervals) for the 940 d Mars design reference mission for cancer and circulatory disease for average solar minimum (Cucinotta *et al.*, 2013b).^a

	% REIC ^b Cancer Incidence	% REID Cancer Death	% REID Circulatory Disease	% REID Combined
<i>45 y Old Females</i>				
U.S. average	9.15 [0.95, 22.2]	5.32 [0.95, 14.3]	1.48 [0.57, 3.05]	6.57 [1.38, 14.8]
Never-smokers	6.66 [1.52, 16.0]	3.56 [0.51, 8.87]	1.55 [0.58, 3.20]	4.98 [1.77, 10.6]
<i>45 y Old Males</i>				
U.S. average	7.41 [1.79, 17.0]	3.52 [0.66, 8.23]	1.53 [0.64, 3.05]	4.94 [1.91, 9.78]
Never-smokers	6.09 [1.56, 14.0]	2.75 [0.63, 6.52]	1.62 [0.68, 3.21]	4.28 [1.86, 8.22]

^aComparison of lifetime risks for 45 y old females and males for U.S. average population and a population of never-smokers. The morbidity for circulatory diseases has not been directly estimated, but the addition of the % REIC (cancer incidence) and % REID (circulatory disease), indicate an upper 95 % confidence limit for the combined morbidity near 20 %.

^bREIC is risk of exposure-induced cancer (incidence).

or may have very low thresholds (<1 Gy) (ICRP, 2012; Neriishi *et al.*, 2012; Worgul *et al.*, 2007). If these findings hold up, it may become necessary to use a probabilistic approach, assuming a linear dose-response curve with no threshold, for certain degenerative noncancer effects. The somewhat limited amount of space-relevant research on radiation-induced cardiovascular/circulatory damage is discussed in Section 4.2, and research priorities are described in Section 5.2.2.

2.2.1 Comments on Noncancer Diseases

The additional mortality and morbidity risks for noncancer diseases of the CNS and cardiovascular system are major concerns because they could increase REID values substantially. It is to be noted that the risks to the CNS may include effects that could occur during missions as well as possible late effects that could cause morbidity and mortality after the crew return to Earth. Current research efforts and future research needs on the biological, neurocognitive and behavioral risks of HZE exposure to the CNS are discussed in Sections 4.1 and 5.2.1, respectively. The types and magnitudes of the risks to the CNS and cardiovascular/circulatory system from high-LET radiation are largely unknown at this time; substantial research effort is needed in this area.

Lastly, a comment on the radiation dose limit for crew members to the lens of the eye is warranted in light of current knowledge. The SPELs limit dose to the eye for 30 d, 1 y, and career to 1, 2, and 4 Gy-Eq, respectively. By comparison, the annual limit to the lens of the eye for radiation workers in the United States is 0.15 Sv (150 mSv) (equivalent dose), although the European Union has recently modified their annual limit for the lens of the eye to 0.02 Sv (20 mSv) (equivalent dose), averaged over 5 y, based on the recommendation from ICRP (2012). ICRP (2012) recommended this change based on new evidence, from both human and animal studies, that supports a low radiation dose for the induction of cataracts. There remains discussion on the suitability of this revised limit and particularly how it can or will be applied in medical situations and perhaps by extension to space missions.

TABLE 2.2—Dose limits for short-term or career noncancer effects (in Gy-Eq^a or Gy) (NASA, 2014a).

	Organ 30 d (Gy-Eq)	Limit 1 y (Gy-Eq)	Limit Career (Gy-Eq)
Lens of the eye ^{b,c}	1	2	4
Skin ^c	1.5	3	6
Blood forming organs ^c	0.25	0.5	Not applicable ^d
Circulatory system ^e	0.25	0.5	1
	(Gy)	(Gy)	(Gy)
CNS ^f	0.5	1	1.5
CNS ^f (Z ≥ 10)	—	0.1	0.25

^aSee gray-equivalent (Gy-Eq) in Glossary. It is recognized that the use of a quantity named gray equivalent (G_T), with the name for its unit also named gray equivalent (Gy-Eq) poses problems with respect to the SI system of units. According to the requirements of the SI system of units, the gray equivalent should neither be used as a named quantity nor as a unit. Neither the gray equivalent (G_T) nor the name for its unit (Gy-Eq) used by NCRP (2000) for radiation protection for deterministic effects (now called tissue reactions) are used universally. For such an application, ICRP (2007) recommends using the quantity RBE-weighted absorbed dose expressed in gray.

^bLens of the eye limits are intended to prevent early (<5 y) severe cataracts (*e.g.*, from an SPE). An additional cataract risk exists at lower doses from cosmic rays for sub-clinical cataracts, which may progress to severe types after long latency (>5 y) and are not preventable by existing mitigation measures; however, they are deemed an acceptable risk to the program.

^cThe values for lens of the eye, skin, and blood forming organs are adopted from NCRP (2000).

^dThe career limit for cancer is more restrictive and would always be expected to result in a lower absorbed dose to the bone marrow for the irradiation conditions in space (NCRP, 2000).

^eCirculatory system doses calculated as average over heart muscle and adjacent arteries. Referred to also as the cardiovascular/circulatory system elsewhere in this Commentary.

^fCNS limits should be calculated at the hippocampus. For Z ≥ 10, a value for 30 d was not given in NASA (2014a); the values for 1 y and career are given as “1,00 mGy” and “2,50 mGy” in NASA (2014a), but as 100 and 250 mGy in NASA (2007). They are presented as 0.1 and 0.25 Gy here.

2.2.2 Comments on Use in Extended Low-Earth Orbit and Exploratory Missions

Until recently, NASA has focused its risk modeling efforts for space mission scenarios on fatal cancer risks. Current dose limits for noncancer endpoints are reasonable for application to 1 y missions in LEO within the framework given by the Chief Health and Medical Officer (Williams, 2012), but for exploration class missions application of the current dose limits for noncancer endpoints is less clear and needs additional review. In response to a growing database on circulatory disease risks to humans from radiation exposure in occupational and medical settings, NASA has considered the risk of death from circulatory diseases in its most recent assessments of % REID for extended LEO and exploratory missions (Cucinotta *et al.*, 2013b). The deterministic effects RBE model of the ICRP (2003) was used to derive a central estimate of risk. Gender-specific or time-dependent factors were not included. As noted earlier, the risks for 45 y old crew members for a 940 d Mars mission, illustrated in Table 2.1, exceed the current NASA limit. The circulatory disease risks considered included cardiovascular disease and ischemic heart disease using excess relative risk estimates from a recent meta-analysis of studies of atomic-bomb survivors and nuclear workers from several countries. The inclusion of circulatory disease risk with the cancer risk results in a value given as % REID (combined) that is ~40 % higher than the value of % REID for cancer alone.

The approach taken thus far should be considered preliminary. There is very little basic biological data available on circulatory disease risks from HZE particles at present and as a result the uncertainties regarding RBEs for circulatory disease endpoints are large. It is essential that additional experimental data with HZE particles be acquired using relevant model systems and relevant doses to provide robust input to refine the current model of cardiovascular risk from space radiation.

Caution must also be exercised with regard to consideration of CNS risks for exploration missions. Recent experimental data for HZE-ion risks obtained with animal models and human-derived culture models (Section 4.1) raise questions about the possibility of neurobehavioral effects at lower doses of HZE particles that may be relevant to exploration class missions. Additional research is needed to determine whether current dose limits for acute effects are sufficiently robust to ensure crew member safety during and after exploration missions.

3. Cancer Risk Estimates

3.1 Introduction

NASA has an extended record of developing strategic plans for the protection of the health of crew members during short-term missions and longer-term exploratory missions. As new data and new approaches for estimating overall health risk have become available, NASA has revised its strategic plan and the allowable mission durations for specific scenarios (Cucinotta *et al.*, 2011a; 2013a; NASA, 1998; 2005). While there is an historical perspective when reviewing these reports *in toto*, the present NCRP Commentary will concentrate on NSCR Models NSCR-2010 (Cucinotta *et al.*, 2011a) and NSCR-2012 (Cucinotta *et al.*, 2013a). The general principles are pertinent to both NSCR-2010 and NSCR-2012, while the more complete discussion of the model, cancer predictions and uncertainties will be based on the most current model NSCR-2012 [as revised based on recommendations from the evaluation by NA/NRC (2012)].

3.2 NASA Risk Projections (NSCR-2010 and NSCR-2012): Unique Features

The approach in the NASA Space Cancer Risk (NSCR)-2010 and NSCR-2012 models for the predictions of cancer risks to crew members as a result of space radiation continued to have as its basis NCRP (2000), with some additions for consistency with NCRP (2006). However, for the NSCR-2010 and NSCR-2012 risk projections and their associated uncertainties, NASA has relied upon the specific information and approaches for estimating cancer risks due to low-LET radiation exposure that are described in the more recent reports from a number of organizations:

- *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2*, Committee on Biological Effects of Ionizing Radiation (NA/NRC, 2006);
- *The 2007 Recommendations of the International Commission on Radiological Protection*, ICRP Publication 103 (ICRP, 2007); and
- “Annex A: Epidemiological studies of radiation and cancer” in *Effects of Ionizing Radiation, UNSCEAR 2006 Report to the General Assembly, with Scientific Annexes* (UNSCEAR, 2008).

What then are the specific features of the NASA approach that require consideration separate from these highly regarded and extensively reviewed reports listed above? The first is that NASA limits crew member exposures to a 3 % REID as opposed to a dose-based limit as is used by other organizations. The basis for this specific REID value is described in Sections 1.3 and 2.1.1. Additional support for the choice of a 3 % REID, although perhaps coincidental in nature, is that using the more common (terrestrial) approach, the lifetime risk of radiation-associated fatal cancer is ~3 %. This calculation uses the current NCRP effective dose limit for occupational exposures of no more than 50 mSv y⁻¹ in any 1 y, with a cumulative limit (age × 10 mSv) after 18 y of age (NCRP, 2000). In contrast, NASA’s career dose limit estimate is based on a quite different set of criteria including the average lifetime risk of accidental death in “equivalent” occupations such as construction and agriculture that is ~1.5 to 3 % [for significantly more dangerous occupations (*e.g.*, test pilot) this risk is assessed as ~10 %], and comparison to dose limits for ground radiation workers. It has to be appreciated that the occupational accident data used for these estimates were collected before 1990 and since that

time, there has been a significant drop in death rates for many occupations in the United States. However NCRP (2000), that formed a basis for the NSCR-2010 and NSCR-2012 models, did conclude that “the choice of a three percent career excess risk of cancer mortality remains reasonable and justified.” Nevertheless, it would seem appropriate to further consider this risk value based on the most recent occupational mortality statistics and the current risk estimates for ground-based workers.

In contrast to other recognized models that use cancer risk point estimates to set radiation exposure limits, the NASA approach takes into account the quite large uncertainty associated with their cancer risk projections by incorporating a 95 % confidence level on the 3 % REID (Sections 1.3 and 2.1.2). The appropriateness of this approach and of the specific confidence level value used is discussed in Sections 1.3, 2.1.2, and 2.1.3.

A third area for which the NASA approach differs somewhat from the more traditional approaches for terrestrial-based dose limits for occupational exposures is that for accounting for real or potential differences between a crew member population and a typical worker population. The age range for crew members is quite narrow (~30 to 60 y) and the careers quite short, and so career dose limits for planning purposes are based on a 3 % risk of fatal cancers for a 10 y career with ages of first exposure of 25, 35, 45, or 55 y. The specific dose limits for a specific mission are calculated for each individual potential crew member under the conditions for that mission.

It is well-established that there are some factors (*e.g.*, lifestyle and genetic) that can increase cancer risk over the lifetime. The crew member population is a so-called “healthy worker” group, particularly they are nonsmokers and of normal weight. Based on this, NASA has calculated cancer risks for a defined nonsmoker, normal weight population, with separate estimates of risk generated for females and males (given that cancer rates differ for the two sexes). The bottom line is that the dose limits for a 3 % REID will be increased for the NASA defined crew member population. Appropriately, NASA notes in its model description (Cucinotta *et al.*, 2011a; 2013a) that other factors could further increase these dose limits but sufficient data are currently unavailable to make reliable adjustments.

The space radiation environment is very different from that on Earth, particularly regarding the presence of a large number of heavy ions that are high-LET in nature, as noted in Section 1.2. The details of the specific exposure scenarios are comprehensively described by Cucinotta *et al.* (2013a). A feature of this unique radiation environment is that account has to be taken of the quality factors that allow for conversion of effects at low-LET (for which risk estimates are more readily available that include robust epidemiologic data as underpinnings) to those at the higher-LETs and for which epidemiologic data are not currently available. The NSCR-2010 and NSCR-2012 models have selected such quality factors but with the full appreciation that these have a relatively high level of uncertainty.

3.2.1 Review of the NSCR-2010 Model by NA/NRC

NA/NRC was requested by NASA to review the report *Space Radiation Cancer Risk Projections and Uncertainties – 2010* (Cucinotta *et al.*, 2011a) prior to its implementation. The review was published as *Technical Evaluation of the NASA Model for Cancer Risk to Astronauts Due to Space Radiation* (NA/NRC, 2012). This evaluation provides a comprehensive review of and recommendations on several components of the NASA risk-assessment model and an overall evaluation of the integrated model; here a summary of the more critical issues is given. This then will lead into a discussion of how NASA addressed these particular issues to derive their final version of the assessment model NSCR-2012 (Cucinotta *et al.*, 2013a).

NA/NRC noted that the overall approach for estimating risks was “state of the art,” being based on the most current national and international methodology. Also, they stated that the several components of the model were well-integrated into the overall model. This integration

can be assessed by viewing a real-time demonstration of the prediction of risks for different space mission scenarios that can be accessed by request (THREE, 2013).

A concern was raised about the use of an “incidence-mortality” approach as developed by NA/NRC (2006) for the estimation of REID. It was appreciated that incidence data (*e.g.*, from the Life Span Study of Japanese atomic-bomb survivors) would generally be more accurate for diagnosis than mortality data, but that the specific approach being recommended by NASA would require more consideration of biases and of the conversion model being proposed. This was viewed as being particularly important given that the change to an incidence-mortality approach leads to a considerable change in REID estimates.

NA/NRC also expressed some concerns with NASA’s selection of the value of 1.75 for the dose and dose-rate effectiveness factor (DDREF) because it was an averaged value based on estimates of other organizations. DDREF is used by NASA for developing the cancer risk estimates at low doses and low dose rates for low-LET radiations as part of their risk projection model. The issue of a reliable value for DDREF (usually taken as being between one and two) has been debated quite extensively (ICRP, 2007; NA/NRC, 2006). The underlying issue is what data should be used to develop a value for DDREF. NASA estimated that one major contributor to the overall uncertainty in their risk projections was contained in the value of DDREF. NA/NRC recommended the application of a central value and distribution that makes the best use of the current epidemiologic data and laboratory animal and cellular data. Whatever approach is used by NASA to calculate DDREF, there will remain quite a high degree of uncertainty.

The largest contributor to the overall uncertainty is the quality factors. NASA has taken a novel approach to quality factor by specifying it as a parameterized function of particle effective charge number (Z^*) and particle velocity (β), instead of as a prescribed function of LET. NA/NRC agreed with the new approach, but recommended that NASA improve the transparency of the basis for their selection of parameter values for the risk model.

Given that the crew member population is one with a limited age range (30 to 60 y) and healthy lifestyle, NASA considered how to account for the absence of some modulating factors that can increase risk and that would not apply to crew members. The impact of the crew member population being nonsmoking was the factor that was likely to have the greatest impact on risk estimates as a result of reductions in lung cancer and other smoking related cancers. NA/NRC agreed that taking account of crew member specific lifestyle factors was appropriate but recommended at this time, because of data availability, that only the effect of nonsmoking on lung cancer risk should be included. In this case, it was also recommended that competing risks be considered in the calculations for lung cancer risk.

Consideration of the various uncertainties that are associated with the risk estimates derived by NASA resulted in NA/NRC being generally very supportive of the approach used. Uncertainties are very important for the consideration of risk projections particularly because protection limits involve the use of safety factors that NASA sets as the SPEL for REID (cancer) based on the 95 % confidence level that takes into account the uncertainties in risk projection models. NA/NRC recommended that particular attention be given to addressing the uncertainty in the quality factor because this is the largest single contributor to the uncertainty in REID. This can be achieved, in part, through an extension of a directed research program that is already part of NASA’s agenda.

As part of the development of their risk projection model, NASA considered the potential impact of so-called nontargeted effects (*e.g.*, bystander effects, genomic instability). NA/NRC agreed with NASA that these might be important in modifying the low dose response to adverse outcomes but at this time insufficient data on their role in cancer induction and risk are available.

Other more minor concerns and recommendations were provided in the NA/NRC technical evaluation and these can be reviewed in their report (NA/NRC, 2012).

3.2.2 NASA Responses to the NA/NRC Evaluation

NASA addressed the issues and concerns raised in the NA/NRC technical evaluation in the Executive Preface to their report, *Space Radiation Cancer Risk Projections and Uncertainties – 2012* (Cucinotta *et al.*, 2013a), with the outcome being the presentation of the final version of their model. A summary of these responses to the major concerns of NA/NRC will provide useful background information for the review of the NSCR-2012 model (Cucinotta *et al.*, 2013a) that is discussed in Section 3.3.

In response to the concern of the use of a specific incidence-mortality conversion approach, NASA performed a new analysis of incidence-mortality conversion models. Such a conversion is required because the Japanese atomic-bomb cancer incidence data are used to develop estimates of the cancer mortality used for REID. As part of the development of incidence-mortality models, the U.S. Environmental Protection Agency (EPA) cancer risk model (EPA, 2011), that was published after NASA's draft model was completed, was considered. NASA considered that the EPA model might be of some merit for those exposed in the past but would not address possible errors in the conversion of incidence to mortality for future risk projections. The use of incidence data is of importance to the final NASA model; incidence data are considered to have less bias than mortality data and the diagnosis is more reliable for cancer incidence than is that of mortality due to a specific cancer. However, the issue of how to convert incidence data into mortality data (for incorporation into REID) continues to require consideration; the NA/NRC (2006) approach was deemed to require some revisions.

The majority (90 %) of crew members are nonsmokers and so NASA incorporated lung cancer rates for nonsmokers into the calculation of REID. NA/NRC agreed that such an approach was valid but that it had to consider competing risks that are specific for nonsmokers. In response, NASA reconsidered the issue of competing risks as a consequence of the longer life-span in nonsmokers. The impact on REID was minimal (<5 %).

To model the transfer of risk estimates from the Japanese to the U.S. population, NASA provided a revision in their final version (Cucinotta *et al.*, 2013a). In this, the weights used for the various factors involved in risk transfer were almost exclusively from NA/NRC (2006) with the exception of lung [incorrect in NA/NRC (2006)] and leukemia. This is in agreement with the position of NA/NRC.

A reliable value for the DDREF remains somewhat elusive and ranges between one and two among the different national and international organizations. This uncertainty is largely the result of a lack of comprehensive data for chronic effects in laboratory animal and cellular studies that can be used for the calculation (there are currently quite limited human data available for cancer and noncancer outcomes following chronic exposures). NASA chose to use an average value of 1.75 based on ICRP (2007) (a value of two) and NA/NRC (2006) (a value of 1.5) estimates. NA/NRC considered this to be somewhat problematic given that equal weights are applied and this is not likely to be appropriate. In response, NASA selected the NA/NRC value of 1.5 for DDREF in their final model. In addition, NASA conducted a comprehensive Bayesian analysis to develop a revised estimate of the DDREF uncertainty distribution.

There is considerable uncertainty associated with the estimates of quality factors for the various high-LET radiations experienced in the space environment. A lack of usable data for laboratory animal and cellular systems is at the heart of this significant level of uncertainty; human data are highly limited or not available at all for HZE particles. In their revised model, NASA expanded the data sets used to set parameter values for the estimation of quality factors but still found these to be quite limited in overall value to the task, especially because of the scarcity of data sets for endpoints closely related to cancer. Planned research is designed to fill this data gap and the new parameterized function for estimation of quality factors should facilitate design of such research.

3.3 Comments on the NSCR-2012 Model for Space Missions

The NSCR-2012 model for space radiation cancer risk projections and uncertainties is based on a comprehensive compilation of the current state of knowledge of radiation epidemiology, radiobiology, and the space environment that is incorporated into radiation protection standards for crew members. It is apparent, as recognized by NASA and in the review by NA/NRC (2012), that there remain significant uncertainties in cancer (and noncancer) risk estimates for low-LET radiations and even more so for predicted effects for high-LET exposures. This uncertainty is due to the current limited knowledge of the relevant biological mechanisms necessary for extrapolation from the results of available epidemiologic studies to the NASA exposure scenarios. These epidemiologic studies are themselves constrained by the limitations of the available data sets. However, it is clear that the NSCR-2012 model has made every attempt to account for these identified uncertainties in the development of REID.

The approach taken by NASA in developing radiation protection standards (SPELs that can be considered in the context of safe days in space) represents a departure from those used over time by EPA, ICRP, and NA/NRC in that they are based on risk directly rather than on a dose-based system used by these other organizations. NCRP Report No. 171 (NCRP, 2012) on uncertainties in the estimation of radiation risks provides a discussion of the advantages of such a risk-based approach. NASA has relied extensively on the data and approaches used by other organizations (*e.g.*, EPA, ICRP, NA/NRC, NCRP) for the calculation of cancer risk estimates for a U.S. population exposed to acute or chronic low-LET radiation. These efforts have received extensive scrutiny and have been accepted as an appropriate methodology.

The review by NA/NRC (2012) identified the major concerns with the NSCR-2010 model (Cucinotta *et al.*, 2011a) and NASA in its revised NSCR-2012 model (Cucinotta *et al.*, 2013a) addressed these in a responsive manner. It remains clear that there are issues especially related to uncertainty in cancer risk estimates (*e.g.*, quality factors and DDREF) but these can only be addressed by additional research. Research plans provided by NASA as part of their model development do begin to address these more significant uncertainties (Section 3.4). No additional concerns have been identified with the NASA cancer risk projection model in this Commentary and it is well suited for use in setting radiation protection standards for space missions.

3.4 NASA Research to Address Uncertainties in Cancer Risk Estimates

In NASA's *Human Research Program Integrated Research Plan* (NASA, 2012), the near-term goals for cancer research focus on reducing the uncertainties in risk projections through the development of tissue-specific models of cancer risks and the underlying mechanistic understanding of these models, together with appropriate data collection at NSRL. NASA (2012) explains that the two major research emphases are on "testing the correctness of the NCRP model" (NCRP, 2000) that is used as the basis of the NASA cancer risk projection model and on "reducing the uncertainties in the coefficients that enter into the cancer projection model." The strategy has been to integrate NASA-funded experimental research, both intramural and extramural, performed mainly with exposures at NSRL into theoretical/analytic work directed towards improvements to the risk-projection models and related tools. Central coordination of the several parts has been provided by the Space Radiation Element of NASA's Human Research Program. NCRP views this as an efficient and effective strategy to tackle the range of difficult interdisciplinary questions that need to be answered for the reduction of uncertainties in risk projections from space radiation.

Sections 3.4.1 and 3.4.2 briefly summarize NASA research results that have already had direct impact on, and were incorporated into, recent development of the current NSCR-2012 model (Cucinotta *et al.*, 2013a). Section 3.4.3 summarizes the scope of the current NASA