I. Executive Summary and Overall Evaluation

The 2015 Space Radiation Standing Review Panel (from here on referred to as the SRP) met for a site visit in Houston, TX on December 8 – 9, 2015. The SRP reviewed the updated Evidence Reports for the Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs), the Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure, and the Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation, as well as the research plan for the Risk of Radiation Carcinogenesis.

The SRP appreciated the time and effort that the Space Radiation Element put into their review documents and presentations. The SRP felt that the 2015 Evidence Reports were very thorough and addressed the majority of the known issues. All three of the Evidence Reports were very clean, well-presented, and a representation of the literature/evidence.

Given increasing evidence suggesting that immune system factors could link the biological effects of space radiation across cancer, cardiac, vascular and CNS systems, it is recommended that a coordinated effort be made across these disciplines in the Space Radiation Element. This may include obtaining additional expertise in immunity, inflammation and neuroinflammation to provide guidance on these studies. Another area that should be developed is the utilization of various forms of biomedical imaging, both as a biomarker and as a potential technique for providing more precise risk estimates.

Overall, the SRP thinks the Space Radiation Element research teams have compiled excellent reports which integrate the majority of background information available in the literature.

II. Review of the Evidence for the Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs) (Acute Risk)

1. Evaluate the 2015 Acute Evidence Report using the following criteria:

   A. Does the 2015 Evidence Report provide sufficient evidence that the Risk is relevant to long-term space missions?

   Yes, the SRP thinks the 2015 Acute Evidence Report provides sufficient evidence that the Risk is relevant to long-term space missions.

   B. Are the Risk Title and Statement properly stated in the current version of the HRP Integrated Research Plan (IRP)?

   Yes, the Risk Title and Statement are properly stated in the current version of the HRP Integrated Research Plan (IRP).
Yes, the SRP thinks the Risk Title and Statement are properly stated in the current version of the IRP.

C. Is the text of the Risk Context provided in the HRP IRP clear?*

The SRP thinks the text of the Risk Context is appropriate, but suggests that the list of “Synergistic Gaps” should be called *Multifactorial Gaps*.

Also, the SRP suggests rewording the Acute - 1 as follows: (suggested edits in bold) Acute - 1: Determine the dose response for acute effects *(focusing on effects that are evident at space-relevant doses)* induced by SPE-like radiation, including additive and possibly synergistic effects arising from other spaceflight factors (e.g. altered gravity (microgravity), stress, altered immune function, or other) that modify and/or enhance the biological response.

D. Does the 2015 Evidence Report make the case for the research gaps presented?

The current Gaps (listed under the Risk Context) still imply you have a problem while some have had solutions. Change these Gaps to Multifactorial Gaps (as stated above).

Is an underlying degenerative disease a risk factor for an acute toxicity to radiation? Many chronic and aging diseases are associated with inflammation that often can lead to fibrotic processes. Given that some astronauts are already in their fifties when they fly and the likelihood that there will be older astronauts on at least the first deep space missions (need for lots of experience that comes with age and number of flights) the SRP suggests that consideration be given to interaction of underlying degenerative disease with radiation toxicity.

E. Are there any additional knowledge-type gaps or areas of fundamental research that should be considered to enhance the basic understanding of this specific Risk?

Absent, multifactorial gaps and underlying disease affecting the acute effects of radiation, the Evidence Report correctly focuses on the blood forming organs and to a lesser extent possible higher skin doses (that do not penetrate in the body) interacting with the central nervous system (CNS) or Blood-forming Organs (BFO) to cause effects at lower total doses than might be expected. However, there is one issue that is still not clearly defined and that should be. This is the effect of dose rate. It is time that fuzzy comments about low dose rate and very low dose rate having effects on ultimate toxicity are clearly specified. For SPE events the Evidence Report clearly shows that 95% or more of the dose will be from protons. There is ample literature that shows that either fractionating or lowering dose rate of proton exposure reduces acute effects. Given the worst case scenario expounded upon in the Evidence Report of the 1972 SPE event and that the shielding engineers seem to be settling on 20g/cm of aluminum it should be possible to calculate the expected dose rate and even though the dose is expected to be below that which will cause acute radiation syndrome (ARS) effects it be tested at the dose rate and at that maximum dose. Resolve this issue once and for all. As far as the small amount of heavy ions (HZE) are concerned the dose rate is
extremely low and again if calculated the SRP suggests this dose is by individual ions separated by significant time and should be considered discrete high dose rate events of small doses. Thus members of the SRP consider it unlikely that dose rate is an issue for HZE particles. (This is also likely true for CNS effects, cardiovascular effects and cancer risk endpoints.

F. Does the Evidence Report address relevant interactions between this Risk and others in the HRP IRP?

The SRP thinks the 2015 Acute Evidence Report addresses existing interactions between the Risk and other Risks in the HRP IRP.

G. Is input from additional disciplines needed?

The SRP thinks the following emerging areas should be considered in the 2015 Acute Evidence Report: expand immunology, coagulopathies, endothelial cells as potential target cells, inflammation as playing a role in the acute response, vascular changes.

H. Is the expertise of the authors sufficient to fully cover the scope of the given risk?

Yes, the SRP strongly believes that the team of authors is very knowledgeable and there are enough team members of different disciplines and backgrounds to make assessments.

I. Is there information from other HRP disciplines that need to be included in the 2015 Evidence Report?

The SRP thinks more interaction with the immune discipline should be part of the 2015 Acute Evidence Report.

J. Is the breadth of the cited literature sufficient?

There is currently not enough immune expertise to inform the 2015 Acute Evidence Report.

K. What is the overall quality and readability of the 2015 Evidence Report?

The SRP thinks the 2015 Acute Evidence Report is well written and organized.

III. Review of the Evidence for the Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure (CNS Risk)

1. Evaluate the 2015 CNS Evidence Report using the following criteria:

   A. Does the 2015 Evidence Report provide sufficient evidence that the Risk is relevant to long-term space missions?
The SRP thinks the 2015 CNS Evidence Report provides sufficient evidence that the Risk is potentially relevant to long-term space missions.

B. *Are the Risk Title and Statement properly stated in the current version of the HRP Integrated Research Plan (IRP)?*

Yes, the SRP thinks the Risk Title and Statement are properly stated in the current version of the IRP.

C. *Is the text of the Risk Context provided in the HRP IRP clear?*

The SRP suggests rewording the Risk Context to (suggested edits in bold and strikethrough):

Possible acute (in-flight) and late risks to the central nervous system (CNS) from galactic cosmic rays (GCR) and solar particle events (SPE) are documented concerns for human exploration of space. Acute CNS risks may include: altered cognitive function, impaired motor function, and behavioral changes, all of which may affect performance and human health. Late CNS risks may include neurological disorders such as Alzheimer’s disease, dementia or accelerated aging. Although detrimental CNS changes are observed in humans treated with high dose radiation (e.g., gamma rays and protons) for cancer and are supported by experimental evidence showing neurocognitive and behavioral effects in animal models, the significance of these results to the morbidity of astronauts has not been elucidated. There is a lack of human epidemiology data on which to base CNS risk estimates and therefore risk projection based on scaling to human data, as done for cancer risk, is not possible for CNS risks. Research specific to the spaceflight environment using animal and cell models must be compiled to quantify the nature and magnitude of CNS changes in order to estimate these risks and to establish validity of the current Permissible Exposure Limit (PEL). In addition, the impact of radiation exposure in combination with individual sensitivity or other spaceflight factors, as well as assessment of the need for biological/pharmaceutical countermeasures will be considered after further definition of CNS risk occurs.

D. *Does the 2015 Evidence Report make the case for the research gaps presented?*

The SRP suggests the following rewording and moving of some of the research Gaps presented in the 2015 CNS Evidence Report (suggested edits in bold and strikethrough):

CNS - 1: **What are Are there** significant adverse changes in CNS performance in the context and time scale of spaceflight operations? **If so, How** how is significance defined, and which neuropsychological domains are affected? **Is there a significant probability** that space radiation exposure would result in adverse changes? **What are the pathways and mechanisms of change?**

CNS - 2: **Does space radiation exposure elicit key events in adverse outcome pathways associated with neurological diseases?** What are the key events or hallmarks, their time sequence and their associated biomarkers (in-flight or post-flight)?
CNS - 3: How does individual susceptibility including hereditary pre-disposition (e.g. Alzheimer’s, Parkinson’s, apoE allele) and prior CNS injury (e.g. concussion, chronic inflammation or other) alter produce significant CNS risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?

Gap CNS – 8 has a higher priority and should become CNS – 4:
CNS - 8: Are there significant CNS risks from combined space radiation and other physiological or spaceflight factors, e.g., psychological (isolation and confinement), altered gravity (microgravity), stress, sleep deficiency, altered circadian rhythms, hypercapnea, altered immune, endocrine and metabolic function, or other?

Gaps 4, 5, 6, and 7 are contingent on one of the previous Gaps being correct. None of the following Gaps will be useful unless there is a real Risk.
CNS - 4: What are the most effective biomedical, exercise and conditioning, or dietary countermeasures to mitigate CNS risks? By what mechanisms are the countermeasures likely to work?
- The SRP recommends adding “exercise and conditioning” to the Gap title. Exercise and conditioning is commonly used in the medical field to talk about ways to get the body in good shape to handle stresses, to have improved range of motion, to strengthen muscles, etc. The official definition is: Exercise is physical activity that is planned, structured, and repetitive for the purpose of conditioning any part of the body. Exercise is used to improve health, maintain fitness and is important as a means of physical rehabilitation.

CNS - 5: How can new knowledge and data from molecular, cellular, tissue and animal models of acute CNS adverse changes or clinical human data, including altered motor and cognitive function and behavioral changes be used to estimate acute CNS risks to astronauts from GCR and SPE?

CNS - 6: How can new knowledge and data from molecular, cellular, tissue and animal models of late CNS risks or clinical human data be used to estimate late CNS risks to astronauts from GCR and SPE?

CNS - 7: What are the best shielding approaches to protect against CNS risks, and are shielding approaches for CNS and cancer risks synergistic?

E. Are there any additional knowledge-type gaps or areas of fundamental research that should be considered to enhance the basic understanding of this specific Risk?

The SRP does not think any additional knowledge-type gaps should be considered, but again, all of the knowledge gaps are contingent on there being a Risk.

F. Does the Evidence Report address relevant interactions between this Risk and others in the HRP IRP?
The SRP thinks the 2015 CNS Evidence Report addresses relevant interactions between this Risk and other Risks in the HRP IRP.

G. Is input from additional disciplines needed?

The SRP thinks there is some missing input from other disciplines/science areas:
- More awareness of changes on-going in the medical imaging field would be useful.
- CNS-based biomarkers are missing (Cerebrospinal fluid (CSF) imaging approaches). Given the difficulties in relating behavioral observations between the animal model studies and those potentially observed in human astronauts, it is essential to utilize CNS biomarkers to begin to develop more clear assessments of risk. This could include fluid and tissue biomarkers, although blood-based biomarkers have not proven terribly reliable for detecting various CNS abnormalities. While CSF is a more relevant biofluid, this may prove more difficult to routinely obtain from astronauts. Another approach recommended by the SRP would be various forms of brain imaging, including MRI and PET, where there have been remarkable advances in detecting and quantifying brain-based alterations.

H. Is the expertise of the authors sufficient to fully cover the scope of the given risk?

Yes, the SRP thinks the team of authors is very knowledgeable and there are enough team members of different disciplines and backgrounds to make assessments.

I. Is there information from other HRP disciplines that need to be included in the 2015 Evidence Report?

The SRP thinks more interaction with the immune discipline should be part of the 2015 Acute Evidence Report.

J. Is the breadth of the cited literature sufficient?

There is currently not enough immune literature cited to inform the 2015 CNS Evidence Report.

K. What is the overall quality and readability of the 2015 Evidence Report?

The SRP thinks the 2015 CNS Evidence Report was well written and organized.

IV. Review of the Evidence for the Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure (Degen Risk)

I. Evaluate the 2015 Degen Evidence Report using the following criteria:
A. Does the 2015 Evidence Report provide sufficient evidence that the Risk is relevant to long-term space missions?

The SRP thinks the 2015 Degen Evidence Report provides sufficient evidence that the Risk is potentially relevant to long-term space missions.

B. Are the Risk Title and Statement properly stated in the current version of the HRP Integrated Research Plan (IRP)?*

The SRP suggests rewording the Risk Title to (suggested edits in bold and strikethrough):

**The Risk of Cardiovascular Cardiac and Vascular Disease and Other Degenerative Tissue Effects from Radiation Exposure.** The risk to the heart and to the vascular system may have both common and also different mechanisms of injury.

The SRP suggests rewording the Risk Statement to (suggested edits in bold and strikethrough):

Given that crew is exposed to radiation from the space environment, there is the possibility that they will develop cardiac and vascular disease and other degenerative tissue effects.

C. Is the text of the Risk Context provided in the HRP IRP clear?*

The SRP suggests rewording the Risk Context to (suggested edits in bold and strikethrough):

Degenerative tissue (non-cancer or non-CNS) effects such as cardiovascular cardiac and vascular disease, cataracts, and others including digestive and respiratory diseases are documented following exposures (e.g., 2y) to terrestrial sources of ionizing radiation (e.g., gamma rays and x-rays). In particular, cardiovascular pathologies such as atherosclerosis are of major concern following gamma ray exposure. This provides evidence suggests a concern for possible degenerative tissue effects following exposures to ionizing radiation in the form of GCRs or SPEs expected during long-duration spaceflight. However, the existence of low dose thresholds at low doses, dose-rate and radiation quality effects, as well as mechanisms and major risk pathways, are not well-characterized. Degenerative disease risks are difficult to assess because multiple factors, including radiation, are believed to play a role in the etiology of the diseases. Data specific to the space radiation environment must be compiled to quantify the magnitude of this risk to decrease the uncertainty in current Permissible Exposure Limits (PELs), and to determine if additional protection or mitigation strategies are required.

D. Does the 2015 Evidence Report make the case for the research gaps presented?

The SRP suggests the following rewording and moving of some of the research gaps presented in the 2015 Degen Evidence Report (suggested edits in bold and strikethrough):

Degen - 1: How can tissue specific experimental models be developed for the major degenerative tissue risks, including cardiac, vascular, lens, and other tissue systems (e.g., immune, endocrine, respiratory and/or digestive) in order to estimate space radiation risks for degenerative diseases?
Degen - 2: What are the mechanisms of degenerative tissues changes in the **cardiac, vascular, lens, digestive, endocrine, and other tissue systems**? What surrogate endpoints do they suggest?

Degen - 3: What are the progression rates and latency periods for radiation-induced degenerative diseases, and how do progression rates depend on age, sex, radiation type, or other physiological or environmental factors?

Degen - 4: How does individual susceptibility, including hereditary predisposition **and age**, alter radiation-induced degenerative disease processes and risk estimates? Does individual susceptibility modify possible threshold doses for these processes in a significant way?

Degen - 5: What quantitative procedures **biomarkers, imaging tools**, or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict degenerative tissue risks in astronauts? How can human epidemiology data best support these procedures or models?

Degen - 6: What are the most effective biomedical, **exercise and conditioning**, or dietary countermeasures to mitigate degenerative tissue risks? By what mechanisms are the countermeasures likely to work? Are these countermeasures additive, synergistic, or antagonistic to other Risks?

Degen - 7: Are there synergistic effects from other spaceflight factors (e.g., altered gravity (microgravity), stress, altered immune function, altered circadian rhythms, or other) that modify space radiation-induced degenerative diseases in a clinically significant manner?

Degen - 8: Are there research approaches using simulated space radiation that can elucidate the potential confounding effects of **traditional risk factors** (e.g., tobacco **smoke, alcohol, environmental pollutants, etc.**) use on space radiation circulatory disease risk estimates?

**E. Are there any additional knowledge-type gaps or areas of fundamental research that should be considered to enhance the basic understanding of this specific Risk?**

The SRP does not think any additional knowledge-type gaps should be considered to enhance the Risk.

**F. Does the Evidence Report address relevant interactions between this Risk and others in the HRP IRP?**

The SRP thinks the 2015 Degen Evidence Report should include a section on exercise and risk mitigation.

**G. Is input from additional disciplines needed?**
The SRP thinks the issues of aging and senescence are covered well in the 2015 Degen Evidence Report and no additional disciplines are needed.

**H. Is the expertise of the authors sufficient to fully cover the scope of the given risk?**

Yes, the SRP thinks the team of authors is very knowledgeable and there are enough team members of different disciplines and backgrounds to make assessments.

**I. Is there information from other HRP disciplines that need to be included in the 2015 Evidence Report?**

The SRP thinks more interaction with the immune discipline should be part of the 2015 Degen Evidence Report.

**J. Is the breadth of the cited literature sufficient?**

There is currently not enough immune literature cited to inform the 2015 Degen Evidence Report.

**K. What is the overall quality and readability of the 2015 Evidence Report?**

The SRP thinks the 2015 Degen Evidence Report is well-written, laid out, and provides compelling evidence that additional research is required to understand the risks of acute CNS and late CNS effects from radiation exposure; all of which could contribute to degenerative effects.
V. 2015 Space Radiation SRP Evidence Review: Statement of Task for the Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs), the Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure, and the Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure

In 2008, the Institute of Medicine (IOM) reviewed NASA’s Human Research Program (HRP) Evidence Books that describe the Risks that were identified in NASA’s Human Research Program Requirements Document (PRD). The 2015 Evidence Reports for the Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs) (Acute Risk), the Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure (CNS Risk), and the Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure (Degen Risk) have not been reviewed since the last IOM review and there have been significant changes to the evidence base for these Risks.

The 2015 Space Radiation Standing Review Panel (SRP) is chartered by the Human Research Program (HRP) Chief Scientist to review the updated Evidence Reports for the Acute, CNS, and Degen Risks. The 2015 Space Radiation SRP will evaluate the Evidence Reports and generate a final report of your analyses of the evidence base, including any recommendations on how to improve the current Evidence Report, and submit it to the HRP Chief Scientist. Your report will also be made available on the Human Research Roadmap (HRR) website.

The 2015 Space Radiation SRP is charged to:

1. Evaluate the 2015 Acute, CNS, and Degen Risks Evidence Reports based on each of the following criteria:

   A. Does the 2015 Evidence Report provide sufficient evidence that the Risk is relevant to long-term space missions?
   B. Are the Risk Title and Statement properly stated in the current version of the HRP Integrated Research Plan (IRP)?*
   C. Is the text of the Risk Context provided in the HRP IRP clear?*
   D. Does the 2015 Evidence Report make the case for the research gaps presented?
   E. Are there any additional knowledge-type gaps or areas of fundamental research that should be considered to enhance the basic understanding of this specific Risk?
   F. Does the Evidence Report address relevant interactions between this Risk and others in the HRP IRP?
   G. Is input from additional disciplines needed?
   H. Is the expertise of the authors sufficient to fully cover the scope of the given risk?
   I. Is there information from other HRP disciplines that need to be included in the 2015 Evidence Report?
   J. Is the breadth of the cited literature sufficient?
   K. What is the overall quality and readability of the 2015 Evidence Report?
2. Provide comments on any important issues that are not covered by the criteria in #1 above.

* Please be aware that any suggested changes to the Risk Title, Statement, and Risk Context by the SRP may need to be approved by the Human Systems Risk Board (HSRB). The HSRB has the overall responsibility to implement and maintain a consistent, integrated process for assessing, documenting, and tracking all risks to the human system associated with spaceflight activities (both in flight and post flight).

**Additional information regarding this review:**

1. Attend a meeting at the NASA JSC on December 8 - 9, 2015 to discuss the Evidence Reports with the Space Radiation Program Element (SRPE). At this meeting, prepare a draft report that addresses each of the evaluation criteria listed in the panel charge (A-K) including any recommendations on how to improve the Evidence Reports. Debrief the HRP Chief Scientist (or designee) and representatives from the SRPE on the salient points that will be included in the final report and specifically the items in the panel charge.

2. Prepare a draft final report within one month of the meeting that contains a detailed evaluation of the Evidence Reports specifically addressing items #1 and #2 of the SRP charge. The draft final report will be sent to the HRP Chief Scientist and he will forward it to the appropriate Element for their review. The SRPE and the HRP Chief Scientist will review the draft final report and identify any misunderstandings or errors of fact and then provide official feedback to the SRP within two weeks of receipt of the draft report. If any misunderstandings or errors of fact are identified, the SRP will be requested to address them and finalize the 2015 SRP Final Report as quickly as possible. The 2015 SRP Final Report will be submitted to the HRP Chief Scientist and copies will be provided to the SRPE and also made available to the other HRP Elements. The 2015 SRP Final Report will be made available on the HRR website (http://humanresearchroadmap.nasa.gov/).
To clarify, the Risk Statement and Risk Context are defined as follows:

**Risk Statement:**
“Given the CONDITION, there is a possibility that a CONSEQUENCE will occur”.

Condition: a single phrase briefly describing current key circumstances, situations, etc. that are causing concern, doubt, anxiety, or uncertainty – something that keeps you up at night.

Consequence: a single phrase or sentence that describes the key, negative outcome(s) of the current conditions.

Notes:
The condition-consequence format provides a more complete picture of the Risk, which is critical during mitigation planning. The condition component focuses on what is currently causing concern. This is something that is true or widely perceived to be true. This component provides information that is useful when determining how to mitigate a Risk.

The consequence component focuses on the intermediate and long-term impact of the risk. Understanding the depth and breadth of the impact is useful in determining how much time, resources, and effort should be allocated to the mitigation effort.

A well-formed Risk Statement usually has only one condition, and has one or more consequences.

**Risk Context:**
Purpose: provide enough additional information about the Risk to ensure that the original intent of the Risk can be understood by other personnel, particularly after time has passed.

Description: capture additional information regarding the circumstances, events, and interrelationships not described in the Risk Statement.

An effective context captures the what, when, where, how, and why of the Risk by describing the circumstances, contributing factors, and related issues (background and additional information that are NOT in the Risk Statement).
VI. 2015 Space Radiation Standing Review Panel Roster

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