REVIEW OF NASA'S HUMAN RESEARCH PROGRAM EVIDENCE BOOKS

A Letter Report

COMMITTEE ON NASA'S RESEARCH ON HUMAN HEALTH RISKS

BOARD ON HEALTH SCIENCES POLICY

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Review of NASA's Human Research Program Evidence Books

A Letter Report

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Independent Report Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Jay Buckey, Dartmouth-Hitchcock Medical Center
Louis Anthony (Tony) Cox, Jr., Cox Associates
James Lackner, Brandeis University
Walter Schimmerling, Consultant
Peter Suedfeld, University of British Columbia
Warren Zapol, Massachusetts General Hospital

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **John R. Ball,** American Society for Clinical Pathology, appointed by the Institute of Medicine, who was responsible for making certain that an independent examination of this report was carried out in accordance

with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES
Committee on NASA's Research on Human Health Risks

June 18, 2008

Richard S. Williams, M.D.
Chief Health and Medical Officer
National Aeronautics and Space Administration
Office of Health and Medical Systems
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Dear Dr. Williams:

At the request of the National Aeronautics and Space Administration (NASA), the Institute of Medicine (IOM)—under the auspices of the Standing Committee on Aerospace Medicine and the Medicine of Extreme Environments—established the Committee on NASA's Research on Human Health Risks to examine NASA's plans to assemble the available evidence on human health risks of spaceflight and to move forward in identifying and addressing gaps in research. The body of this letter report provides the committee's findings and recommendations regarding NASA's compilation of the available evidence into reviews, or evidence books, as well as NASA's risk identification and assessment process. Overall, the committee believes NASA has developed a thorough and well-conceived framework for documenting the evidence base, establishing research priorities, and integrating research findings into occupational health and safety measures for the space crew. With the goal of further improving the process, the report offers its findings and recommendations (details below) relevant to:

- Strengthening the content and format of the evidence books; and
- Enhancing the process for updating and disseminating the evidence books.

In addition, the committee offers specific suggestions to improve four of the evidence books as well as assessments of each evidence book (Appendix C).

CHARGE TO THE COMMITTEE

In response to a request from the NASA Human Research Program, the IOM established an ad hoc committee to review each evidence book and assess the relevance of the identified human health-related risks for long-term spaceflight; appraise and clarify the descriptions of the risks; and assess the associated gaps in knowledge and identify additional areas for research (Box 1).

Responding to NASA's request, the IOM appointed the 12-member Committee on NASA's Research on Human Health Risks with expertise in aerospace medicine, occupational health, preventive medicine, radiation medicine, bone loss, physiology/kinesiology, risk assessment and risk management, behavioral health, human performance, and cardiovascular and renal medicine. The committee met twice during the course of

BOX-1
Statement of Task

An ad hoc committee will assess the set of human health-related risks for long-term spaceflight and related research gaps identified by the National Aeronautics and Space Administration (NASA).

The committee will build on the 2006 Institute of Medicine report, *A Risk Reduction Strategy for Human Exploration of Space: Review of NASA's Bioastronautics Roadmap*, in assessing the set of risks identified in NASA's Human Research Program Requirements Document (PRD). The committee will also draw on supplemental information compiled by NASA in a series of evidence books, which will be publicly available. Specifically, the committee will:

- Assess the relevance of the identified health risks as potential threats to long-term space missions, including an assessment of the selection of these risks from the larger set described in the Bioastronautics Roadmap;
- Appraise and clarify the descriptions of the human health-related risks in the PRD; and
- Assess the associated gaps in knowledge and identify additional areas for research as necessary.

its work (Appendix A: Meeting Agenda). The first meeting was held in conjunction with a public data-gathering session with NASA staff, who provided program background and a review of the process used to generate the evidence books. In addition, NASA staff provided the first four evidence books for initial discussion. At the second meeting, the committee reviewed and assessed each evidence book, specifically evaluating each based on the following criteria:

- Does the evidence book provide sufficient evidence that the risk is relevant to long-term space missions?
- Is the text of the short description of the health risk provided in the Program Requirements Document (PRD) clear?
- Does the evidence book make the case for the research gaps presented?
- Are there any additional gaps in knowledge that should be considered for this specific risk?
- Does the evidence book address relevant interactions among risks?
- Is the expertise of the authors sufficient given the risk?
- Are additional disciplines needed?
- Is the breadth of the cited literature sufficient?
- What is the overall readability and quality?

The committee's assessment of each of the 25 evidence books is provided in Appendix C. In discussing these assessments, the committee identified several overarching issues that it believed would be important for NASA to consider. Additionally, the committee examined NASA's process for compiling and updating the evidence books. This letter report is based on the committee's expert judgment and assessment of the evidence books provided by NASA. The committee did not conduct a formal assessment of research needs. This type of in-depth effort was not possible within the time allotted to the committee given the breadth of the topics and the scope of such a review.

BACKGROUND

Planning for long-duration space flights requires consideration of complex disease prevention, behavioral health, and clinical treatment issues—issues resulting from the hazards of the space environment and

from limitations to in-mission medical care. These research and development needs have prompted NASA to seek and coordinate assessment from both national and international space medicine practice as well as biomedical research communities.

In considering the multiple potential hazards and health issues related to long-duration spaceflight, NASA staff developed the Bioastronautics Roadmap—a framework developed and used by NASA to assist in identifying research priorities and technology development, establishing exposure standards, and guiding resource allocation. In 2003, NASA requested that The National Academies conduct an evaluation of the Bioastronautics Roadmap. The resulting IOM report, *A Risk Reduction Strategy for Human Exploration of Space: A Review of NASA's Bioastronautics Roadmap* (IOM, 2006), focused its findings and recommendations on accelerating countermeasure and technology development; establishing a safe radiation exposure level for all relevant risks; and improving the process by which the content of the Roadmap was represented, communicated, and kept current. Among the recommendations relevant to this study were incorporating quality-of-evidence measures for risks; representing risk severity separately from the state of the mitigation strategy or countermeasure; using standard uncertainty analysis techniques to quantify risk uncertainty; and ensuring that the Roadmap is viewed as a dynamic and current database rather than simply a static document. In addition, in 2007 the IOM released a letter report, *Review of NASA's Space Flight Health Standards-Setting Process: Letter Report*, that provided NASA with a set of recommendations on how it establishes space flight health standards for human performance (IOM, 2007).

Building on the Bioastronautics Roadmap, NASA's Human Research Program (HRP) has developed a new process within the past year to ensure proper attention is given to addressing potential human health risks. This process includes the compilation of the Program Requirements Document, which focuses on 28 specific health risks (see Appendix B for a table showing the relationship of these risks with the risks in the Bioastronautics Roadmap and PRD) (NASA, 2008a). The evidence base was compiled into a series of 25 evidence books, each of which reviews the spaceflight and ground evidence relevant to the specific risk (NASA, 2008b). The initial set of evidence books was compiled by NASA using specific guidelines developed by NASA and provided to the committee for their review. The purpose of the evidence books is to document and review the available evidence supporting the identification

of each performance risk identified in the HRP Program Requirements Document but not to provide strategic guidance for how NASA may wish to mitigate the associated risks. The goal is to periodically update these reviews and establish a record of the current state of knowledge associated with each risk (NASA, Human Research Program Integrated Research Plan, HRP 47065). The content of these evidence books and the process by which risks were selected for inclusion provides the basis for this letter report.

At the committee's first meeting, NASA staff provided a briefing on the Human Research Program's continuous risk management process—an iterative process focused on assessing how best to prevent and treat injuries, illnesses, or concerns regarding the health of the spaceflight crew. The process being set in place by the HRP calls for the following:

- Identification of the health risks through the Bioastronautics Roadmap and through the risk forums (Box 2);
- Assessment of the evidence base through the development and refinement of the series of evidence books:
- Review of the evidence and gaps in the research base through the risk forums and reviews by standing review panels (Box 2);
- Developing, awarding, and implementing research grants and contracts; and
- Review of research results by NASA.

Research data from multiple sources are then incorporated into prevention and mitigation strategies used in spaceflight; these can serve as the basis of future research and of improvements for future spaceflights. This report addresses the early stages of this process.

FINDINGS REGARDING SPECIFIC EVIDENCE BOOKS

The committee commends NASA for taking the initial steps of assembling the documentation of scientific knowledge regarding the risks that have highest relevance to human health during long-duration spaceflight beyond low Earth orbit. These evidence books are part of a broader process to prioritize risks and associated research needs and to identify mitigation strategies. While the committee found specific areas for improvement in each of the evidence books—including in some cases

BOX-2
Human Research Program Risk Forums and the Human System Risk Board

NASA's Human Research Program (HRP) is in the process of establishing and implementing risk forums, which will meet regularly (as often as twice a month) to promote cross-disciplinary discussion about each health risk as well as considering potential new topics that should be explored. The membership of the forum includes the chief medical officer, who serves as the forum's chair; the senior flight surgeon; a senior representative for Physiology; a senior representative for Environmental Factors; a senior representative for Human Factors; a representative from the Astronaut Office; an International Space Station/Shuttle Transportation System representative; a Constellation Program representative; and the Program Manager from HRP. These individuals also make up the membership of the Human System Risk Board, which is responsible for ensuring that a consistent, integrated process is established and maintained for managing human system risks; advising the Health and Medical Technical Authority and other relevant program representatives concerning the status, coordination, integration, mitigation, and research strategy of all human system risks; and facilitating human system risk management in support of the chief medical officer (Personal communication, C. Kundrot, NASA, April 1, 2008).

Anyone is permitted to bring forward a potential health risk to the Human System Risk Board. To do so the board requires that the potential risk be described in the form of a "risk statement," describing the risk context and any available evidence. For example, the statements include any available evidence of pre- or postflight incidence, similar risks in analog terrestrial populations, relevant case studies, and expert opinion from relevant communities. The Board also reviews the potential risks for relevance to the mission, including, among other things, operational mission impact, acute and long-term health risks, and performance impacts.

the need to improve the relevancy of the identified risks and discussion of additional knowledge gaps and potential associations between related risks—overall the committee believes that they are valuable resources and important components to the overall process, reflecting the current state of knowledge on health risks associated with spaceflight, and believes if the evidence books are kept current, their value will increase over time. Through continued improvements and updates the evidence books will help communicate gaps in knowledge and the resulting needs for research and development and will provide an archive of progress made in understanding health risks of human space flight.

The committee offers its findings and recommendations with the goal of improving future versions of the evidence books. The committee

hopes that maintaining these up-to-date summaries of the state of knowledge on human health risks of spaceflight will continue to be a priority at NASA and that the committee's comments will be useful in improving the process by which that is done.

In addition to the committee's overall findings and recommendations, this report offers specific comments for each evidence book that are included in Appendix C. Further, the committee makes a number of suggestions to address instances in the set of evidence books where there was unevenness, lack of clarity in the scope of the review, readability issues, or other issues such as lack of definition of physiological requirements and benchmarks.

Modifying the Scope and Focus of the Evidence Books

The committee found the identified health risks to be largely relevant as potential threats to long-term space missions. As discussed below and in the individual reviews in Appendix C, some of the evidence books would benefit from increased clarity or change in scope. In a few cases, the committee found that although the risks that were identified in the PRD were of clear significance, the focus of the evidence books could be broadened to better address the breadth of potential risks and research gaps. In particular, the committee has the following comments regarding four specific evidence books:

- #7: Operational Impact of Prolonged Daily Exercise;
- #10: Cardiovascular Effects on Performance and Operational Limitations;
- #16: Behavioral and Psychiatric Conditions; and
- #23: Lack of Human-Centered Design.

Operational Impact of Prolonged Daily Exercise

Evidence book #7, Operational Impact of Prolonged Daily Exercise, discusses an issue that is considerably broader in scope than the current title implies. Exercise is only one possible countermeasure against physiological deconditioning, and is neither fully effective nor operationally satisfactory at this time. The current iteration of the evidence book provides a brief overview of the issue and acknowledges that no

evidence exists to support this potential risk; furthermore, no references are provided. As written, there is no evidence to support the inclusion of this risk in the PRD. However, the committee agrees that it is self-evident that a competition for time exists between countermeasure programs and other mission demands. In a broader context, many operational tensions are present for any human risk mitigation (countermeasure) strategy, including competition for consumable resources (e.g., food, water, oxygen) as well as the mass, volume, and power that a countermeasure may require (e.g., exercise equipment, radiation shielding). Thus, the problem is one of systems engineering in which the human is a recognized subsystem. The committee believes this is a valid area for research and development that has characteristics unique to spaceflight.

Because the central challenge is one of systems engineering, this risk spans the Human Research Program and the Exploration Technology Development Program. To some extent, research from analog environments may help populate the evidence base. For example, data collected from nuclear submarines may be relevant in some circumstances since submarines have volume, time, and consumable resource restraints not altogether different from spaceflight. The committee suggests changing the scope of the evidence book to Operational Impact of Countermeasures. The scope of this risk should be broadened to include the effects of countermeasure testing, effectiveness, crew acceptability, and implementation on both spacecraft and mission design.

Cardiovascular Effects on Performance and Operational Limitations

The committee found that the topic of evidence book #10, Cardiovascular Effects on Performance and Operational Limitations, is a subset of the broader issue of the effects of decrements in work capacity on operational performance. In some cases that involve sustained higher level energy expenditure (e.g., "the lunar 10K walk back" scenario), the cardiovascular system may indeed be limiting. In other cases such as extra vehicular activity, muscle strength and endurance may be limiting factors. The committee believes the common consideration is that physiological systems may limit physical work capacity, but the specific system that creates a concern will depend on the unique requirements of an operational task.

The committee suggests that this risk should be redefined to Physiological Limits on Performance and Operations to include effects such as cardiovascular, metabolic, strength, and thermal limits that might cause operational tasks to be limited or redefined. Setting physiological requirements for mission-related tasks and adequate assessment methods for each will help guide the effectiveness of the countermeasure program in maintaining each system for operational performance.

Behavioral and Psychiatric Conditions

In reviewing evidence book #16, Behavioral and Psychiatric Conditions, the committee found that it did not include any substantive review of those features of personality and behavioral performance that would be most likely to promote effective crew performance (and thus might become "select-in" criteria). Such a review would be a valuable addition to the white paper that would likely identify important knowledge gaps in the behavioral assessment plan. Current research and understanding of the manifestation of behavioral and psychiatric problems in space are, simply stated, inadequate, and from the perspective of a balanced approach, little attention has been paid to potential psychological benefits of spaceflight. The committee appreciates that the absence of a body of detailed quantitative evidence concerning behavioral and psychiatric problems in space is understandable, given the sensitivity of the topic and privacy concerns. Behavioral and psychiatric problems have been viewed as operational medical issues that are held confidential, rather than as a health-related research agenda that deserves co-equal status with somatic health issues. The committee believes the potential seriousness of the psychological and behavioral health risks highlights the need for the evidence book to contain a review and any relevant data, including an analysis of newer instruments and scales for evaluating more subtle personality differences. Including this information will also point to potential associated research gaps. In addition, the committee notes that the extensive list of current countermeasures is tied neither to the published evidence base of psychological interventions nor to measures of effectiveness. A systematic evaluation of current and proposed countermeasures should be included in future iterations of the evidence book.

Lack of Human-Centered Design

Evidence book #23, entitled Lack of Human-Centered Design, addresses three risks related to human factors—inadequate information, poor human factor design, and poor task design. The committee had three concerns with this evidence book. First, the committee believes the information-related issues are sufficiently distinct from the other human factors issues, and sufficiently related to other issues beyond the human factors issues, to warrant a discussion and review of the evidence in a stand-alone evidence book. Moreover, this review should consider not only inadequate information, but also excessive information and the potential cognitive overload resulting from an overabundance of information of varying degrees of priority, improperly presented, that can increase the risk of error or jeopardize safety. Second, the topics of task design and human factor design need to be more clearly defined and more sharply distinguished from each other. The risks are important, but they need to be presented in a manner that more closely reflects the established discipline of human factors engineering, and less in general terms of systems effectiveness. The committee suggests that the differences and interrelationships between these two areas be clarified so that the redundancies and overlaps in the current evidence book can be eliminated. The committee recommends that the evidence books focus on examples that are of greater specificity and relevance to spaceflight human factors issues, rather than more generalized examples of crises. The committee believes that by eliminating or greatly shortening many of the ground-based examples, such as Three Mile Island or the Titanic, in the current evidence book the value of specific human factor examples in space will be significantly enhanced.

OVERARCHING FINDINGS AND RECOMMENDATIONS

The committee organized its recommendations into two broad areas: (1) issues focused on strengthening the content and format of the evidence books, and (2) issues relevant to improving the process of updating and disseminating the evidence on human health risks.

Strengthen the Content and Format of the Evidence Books

Recommendation 1: <u>Strengthen the Content and Format of the Evidence Books</u>
NASA should continue to refine its evidence books and work to ensure further consistency and depth of analysis. Specifically, NASA should:

- **Require that all evidence reviews use the quality-of-evidence criteria;**
- **Encourage a broader review of all relevant literature and knowledge bases, including in-flight data and other relevant data sources (e.g., NASA Life Sciences Data Archive, Longitudinal Study of Astronauts' Health, data from other space agencies);**
- **Include, or link to, a summary of the current state of knowledge regarding countermeasures and the plan to mitigate risk;**
- **Improve the consistency and organization of the discussions on identified research gaps;**
- **Increase the emphasis on potential postflight and long-term health outcomes; and**
- **Develop evidence books on additional risks, including alterations in microbe and host interactions and impaired healing function.**

Expand the Literature Base and Categorize the Quality of Evidence

The authors of the evidence books were asked to include the risk statements as they were written in the PRD, and review the risks based on published and unpublished scientific and clinical evidence from data collected from space- and ground-based research on humans, animals, and other models. This resulted in a wide variety and quality of cited data, such as unpublished results, observational studies, meta-analyses, and randomized trials.

In this context, the evidence books varied considerably in the scope of the published and unpublished data reviewed. In addition to a comprehensive review of all relevant terrestrial and space published data, the

committee encourages the authors to explore data from other sources. For example, reviews of data from international space agencies are particularly relevant and should be added where possible. Furthermore, authors should be encouraged to review the NASA Life Sciences Data Archive for relevant data (http://lsda.jsc.nasa.gov/). However, the committee recognizes the potential limitations associated with these data sources and encourages NASA's HRP to collaborate with its programmatic partners to expand pre-, in-, and post-flight data collection.

In NASA's instructions the authors of the evidence books were encouraged, but not required, to label evidence using its four categories.[1] However, to clarify the type of evidence presented and to provide additional information regarding the strength of evidence, the committee believes NASA should require authors to use categories of evidence in future versions of the evidence books, while recognizing that experience with the explicit categorization of evidence may be refined over time, particularly regarding the categories used. Apart from the absence of quality-of-evidence criteria, the first evidence book, Impaired Ability to Maintain Control of Vehicles and Other Complex Systems, stands out as a model for the clear presentation of a risk, the relevant evidence, and associated research gaps.

As a general observation, the committee found that the evidence books focused more on short-term health outcomes associated with specific risks, and in several circumstances did not include a discussion of the relevant potential long-term health outcomes associated with that risk. The committee encourages NASA to expand its reviews to acknowledge potential long-term health outcomes. Consideration should be given to including this as a standard element of an evidence book outline, wherever appropriate.

[1]Type I: at least one randomized, controlled trial. Type II: at least one controlled study without randomization, including cohort, case-control, or subject operating as own control. Type III: nonexperimental observations or comparative, correlation, and case or case-series studies opinion. Type IV: expert committee reports or opinions of respected authorities based on clinical experiences, bench research, or "first principles" (NASA, 2008b).

Improve Consistency of Writing Teams

The composition of the writing group and their understanding of the task varied considerably across the evidence books. Because the evidence supporting a particular risk must capture and summarize the knowledge base adequately, the teams constructing the evidence books must be knowledge-domain experts, working in a manner that is collaborative (teamwork), scholarly (academic), and egalitarian (nonadvocates for funding in their research area, working for the overall health and safety of astronauts).

Some evidence books were authored by a dozen or more individuals with a mix of knowledge experts and program managers, while others were authored by a single individual. The committee recognizes that team quality contributes directly to the scientific rigor and excellence of the evidence book; however, NASA did not appear to use a standard set of selection criteria for choosing the authors for each evidence book. In addition, once chosen it was not clear how each team member interacted and contributed to the final evidence book. Consequently, NASA should develop a consistent process for selecting authors and should implement standards for authorship based on assigning responsibility and giving credit for intellectual work, similar to those used by peer-reviewed journals. Statements regarding disclosure of conflicts of interest should also be required.

Summarize the State of the Knowledge on Countermeasures

Each evidence book included the primary knowledge gaps associated with each risk, as identified by the authors. Although the authors were instructed not to address potential mitigation strategies or known mitigation gaps, the committee believes that countermeasures are an important component of the evidence books and are integral to understanding the current state of scientific knowledge and the severity of the potential impact of the risks on the individual and the mission. To this end the authors should provide a link to a review of the state of knowledge on countermeasures. This review should include a discussion of the impact that countermeasures have had on risk mitigation and the identified research gaps, including countermeasures that have been implemented in space and those that been tested on the ground. Please note that, consistent with the Bioastronautics Roadmap review, care should be taken

to separate the description of the risk from the description of countermeasures.

Improve Consistency and Organization of Research Gaps

There is a great deal of variability in how the evidence books present and organize the associated gaps in knowledge and research. Since one of the major goals of the evidence books is to provide the evidence base on which to improve human health and reduce health risks associated with spaceflight, it is important to organize the discussion of research gaps so that their operational impact will be evident and the type of research or other actions needed to move forward is clearly defined. Therefore, the committee encourages NASA to develop a more uniform approach to how the gaps associated with each risk are presented. Each evidence book would be strengthened, for example, if it identified and organized the section on research gaps according to the following 5 specific categories or a similar categorical system:

1. Preventing and screening for avoidable in-flight events;
2. Managing the physiological adaptation to spaceflight during missions and to prevent long-term health consequences afterward;
3. Management of environmental factors, their effects, and potential countermeasures to these effects (e.g., radiation, lunar dust, atmospheric pressure, hypoxia);
4. Providing optimal treatment for biomedical events in space, recognizing limitations associated with space travel; and
5. Improving human factors design and the human-machine interface.

In circumstances when the above categorization is not directly applicable to the research gap, NASA should encourage the authors to provide details on recommended next steps.

Add Additional Health Risks

In its assessment of the set of evidence books, the committee noted two potential risks that were not addressed, but that the committee be-

lieved should be given consideration for inclusion in at least the "watch list" of possible risks. These include the risk of alterations in microbe and host interactions and the risk of impaired healing function. The risk of alterations in microbial pathogenicity was highlighted by a recent publication describing the bacterial pathogen Salmonella typhimurium grown aboard space shuttle mission STS-115 and compared with identical ground control cultures. Spaceflight samples exhibited enhanced virulence in a murine infection model and extracellular matrix accumulation consistent with a biofilm (Wilson et al., 2007). The risk of impaired bone and wound healing function was derived from experiments conducted with rats on STS-57 and Cosmos 2044 missions (Davidson et al., 1999) and rat hind-limb unloading models (Radek et al., 2008). In addition, there is anecdotal evidence from Mir to suggest that healing of minor cuts or abrasions may be delayed. The implications of poor wound healing, combined with the statistical prediction of the likelihood of traumatic injury contained in the evidence book on the risk of inadequate medical care, make a compelling case for an expanded research program in this area.

Continue to Improve NASA's Process for Updating and Disseminating the Evidence on Human Health Risks

The committee believes NASA has developed a thorough and well-conceived framework for documenting the evidence base, establishing research priorities, and integrating research findings into occupational health and safety measures for the space crew. The process may benefit from (1) enhanced mechanisms to review and update the evidence books, especially through the involvement of the extramural research community; (2) developing a public dissemination strategy; and (3) using all available data sources.

Recommendation 2: <u>Enhance the Process for Updating and Disseminating the Evidence Books</u>
NASA should continue to refine and strengthen its processes for updating the evidence books, identifying potential new risks, and revisiting retired risks. Specifically, NASA should:

- **Create a transparent, verifiable process for PRD risk definition and inclusion;**
- **Summarize the evidence for potential risks that are listed on the watch list;**
- **Engage a broad community of experts in reviewing and updating the content of the evidence books, including experts from outside the intramural NASA program;**
- **Update the evidence books via periodically scheduled and event-driven reviews (e.g., after major new studies are published);**
- **Create a process to retain and update the evidence base for risks that have been mitigated to an acceptable level; and**
- **Disseminate the evidence books to all relevant stakeholders and the general public.**

Reviewing and Updating the Evidence Books

The committee encourages NASA to broaden the responsibility of the risk forums and Human System Risk Board by integrating into these mechanisms a formal and documented strategy for periodically reviewing and updating the evidence books.

NASA plans annual reviews of the current set of evidence books; however, the process for these reviews is still in development. The committee believes the following issues need clarification:

- How were the risks in the evidence books defined? For example, what were the criteria used to change wording, collapse a Bioastronautics Roadmap risk into a single PRD risk, or decompose a Roadmap risk into many PRD risks (see Appendix B)?
- Are alterations in a risk definition validated with the Roadmap authors to ensure correct translation of the risk?
- What are the decision criteria used to choose which risks are selected for the active list and developed into evidence books and which are left on the "watch list"?
- What is the decision-making process to move or remove a risk to or from the "watch list"?

NASA is encouraged to establish a formal and documented plan for defining and updating risk statements. Furthermore, NASA should review not only the risks described in the evidence books, but also those that have been placed on the "watch list" and potential new risks that may not have been examined previously, to determine whether they may be affected by any new scientific or clinical results. Specifically, the committee believes it would be useful to develop evidence books on risks that are on the "watch list" to make explicit the current level of evidence. The concept of "retiring risks" when adequately effective countermeasures become available seems fraught with the concern that those risks, although adequately mitigated, will cease to be considered as hazards for operational planning. Therefore the committee recommends that they be maintained in a category named "risks with adequate countermeasures" rather than "retired" unless some fundamental change in the environment or mission profile renders them irrelevant and their associated countermeasures unnecessary.

In some circumstances a formal, quantitative uncertainty analysis approach would provide structure, discipline, and transparency for the decision process. The process provides a basis for interim decision making in the absence of needed data and for identifying questions for which more information is most needed because of possible or likely consequences for mission success and long-term health effects (IOM, 2006). Used elsewhere in NASA, this approach could assist in the evaluation of the evidence books and as part of the overall process of NASA's priority-setting and risk management decision-making.

It may also be valuable for NASA to attach to each risk two numbers (or interval estimates of two numbers): (1) rough (order-of-magnitude) estimates of severities of health effects (e.g., measured in quality-adjusted life years); and (2) rough estimates of their probabilities, for different scenarios (e.g., with and without deployment of specific countermeasures). The goal would be to provide NASA health risk managers and other stakeholders with an indication of the approximate sizes of the risks for different health effects (based on their probability and severity estimates), and of the sizes of risk reductions achieved by different countermeasures. This may help NASA to set priorities and allocate its limited resources to benefit astronaut health as much as possible. Basic comparative information regarding probabilities and severities of risks relative to one another may contribute to understanding, interpreting, and communicating the practical risk management implications of the research summarized in the evidence books.

Expanding the Evidence Base and External Input

The authors of each evidence book included representatives from the NASA research and medical operations community and the National Space Biomedical Research Institute. However, to help ensure that relevant scientific and clinical evidence not traditionally considered by NASA scientists is included in the evidence book, NASA is encouraged to include expertise from outside the immediate intramural and extramural NASA community in drafting and reviewing the evidence books. Furthermore, NASA should establish a formal peer-review, publication, and public dissemination strategy to help ensure that all evidence and statements included in the evidence books meet the appropriate high standards used for each particular area of interest. External input would also be valuable as part of the risk forum process (Box 2) that NASA is using to identify new risks and to move forward in refining NASA's risk management strategy. NASA is encouraged to proactively and periodically survey a broader external community—including individuals not associated with its human health risk program—to assist in the above efforts and to identify any new potential risks that may have been overlooked before. NASA may wish to take advantage of newer methods of community-based editing, such as the Wikipedia model, by inviting appropriately credentialed and authorized experts in the areas covered by the risk evidence books to interactively update the current best evidence online.

Because opportunities for data collection on human response to microgravity and other relatively unique aspects of space exploration are so limited, NASA needs to fully employ the available methods and venues to collect and analyze astronaut health data. This report acknowledges the issues discussed in previous IOM reports (IOM, 2001, 2004, 2006, 2007) regarding taking full advantage of opportunities for data collection on the health of the space crew. Further, studies of the experiences in polar environments and of Navy submarine crews are excellent sources of data on analog environments. In addition, to expanding the inclusion of relevant spaceflight and outcomes data, authors should be encouraged to use all available data sources, such as the NASA Life Sciences Data Archive (including the Longitudinal Study of Astronauts' Health), and data from other space agencies. Attention to intercultural issues and challenges in communication and relationships are among the many issues to be explored through data from multinational efforts.

SUMMARY

Overall the committee was encouraged by the progress NASA has made in such a short period of time to develop the first iteration of the evidence books and NASA's willingness to request this external review early in the program's history. The committee's recommendations to strengthen the content, composition, and dissemination of the evidence books are intended, in a fashion similar to recommendations made regarding the Bioastronautics Roadmap, to improve future versions of these critical documents. These evidence books should be the continuously updated knowledge base of best evidence regarding risks to human health associated with spaceflight, particularly spaceflight beyond low Earth orbit and of long duration. Such a knowledge base will serve the interests of mission planners, researchers, and ultimately the individuals who accept those risks in their role as space travelers.

Daniel Masys, *Chair*
Committee on NASA's Research
on Human Health Risks

Appendix A Meeting Agenda
Appendix B Risk Descriptions from the Bioastronautics Roadmap, Program Requirements Document, and Evidence Books
Appendix C Committee Reviews of the Evidence Books

REFERENCES

Davidson, J. M., A. M. Aquino, S. C. Woodward, and W. W. Wilfinger. 1999. Sustained microgravity reduces intrinsic wound healing and growth factor responses in the rat. *FASEB Journal* 13(2):325-329.

IOM (Institute of Medicine). 2001. *Space Passage: Astronaut Care for Exploration Missions*. Washington, DC: National Academy Press.

IOM. 2004. *Review of NASA's Longitudinal Study of Astronaut Health*. Washington, DC: The National Academies Press.

IOM. 2006. *A Risk Reduction Strategy for Human Exploration of Space: A Review of NASA's Bioastronautics Roadmap*. Washington, DC: The National Academies Press.

IOM. 2007. *Review of NASA's Space Flight Health Standards-Setting Process: Letter Report*. Washington, DC: The National Academies Press.

NASA. 2008a. *Human Research Program Requirements Document*, February 2008. Houston, TX. NASA.

NASA. 2008b. *Human Research Program Evidence Book*. Houston, TX. NASA.

Radek, K. A., L. A. Baer, J. Eckhardt, L. A. DiPietro, and C. E. Wade. 2008. Mechanical unloading impairs keratinocyte migration and angiogenesis during cutaneous wound healing. *Journal of Applied Physiology* 104(5):1295-1303.

Wilson, J. W., C. M. Ott, K. Honer zu Bentrup, R. Ramamurthy, L. Quick, S. Porwollik, P. Cheng, et al. 2007. Space flight alters bacterial gene expression and virulence and reveals a role for global regulator Hfq. *Proceedings of the National Academy of Sciences (U.S.A.)* 104(41):16299-16304.

A

Meeting Agenda

Committee on NASA's Research on Human Health Risks
February 11, 2008
Keck Center, Room 201
500 Fifth Street, NW, Washington, DC 20001

Monday, February 11, 2008 – Room 201

OPEN SESSION – CAMMEE and Health Risks Committees

10:45–11:15	**Welcome and Introductions** *Daniel Masys*, Chair
	Overview of the Study Task
11:15–12:30	**Context for the Study**
11:15–11:45	IOM Perspective – Bioastronautics Roadmap and Prior IOM Reports *David Longnecker,* Chair, CAMMEE Standing Committee
11:45–12:30	NASA Introduction *Dennis Grounds,* Human Research Program (HRP) Program Manager
	NASA Perspective – The New Exploration Thrust at NASA *John Charles,* HRP Program Scientist

12:30–2:00 **Working Lunch**

Goals for this Review and Charge to the Committee

Craig Kundrot, HRP Science Management Office

Discussion

The Bioastronautics Roadmap and the Human Research Program Requirements

Ned Penley, HRP Program Integration Office

Discussion

2:00–2:15 **Break**

2:15–4:30 **Discussion of Sample White Papers**

2:15–3:00 Risk of Crew Adverse Health Event Due to Altered Immune Response

- Areas and Nature of Analysis Needed
  Craig Kundrot

Committee Discussion – structure/content

3:00–3:30 Risk of Adverse Health Effects from Lunar Dust Exposure

- Areas and Nature of Analysis Needed
  Craig Kundrot

Committee Discussion – structure/content

3:30–4:00 Risk of Performance Errors Due to Sleep Loss, Circadian Desychronization, Fatigue, and Work Overload

- Areas and Nature of Analysis Needed
  Craig Kundro

Committee Discussion – structure/content

4:00–4:30	Risk of Accelerated Osteoporosis • Areas and Nature of Analysis Needed *Craig Kundrot*
	Committee Discussion – structure/content
4:30–5:15	**Revisit the Statement of Task**
	Discussion
5:15	**Adjourn**

B

Risk Descriptions from the Bioastronautics Roadmap, Program Requirements Document, and Evidence Books

Bioastronautics Roadmap (BR)	NASA Program Requirements Document (PRD)	Human Research Program Evidence Books
Risk descriptions from the BR that were not significantly modified in the PRD		
Renal stone formation	Risk of renal stone formation	Same as PRD
Inadequate nutrition	Risk of inadequate nutrition	Same as PRD
Carcinogenesis	Risk of radiation carcinogenesis	Same as PRD
Acute and late central nervous system risks	Risk of acute or late central nervous system effects from radiation exposure	Same as PRD
Chronic and degenerative tissue risks	Risk of degenerative tissue or other health effects from radiation exposure	Same as PRD
Acute radiation risk	Risk of acute radiation syndromes due to solar particle events	Same as PRD
Provide space suits and portable life support systems	Risk of compromised EVA performance and crew health due to inadequate EVA suit systems	Same as PRD

Bioastronautics Roadmap (BR)	NASA Program Requirements Document (PRD)	Human Research Program Evidence Books
Risk descriptions from the BR that required significant modifications to ensure focus on mission relevance		
Injury to joints and intervertebral structures	Risk of intervertebral disk damage	Same as PRD
Occurrence of cardiac dysrhythmias	Risk of cardiac rhythm problems	Same as PRD
Pharmacology of space medicine delivery	Risk of therapeutic failure due to ineffectiveness of medication	Same as PRD
Human performance failure due to neurobehavioral problems	Risk of behavioral and psychiatric conditions	Same as PRD
Circadian rhythm problems	Risk of performance errors due to sleep loss, circadian desynchronization, fatigue, and work overload	Same as PRD
Maintain food quantity and quality	Risk factor of inadequate food system Risk factor of an inefficient food system	Risk of inadequate food system
Reduced muscle, strength, and endurance	Risk of impaired performance due to reduced muscle mass, strength, and endurance	Same as PRD
Increased susceptibility to muscle damage	Risk of operational impact of prolonged daily required exercise	Same as PRD
Limits for contaminants in air and water	Risk of adverse health effects from lunar dust exposure	Same as PRD

Bioastronautics Roadmap (BR)	**NASA Program Requirements Document (PRD)**	**Human Research Program Evidence Books**
Poorly integrated ground, crew, and automation functions[1]	Risk of performance errors due to poor team cohesion and performance, inadequate selection/team composition, inadequate training, and poor psychosocial adaptation	Same as PRD
Mismatch between crew cognitive capabilities and task demands[1]	Risk associated with poor task design	Lack of human-centered design: Subrisk associated with poor task design
Mismatch between crew physical capabilities and task demands	Risk of reduced safety and efficiency due to poor human factors design	Lack of human-centered design: Subrisk of reduced safety and design due to poor human factors design
Risk descriptions from the BR that were split into multiple risks in the PRD to be more specific		
Bone loss and fracture risk	Risk of bone fracture Risk of accelerated osteoporosis	Same as PRD Same as PRD
Diminished cardiac and vascular function	Risk of reduced physical performance capabilities due to reduced aerobic capacity	Cardiovascular effects on performance and operational limitations: Subrisk of reduced physical performance capabilities due to reduced aerobic capacity

Bioastronautics Roadmap (BR)	NASA Program Requirements Document (PRD)	Human Research Program Evidence Books
Diminished cardiac and vascular function (continued)	Risk of unnecessary operational limitations due to inaccurate assessment of cardiovascular performance	Cardiovascular effects on performance and operational limitations: Subrisk of unnecessary operational limitations due to inaccurate assessment of cardiovascular performance
	Risk of orthostatic intolerance during re-exposure to gravity	Same as PRD
Risks from the BR that were combined with others to show contributing factors		
Impaired sensory-motor capability to perform operational tasks during flight, entry, and landing Impaired sensory-motor capability after landing	Risk of impaired ability to maintain control of vehicles and other complex systems	Same as PRD
Monitoring and prevention Major illness and trauma Ambulatory care Rehabilitation on Mars Medical skill training and maintenance	Risk of inability to adequately treat an ill or injured crew member	Same as PRD
Poorly integrated ground, crew, and automation functions Human performance failure due to poor psychosocial adaptation	Risk of performance errors due to poor team cohesion and performance, inadequate selection/team composition, inadequate training, and poor psychosocial adaptation	Same as PRD

Bioastronautics Roadmap (BR)	**NASA Program Requirements Document (PRD)**	**Human Research Program Evidence Books**
Poorly integrated ground, crew, and automation functions[1] Mismatch between crew cognitive capabilities and task demands[1]	Risk of error due to inadequate availability of information	Lack of human-centered design: Subrisk of error due to inadequate information
Immune dysfunction Interaction among factors: infections and malignancy	Risk of crew-adverse health event due to altered immune response	Same as PRD

[1]Poorly integrated ground, crew, and automation functions and mismatch between crew cognitive capabilities and task demands map both individually to specific risks in the PRD. In addition, each of these was combined to result in an extra risk being identified in the PRD and Evidence Books.

The following risks were added to the PRD and subsequently transferred to the SLSD (Q: spell out) watch list: Risk of urinary tract dysfunction, risk of impaired vision due to refractive visual changes during long-duration spaceflight, risk of adverse health effects due to exposure to hypoxic environments, and risk of adverse health effects due to prolonged exposure to elevated carbon dioxide levels.

The following risks appeared in the BR, but not the PRD or Evidence Books: medical informatics, technologies, and support systems; monitor air quality; monitor external environment; monitor water quality; monitor surfaces, food, and soil; provide integrated autonomous control of life support systems; maintain acceptable atmosphere; maintain thermal balance in habitable areas; manage waste; provide and maintain bioregenerative life support systems; provide and recover potable water; alterations in microbes and host interactions; motion sickness; and impaired fracture healing.

C

Committee Reviews of the Evidence Books

Sensorimotor

Chapter 1	Impaired Ability to Maintain Control of Vehicles and Other Complex Systems

Bone

Chapter 2	Accelerated Osteoporosis
Chapter 3	Bone Fracture
Chapter 4	Renal Stone Formation
Chapter 5	Intervertebral Disk Damage

Muscle

Chapter 6	Impaired Performance Errors Due to Reduced Muscle Mass, Strength, and Endurance
Chapter 7	Operational Impact of Prolonged Daily Required Exercise
Chapter 8	Compromised EVA Performance and Crew Health Due to Inadequate EVA Suit Systems

Cardiovascular

Chapter 9	Orthostatic Intolerance During Re-Exposure to Gravity
Chapter 10	Cardiovascular Effects on Performance and Operational Limitations
Chapter 11	Cardiac Rhythm Problems

Nutrition

Chapter 12 Inadequate Nutrition

Immunology

Chapter 13 Crew Adverse Health Event Due to Altered Immune Response

Behavioral Health and Performance

Chapter 14 Performance Errors Due to Sleep Loss, Circadian Desynchronization, Fatigue, and Work Overload

Chapter 15 Performance Errors Due to Poor Team Cohesion and Performance, Inadequate Selection/Team Composition, Inadequate Training, and Poor Psychosocial Adaptation

Chapter 16 Behavioral and Psychiatric Conditions

Space Radiation

Chapter 17 Acute Radiation Syndromes Due to Solar Particle Events

Chapter 18 Degenerative Tissue or Other Health Effects from Radiation Exposure

Chapter 19 Acute or Late Central Nervous System Effects from Radiation Exposure

Chapter 20 Radiation Carcinogenesis

Pharmacology

Chapter 21 Therapeutic Failure Due to Ineffectiveness of Medication

Exploration Medical Capabilities

Chapter 22 Inability to Adequately Treat an Ill or Injured Crew Member

Space Human Factors and Habitability

Chapter 23 Lack of Human-Centered Design

A. Sub-Risk of Reduced Safety and Efficiency Due to Poor Human Factors Design
B. Sub-Risk of Error Due to Inadequate Information
C. Sub-Risk Associated with Poor Task Design

Chapter 24 Inadequate Food System

Chapter 25 Adverse Health Effects from Lunar Dust Exposure

Chapter 1
Impaired Ability to Maintain Control of Vehicles and Other Complex Systems

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. Experimental and observational findings from prior missions, including Apollo, aviation, ground-experimental, and patient data are quite thoroughly described. Additional data and discussions would be helpful to add as described below.

Is the text of the short description of the health risk provided in the PRD)clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
Yes. However, an additional sentence relating the risk to existing Apollo data would be helpful.

Does the evidence book make the case for the research gaps presented?
Yes. The paper presents a comprehensive review of the literature. The implications for future lunar and Mars missions are clearly spelled out. The documentation in the appendix of apparently all U.S. and Russian neurological and sensorimotor experiments conducted in space is highly informative.

Additional risks to be considered for review in this paper include the possible impact of alterations in cortical maps of motor control and somatosensation, and the physiologically relevant factors associated with cognitive and sensorimotor adaptations to abnormal force conditions.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes, there should be some discussion of the relationship to the basic performance measures (reaction time, short-term memory, etc.) in spaceflight. A discussion of fractional g-levels and sensorimotor adaptation is also needed.

Does the evidence book address relevant interactions among risks?
Yes. A consideration of sleep deprivation and stress effects on sensorimotor performance is indicated.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The paper is highly readable, scholarly, and quite comprehensive in its coverage. The amount of material covered and the implications of the findings for future lunar and Mars missions are highly informative. The paper clearly specifies the potential risks in future space activities based on the sensorimotor deficit findings from previous studies. It would be helpful if the paper had a discussion of the caveats relevant to assessing the reliability of data from these types of space flight experiments that involve few subjects and lack adequate controls.

A more thorough review of the literature on vestibulo-ocular reflex function could be added. The committee had concerns that the section on tilt translation and tilt gain illusions seems exceedingly long given the sparse information actually available. Discussions of the issues regarding the theories that are proposed to explain these illusions should be added, as should a discussion of oculogravic illusions. The section on computer-based simulation information presents a number of the classic early studies in the field but more recent modeling data need to be described (data based on more biological considerations than on analogies with inertial guidance systems). Future reviews would benefit from a more diverse group of contributors that could add a focus on these additional topics.

Minor issue:
There is an error in the table of contents in which "Risk of Accelerated Osteoporosis" is listed as the title of the risk.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The paper provides a clear and succinct review of the space and other literature related to sensorimotor problems during and after spaceflight. The extrapolation of these data to potential risks in vehicle control for lunar and Mars missions is informative, particularly discussions about landing a vehicle on the Mars surface. The issue of predictors of astronaut performance from preflight measures is highly relevant.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

Space motion sickness should still be considered an unsolved risk, and there is ample reason to keep it on the gap and critical path lists.

Chapter 2
Accelerated Osteoporosis

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?

Generally, yes. The evidence book is an excellent review and analysis of the evidence. Some areas deserve additional comment, at least in part because they may lead to the identification of more knowledge gaps.

1. Although mentioned, the considerable heterogeneity in the rate of bone loss is of potentially huge importance, and should be further emphasized. Some flight personnel apparently experience particularly rapid bone loss, and these individuals may be at particular risk. Are flights imperiled more by the astronauts with greatest bone loss rather than the average bone loss of the crew? As the evidence book notes, there is also heterogeneity in the degree of recovery from bone loss after landing.
2. The evidence book mentions the lack of evidence concerning the effects of long-term flight (> 6 months) on bone, but fails to discuss the relevant data concerning long-term spinal cord injury (SCI). One of the potential failings of the comparison of bone loss in spaceflight to menopause is that it could lead to the assumption that the bone loss in space is self-limited. On the other hand, long-term SCI studies suggest that bone loss continues for long periods after immobilization begins and results in truly dramatic reductions in bone mass. Moreover, some data indicate that markers of bone resorption remain elevated for long periods, further raising the concern that accelerated bone loss could be prolonged with more impressive implications for long-term flights. These considerations seem important to discuss. See the reviews of SCI and bone by Giangregorio and Blimkie (2002) and Jiang et al. (2006).
3. The paper concentrates on the effects of the unloading that accompanies weightlessness, but little attention is given to known or possible effects of long-term reduced gravity environments such as those that might be experienced with future lunar missions.
4. A discussion of the potential biomechanical trauma anticipated on bone during flight and planetary/lunar stays seems important. Although it could also be presented in the evidence book on fractures (and just referenced in this section), the current evidence book does a good job of presenting finite

element analyses of the strength of bone, and the corollary of that discussion is that of the load-to-strength ratio (factor of risk). In other words, is the level of trauma risk anticipated (load) likely to be greater than the ability of the weakened bone to resist it (strength)? The issue of trauma would seem relevant given the possibility of flight turbulence, landing, and extravehicular excursions. Are there forms of trauma expected that might affect specific bones, and are those bones particularly weakened (e.g., hip)? In addition to the possibility of trauma from factors such as turbulence, it may be worth mentioning the possibility of physical stresses from tasks requiring forceful movements and torque (although such tasks might be more likely to put stress on the upper extremities, where the bone changes are not as great). Should space suits or in-flight clothes contain force-mitigating pads during long flights? The degree of concern for in-flight fracture ultimately rests on the ability of the bones on the flight (and potentially the weakest bones) to resist the extant trauma.

5. The emphasis on unloading as the etiology of bone loss is necessary and appropriate, but the other potential causes of bone loss during missions may deserve more discussion. Although unloading is undoubtedly a dominant factor, other possible contributors to bone loss could be considered. These include chronic stress, weight loss, sleep disturbance, gonadal abnormalities, etc. Some of these are suspected to be problems, while others have not been examined. The possibility that unexpected effects on bone may be encountered during spaceflight should not be ignored. More discussion is warranted. This may deserve special attention in light of the interindividual variation in bone loss. The factors mentioned, such as chronic stress and sleep disturbance, would be expected to vary substantially from person to person.
6. In the introduction, the authors appropriately point out that, despite their use of the menopausal and aging comparisons, that spaceflight is *neither* of those things. However, the possibility that spaceflight causes a distinct form of metabolic bone disease should be more carefully considered. For example, spaceflight is *not* like postmenopausal osteoporosis because there may be an absolute (or more marked) reduction in bone formation during flight whereas postmenopausal bone loss is characterized by increased bone formation (with an even more increased rate of resorption). If the nature of flight-induced bone loss is different from the aging or postmenopausal conditions, perhaps more akin to glucocorticoid-induced bone loss (where—like spaceflight—there is also a state of increased bone resorption and reduced bone formation), it could result in an altered fracture threshold. Another example of differences may be that hip bone loss seems to out of proportion to that seen in postmenopausal women, apparently indicating distinct pathophysiological mechanisms. Should these and other potential differences be examined to best understand how to mitigate risk?

7. Bone strength is the result of a number of factors, including the amount of bone, its structure, and its quality. The evidence book should mention the possibility that bone material properties could be altered by flight. Some data from the SCI literature indicate that bone formation is altered, potentially affecting material properties and strength.
8. Efforts undertaken so far to prevent bone loss during flight, and their effectiveness, should be discussed.
9. The recent occurrence of a hip fracture in a previous astronaut is potentially important, especially because traumatic fractures are highly related to lower bone mineral density (BMD) (Mackey et al., 2007). Perhaps this should be presented.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.

1. "…unloading of the skeleton. *In moderate-duration flights (6 months) average loss rates are approximately 1 percent per month, but some individuals lose at a greater rate. It is unclear whether this bone mineral loss will stabilize at a lower level or continue for the duration of longer flights. The causation and specific nature of the loss are unknown. Efforts to devise methods to prevent loss during flight have not been successful.* Mission-related bone loss…"
2. Also, the statement that "mission-related bone loss cannot be corrected by. . . " may be too strong. Perhaps " . . . cannot be reliably . . . " or " . . . cannot be completely . . . " would be more correct.

Does the evidence book make the case for the research gaps presented?

Yes, there is an excellent presentation of research gaps.

Are there any additional gaps in knowledge that should be considered for this specific risk?

Additional gaps to be considered include:

1. Does the loss of bone during flight result in structural alterations that are unique (different from the aging or postmenopausal states) that have distinct biomechanical implications?
2. Apart from unweighting, the factors that contribute to bone loss are unclear.
3. The effects of long-term flight on bone are unknown (the authors clearly note this, but it is not listed as a gap).
4. The preflight or during-flight factors that affect the rate of bone loss during flight are unknown.

5. The expected forces (trauma) that may be exerted on bone during flight or extravehicular activity are unknown. The bones at particular risk are unknown.
6. The best methods for measuring bone structure and strength are not known.
7. The usefulness of new bone formation drugs are not known—either during flight or after return to Earth.
8. In-flight metabolic alterations that could affect bone are not known.

Does the evidence book address relevant interactions among risks?
Some possibilities are as follows:

1. The risk of renal stones from increased bone resorption is noted, but other possible problems may flow from alterations of bone metabolism. For instance, there are probably vitamin D reductions during flight, and muscle strength is reduced by vitamin D insufficiency. The danger of hypercalcemia is clearly increased in SCI (especially under certain circumstances, such as dehydration). Hypercalcemia has been linked to nausea, mental status and mood abnormalities, cardiac arrhythmias, etc.
2. Nutrition is an area of potential overlap.
3. Human Factors Design and Task Design are areas of potential overlap.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*
    - Author expertise appropriate: The authors are outstanding. An expert in mineral metabolism and related endocrine issues would be useful. A bone biomechanic would provide benefit, and an expert in human factors engineering may be useful.
    - Literature presented; generally very good. As noted previously, additional areas of interest would be the long term effects of SCI and bone/mineral endocrinology.
    - Overall readability: excellent.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
Key issues raised include:

1. Concern about overreliance on the models of postmenopausal and age-related bone loss.
2. A minimal emphasis on the heterogeneity of bone loss, and the implications of the "weakest link" consideration.
3. Need for linking the strength of bone to the trauma expected during flight.
4. The paucity of good data concerning the metabolic/environmental abnormalities potentially contributing to bone loss (apart from unweighting).

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

Other risks: The possibility of metabolic disturbances resulting from accelerated bone remodeling/loss (vitamin D deficiency, hypercalcemia).

REFERENCES CITED

Giangregorio, L., and C. J. Blimkie. 2002. Skeletal adaptations to alterations in weight-bearing activity: A comparison of models of disuse osteoporosis. *Sports Medicine* 32(7):459-476.

Jiang, S. D., L. Y. Dai, and L. S. Jiang. 2006. Osteoporosis after spinal cord injury. *Osteoporosis International* 17(2):180-192.

Mackey, D. C., L. Y. Lui, P. M. Cawthon, D. C. Bauer, M. C. Nevitt, J. A. Cauley, T. A. Hillier, et al. 2007. High-trauma fractures and low bone mineral density in older women and men. *Journal of the American Medical Association* 298(20):2381-2388.

Chapter 3
Bone Fracture

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?

Yes. In general the evidence book is a scholarly and complete examination of the issue. There are additional knowledge gaps that should be considered.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.

Yes, in general the short description is clear and complete. Consider a final sentence "Additional data is needed to understand the alterations in bone biology

that could increase the potential for stress fracture or impaired fracture healing in flight."

Does the evidence book make the case for the research gaps presented?
Yes. The research gaps identified are well substantiated.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. Additional gaps in knowledge to be considered include:

1. The evidence book concentrates on fracture risk during flight. Although this is an appropriate concern, there is less attention paid to the risks of fracture after return from flight. As there have been several fractures now in previous astronauts, and the to-some-extent irreversible bone loss associated with flight is well known, post-flight fracture risk should be more prominently considered.
2. Fracture due to severe trauma is prominently considered (as it should be) but there may be additional mechanisms of potential importance (particularly in a situation associated with low bone formation). One is stress fracture due to repetitive lower level force. Unusual stress and impaired responses to it may be encountered during flight/EVA. Another may be static forces and torque or torsional forces during mission activities such as construction tasks or EVAs.
3. In addition to the biomechanically oriented fracture risks considerations included in the evidence book, some attention should be paid to fracture healing in space. There is evidence to suggest that remodeling is altered, but little data concerning the adequacy of healing. Certainly, if a fracture occurs during flight, inadequate healing would add to the problem.

Does the evidence book address relevant interactions among risks?
Related risks that were not addressed. They might include:

1. Reduced muscle mass
2. Poor human factors design
3. Bone loss
4. Impact of prolonged exercise
5. Inability to provide clinical treatment
6. Nutrition
7. Poor task design
8. Orthostatic intolerance

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

Additional expertise in fracture biology and in human factors engineering (to give more full attention to the relationship between environmental design and physical stress on bones and joints) might be helpful. The literature search is complete. Readability is good.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
In general the evidence book is excellent. Additional attention should be directed at postflight fracture risk, fracture healing during low-G situations, and the possibility of stress fracture.

Although there are distinct features of this evidence book on fracture risk, it could be argued that it could be combined with that on bone loss.

Two minor issues:

1. Figure 3-1 may have an error. The aBMD ascribed to the three bone geometries is consistently 1, but in fact the aBMD is progressively lower going left to right.
2. On p. 3-9 it is noted that " . . . planetary surfaces provide unique scenarios that may:
   - reduce the forces applied to bone structures."

In fact, planetary surfaces may *increase* forces when considered in comparison to previous 0 G conditions. That could be a critical consideration regarding fracture risk.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 4
Renal Stone Formation

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. In general the evidence book is complete. A few additional gaps should be considered.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
Yes. The short description is clear and concise. Consider a change to the final sentence: "Alterations in hydration state (relative dehydration) and accelerated bone loss during exposure to microgravity may contribute to an increase in the risk of kidney stone formation. Other metabolic derangements may also contribute. It is unclear which mitigation strategies would be most effective."

Does the evidence book make the case for the research gaps presented?
Yes. The research gaps identified are well substantiated.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. Additional gaps in knowledge to be considered include:

1. Although increased bone resorption is likely to contribute to increased calcium excretion during flight, there may be other factors. This gap should be recognized. For instance:
   - Preflight renal stones suggest pre-existing propensity to stones, potentially on a genetic basis.
   - Dietary factors could influence calcium excretion (e.g., protein intake).
2. From the data presented, it is clear that renal stones are not uncommon in astronauts before flight. This means other factors contribute to stones, and those factors could be exacerbated by flight. There may be a gap in understanding preflight contributors to renal stone propensity. This may influence the selection of mitigating measures (e.g., on the basis of preflight risk factors).
3. Although the evidence book refers to other potential causes of stones (e.g., hypocitraturia, urates), it concentrates on hypercalciuria. In fact the increases in urine calcium have been modest, and these other risk factors may be important. One of the gaps listed ("Data mining . . . ") may address the need for additional data about the confluence of risk factors, but the need for more information about the nature and etiology of metabolic changes associated with flight should be more clearly identified as a gap.

4. An additional gap is that the real incidence of renal stones isn't known because the only data are via symptomatic disease. Perhaps imaging studies (e.g., computerized tomography or CT) would help.
5. It is not currently known how genetic susceptibility to stone formation might be used to individualize preventative strategies. Samples should be collected and archived so that the information can be incorporated as genes become known.

Does the evidence book address relevant interactions among risks?
Related risks were not adequately addressed. They might include:

1. Bone loss/fracture risk.
2. Inability to provide clinical treatment.
3. Nutrition and hydration.
4. If a pharmacologic solution is planned, then there is potential for interaction with "Risk of Therapeutic Failure Due to Ineffectiveness of Medication" for prolonged voyages (e.g., to Mars).

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

Additional expertise in mineral metabolism might be helpful, but the literature search is complete and readability is good. One minor issue is that Figure 4-1 is said to illustrate calcium excretion, but in fact shows calcium balance. From that data alone, it is not possible to infer urine calcium excretion. Balance goes down, but calcium nutrition and absorption contribute as well.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
In general the evidence book is good.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 5
Intervertebral Disk Damage

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
No. The paper presents three facts, each of which is a valid concern that deserves further consideration, but it does not combine these facts into a sufficiently clear argument that there is enough evidence to define an evidence book risk.

The first fact is that 68 percent of surveyed astronauts reported generalized back pain during spaceflight. Although there are several possible explanations for this finding, the evidence book is too quick to state "at face value, the cause of the back pain in space appears to be associated to the elongation of the vertebral column by IVD expansion or other causes."

The second fact is that 3 astronauts developed cervical or lumbar herniated disks on landing day and another 11 developed herniated disks within 12 months of landing. The evidence book references an unpublished study comparing disk injuries among 321 astronauts with disk injuries among 482 age-matched, nonflying civil servants of NASA. The incidence of herniated disks among the astronauts was more than 15 times that of the control group. The evidence book seems to presume that this increased risk is causally related in some fashion to spaceflight. However, the evidence book also notes that astronauts with backgrounds as high-performance jet aviators were at the greatest risk and that excessive G forces commonly experienced by such aviators may be an important risk factor for disk herniation. Without comparing the astronaut group with a control population having similar aviation experience except for spaceflight, it is premature to conclude that disk herniation is a risk of spaceflight.

The third fact is that weightlessness and the associated absence of normal axial and muscular loading of the spine results in swelling of the intervertebral disks, elongation of the spine, and loss or lordotic curvature. The evidence book does make a plausible argument that this biomechanical distortion may predispose to back injury when crew members experience reloading during and after landing and when they undertake various physical mission tasks. However, the only pieces of evidence offered in support of this hypothesis are the back pain and herniated disk finding described above.

The evidence book's basic conclusion (that more evidence needs to be acquired "to establish whether the lengthening of the spinal column . . . exacerbates the risk for IVD damage with loading") is both appropriate and necessary, but it is not sufficient. It is also necessary to evaluate other possible causes for back pain during spaceflights and for herniated disks after them.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.

No. The one-sentence description states a hypothesis, namely that extended exposures to microgravity may be a risk for spinal nerve compression and back pain. Although this is a legitimate issue deserving attention, it is stated so narrowly that it diverts attention from equally compelling questions. It would be more productive to frame the description around the findings of back pain during spaceflight and disk herniation following spaceflight and the need to identify their causes. The possible effect of IVD volume changes on back injury would then become one part of a comprehensive agenda rather than its dominant component.

Does the evidence book make the case for the research gaps presented?

No. The gaps are aimed principally at learning more about the characteristics and impacts of the IVD changes with gravitational unloading. These are real gaps, but it is hard to assess their importance without knowing more about the possible causes for the observed back pain and disk herniations among astronauts. Two additional gaps, described below, may have higher priority.

Are there any additional gaps in knowledge that should be considered for this specific risk?

Yes. Additional gaps in knowledge to be considered include:

1. Biomechanical and human factors evaluations of the physical stresses and forces required during mission-related activities that may be risk factors for back pain (e.g., prolonged awkward postures with excessive static muscle loading).
2. Epidemiological study of disk herniation following spaceflight, using a better control population than was used in the preliminary study.
3. The etiology of back pain during spaceflight is not clearly understood. Potential causes should be investigated.
4. The apparent increase in cervical events among astronauts merits evaluation.

Does the evidence book address relevant interactions among risks?

Other related risks that were not, but might be, addressed were the following:

1. Reduced muscle mass
2. Poor human factors design
3. Degenerative tissue
4. Bone fracture
5. Accelerated osteoporosis

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The team might be strengthened with additional experts who have specific research experience with the application of human factors engineering and epidemiology to back disorders.

The readability is sufficient for a nonexpert audience.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The paper focused too narrowly on one possible cause of back pain and disk herniation experienced by astronauts. It would be more productive to organize the paper around the need to study the possible causes for these adverse events. The biochemical and biomechanical changes in intervertebral disks would then be set in a more meaningful context, instead of dominating the whole evidence book.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 6
Impaired Performance Errors Due to Reduced Muscle Mass, Strength, and Endurance

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. The paper provides strong evidence that human skeletal muscles undergo atrophy and loss of function during short-term and long-term spaceflight. Evidence is presented to indicate the atrophic response is exacerbated with increasing durations of spaceflight/unloading. The atrophic response is strongly linked to alterations in cell biology. To date, exercise has shown promise in mitigating these effects. However, more research is warranted to titrate the most effective

combination of the exercise countermeasure suite for long-duration missions. Good evidence is presented linking loss of muscle mass to health and task-related risks to humans while in space.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
No. The concept that human control subjects cannot be used due to ethical reasons in the microgravity of space is true, but for ground-based analogs this is not true. Several ground-based analog studies have included control subjects that have furthered our understanding of muscle loss with unloading. The concept needs to be revised with regard to feasibility and priority.

Does the evidence book make the case for the research gaps presented?
No. A more thorough overview of the progress that has been made in preventing muscle atrophy and functional deficits, especially in humans, is warranted. This will provide greater depth and direction to the gaps identified.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. Additional gaps in knowledge to be considered include:

1. Potential gender-related issues regarding muscle mass and function loss during unloading.
2. Effectiveness of various exercise modalities for preserving muscle.

Does the evidence book address relevant interactions among risks?
Yes. The interactions among exercise, partial-gravity environments, and EVAs for protecting skeletal muscle are highlighted.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The expertise of the authors is outstanding. A number of the team members are leaders in the field of muscle biology and unloading. The background information on the space program and data obtained from the various eras of spaceflight

were excellent. The review of muscle biology as it pertains to functional loss was well defined. Generally, the paper was well structured and easy to read.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The summary of the muscle literature contained in the report was excellent. The limitations of spaceflight research and breadth of knowledge gained from ground-based analogs and animal models were highlighted. The report could be strengthened with a more in-depth review of human countermeasure development/progress (e.g., intensity, frequency, mode) that has been made for skeletal muscle using ground-based analogs (e.g., bed rest and unilateral lower limb suspension). This information is critical to further define the gaps for skeletal muscle during long-duration space missions.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

A potential crosscutting issue is the interactive effects of nutrition on skeletal muscle properties with prolonged space travel.

Chapter 7
Operational Impact of Prolonged Daily Required Exercise

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
No. The evidence book focuses almost exclusively on the time-consuming nature of exercise protocols and the lack of knowledge present in its effectiveness. Both of these findings are significant; however, the case for further research addressing this topic, which can and should be made, is not present. Additional areas where the evidence book could be improved include:

1. The concept of human health countermeasures and their impact on mission operations has historically been a potential concern. As discussed, there is no strong evidence that physical exercise has negatively impacted mission operations. However, there has generally been a consensus to optimize the physical exercise program to protect crew health while minimizing the impact on crew time. A further challenge, as highlighted in the report, is that benchmarks for crew health/performance have not been established.
2. This report needs to be strengthened by the database from International Space Station (ISS) crew members and the limited data available in the literature. Several physical traits of human physiology/biology have been assessed before and after long-duration stays in space. Are the

current programs effective? Although the benchmarks have not been established, anchoring these physical capacities to preflight levels would provide a starting point to help establish performance benchmarks.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
No. Because benchmarks are not defined and there appears to be no negative impact on current mission operations; more justification is needed for this to be a major issue moving forward. The more significant risk lies in the inadequacy of this single countermeasure in preventing the deconditioning of bone, muscle, neurovestibular, and cardiovascular systems.

Does the evidence book make the case for the research gaps presented?
No, the research gaps seem reasonable, but are very limited in scope and loosely defined. The paper also does not address the supposed adequacy of exercise as present in the lunar EVA as sufficient to avoid deconditioning of bone, heart, and muscle during extended lunar stays.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. Exercise needs to be evaluated in conjunction with other countermeasures, such as artificial gravity, lower body negative pressure (LBNP), and pharmacological treatments.

Does the evidence book address relevant interactions among risks?
No. The relevant interactions are vaguely defined. The risk interactions need to be more closely linked to the EVA profile and potential risk to the microgravity tasks, partial-gravity environment tasks, and return to 1 G tasks. The evidence book should also discuss the interaction of prolonged exercise with bone and cardiovascular risks, which could be significant in missions of extended weightlessness or lunar stays.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*

- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

Adding relevant data about the crew's physical capacities preflight and postflight as highlighted earlier would strengthen this report. As is currently written, the report lacks any relative or absolute data concerning benchmarks and meeting those targets. Additional insights may be gained from personnel involved with crewmember health (medical profession, crew members, trainers, etc.).

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
Exercise, as currently employed as a countermeasure on the ISS, is very time consuming and its effectiveness has not been quantified. It remains a centerpiece of future space missions, whether in microgravity or on the Moon, probably in conjunction with other methods of minimizing deconditioning. The most effective combinations of exercise and other countermeasures can be studied in bed rest experiments as well as on orbit.

As noted in the letter report, the committee suggests that the scope of this evidence book be expanded and changed to "Operational Impact of Countermeasures."

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

Several crosscutting areas here appear to be related to human health, human performance, and psychological aspects.

Chapter 8
Compromised EVA Performance and Crew Health Due to Inadequate EVA Suit Systems

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. It underscores the vast increase in EVA suit use and exposure in the coming decades and supports the need for research regarding prebreathe and pressure requirements as well as the metabolic cost of walking in current suits. Mechanical difficulties in current boots and gloves are clearly identified. The case, however, would be stronger if the evidence book also discussed the risk of inadequate suit systems to crew safety.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.

No. The healthy risks described are adequate—but it has not dealt with the following important concerns:

1. The risk of suit depressurization by a fall or impact with a protruding edge.
2. The risk of falling as increased by the absence of haptic and proprioceptive cues from the pressurized boots.
3. Crew safety.

Does the evidence book make the case for the research gaps presented?
Yes. There is an excellent summary of experience from earlier EVA suits, lack of oxygen reserves in Apollo, and problems with food and water as well as thermal control. Good treatment of the decompression sickness issue and choice of prebreathe protocols.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. Additional gaps in knowledge to be considered include:

1. Reduce the risk of falling through use of better boots, gloves, biosuit (skin-tight suits), auxiliary displays, and navigation and terrain information.
2. Study of alternate joint designs.
3. The detrimental effect of lunar dust, identified as a major problem in Apollo, is not treated.

Does the evidence book address relevant interactions among risks?
No. Two types of potential risk interactions are not explicitly addressed. One is the risk of poor task design. The design of tasks that necessitate EVA must necessarily consider the physical and other limitations created by the suit. The other is risks related to environmental threats. Two environmental threats that also have evidence papers but are not discussed here are radiation and lunar dust.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

This is a very good summary of highly relevant research, especially the metabolic costs of activities, including the "walk back" tests. The misuse of the Coo-

per Harper scale (specifically designed for aircraft-handling qualities) is easily correctable. The evidence book is highly readable and well illustrated. However, the literature cited is largely limited to that of the authors and their Houston colleagues—ignoring the wealth of research outside of Johnson Space Center (JSC). Newer cooling methods and ease of food intake and outflow need consideration.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The current generation of suits is inadequate to meet the demands of the extensive use foreseen on the Moon. Both performance (ease of use and metabolic cost) and safety (decompression sickness, depressurization, and falls) are of concern. Damage to extremities and joints are common in current suits and the injury rate is unacceptable.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 9
Orthostatic Intolerance During Re-Exposure to Gravity

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. The report describes in detail past experiences with presyncope/orthostatic intolerance following spaceflight of varying durations. The risk is most prominent during transition states from microgravity to partial-gravity environments and is a particular concern for female astronauts, in whom the incidence of orthostatic intolerance is much higher than in men. Although bed rest studies in humans and lower extremity unloading studies in animals help to elucidate the mechanisms of orthostatic intolerance related to microgravity, the complex etiology that has been revealed presents challenges to the development of countermeasures. The report also makes it clear that because there is no experience with long-term space missions, the risk of orthostatic intolerance in astronauts subjected to long-term spaceflight and long-term residence in reduced gravitational environments on the Moon and Mars are difficult to predict and may be very large. To date, exercise, volume loading, and pharmacological interventions have shown promise to partially mitigate the effects of orthostatic intolerance when returning to 1-G environments. The development of the Digital Astronaut Program may be helpful in clarifying the predictions of risk, but further studies of humans at fractional gravity exposures are clearly needed to fully assess the risk and develop useful countermeasures.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
Yes. This is very clear and appropriately emphasizes the importance of developing and evaluating countermeasures to combat orthostatic intolerance during space missions.

Does the evidence book make the case for the research gaps presented?
Yes. The evidence book emphasizes the lack of information about the effects of exposure to microgravity followed by partial gravity on orthostatic tolerance and also emphasizes the lack of full evaluation of suggested countermeasures, such as midodrine and somatostatin. It also emphasizes the importance of developing and testing more effective antigravity suits.

Are there any additional gaps in knowledge that should be considered for this specific risk?
No.

Does the evidence book address relevant interactions among risks?
No. The risks of orthostatic intolerance are related to the reduced muscle-mass strength and endurance and possibly to the central nervous system (CNS) effects of radiation exposure that could be experienced by astronauts during prolonged spaceflight. Countermeasures, such as formal exercise programs, designed to preserve or prevent the loss of muscle mass could clearly improve orthostatic tolerance at the end of spaceflight and should be considered in the context of reduced orthostatic tolerance.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The expertise of the authors was very good. The literature review was appropriate and extensive. The background information on the space program and data obtained from the various eras of spaceflight and analog-related research were excellent. Generally, the paper was well structured and easy to read.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
Key issues raised are that postflight orthostatic intolerance is likely to be nearly universal in astronauts after long-duration spaceflight, and the need for developing effective countermeasures is urgent. The key areas identified for moving forward relate to gender and transition states (from microgravity to partial-gravity environments). A particular concern is the total lack of information about whether partial-gravity exposure (1/6 G on the Moon and 3/8 G on Mars) will exacerbate or mitigate effects against orthostatic intolerance following prolonged spaceflight. Ground-based studies directed toward answering these questions are underway, but it is not clear that these can fully reproduce the effects of prolonged exposure to microgravity in space. To date, an effective countermeasure for orthostatic intolerance has not been fully identified.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

Additional risks that should be included in their report include the possibility of cardiovascular events, including ischemic events and arrhythmias resulting from volume depletion and dysautonomia/disorders of peripheral vascular regulation resulting from prolonged exposure to microgravity.

A potential crosscutting issue relates to drug delivery/pharmacokinetics as a countermeasure due to the possibility of interactive effects with other physiological systems.

Chapter 10
Cardiovascular Effects on Performance and Operational Limitations

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. The paper provides a good deal of support for cardiovascular deconditioning during short-term and long-term exposure to microgravity. Although some controversy remains regarding the degree of in-flight deconditioning, the postflight reduction in cardiovascular capacity is compelling. Strong evidence is also given for alterations in submaximal responses to exercise. Although a host of potential mechanisms have been studied to help explain the cardiovascular changes as a result of spaceflight, hypovolemia is perhaps the strongest candidate, with several secondary alterations contributing to this reduction in aerobic performance.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
No. The risk generally pertains to potential emergency contingencies (e.g., egress, safety). To date, it appears that crew members have not been challenged with activities that would exceed cardiovascular capacity. However, little data from long-term spaceflight are available, with no in-flight data (long term) on aerobic capacity. This is an open issue for long-duration spaceflight. Finally, defining the operational requirements related to cardiovascular capacity for planetary exploration is needed.

Does the evidence book make the case for the research gaps presented?
No. All the gaps appear to have merit. However, they are very general and sweeping in nature. Given the extensive literature on this topic, it is suggested that the gaps be framed in a more focused and directed fashion.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. The gaps should include preflight fitness requirements for cardiovascular capacity relating to prolonged space travel. Gender should also be considered as a potential gap. Although gender-related data are limited, it does point to a potential issue. Gaps 4 and 6 should include cardiac and skeletal muscle mass as potentially important contributors to cardiovascular performance.

Does the evidence book address relevant interactions among risks?
Yes, for emergency egress situations (more related to 1G). Links to several physiological systems are highlighted and appropriate. Because benchmarks for cardiovascular performance are not presented, the risk assessment during long-term space travel and planetary exploration cannot be adequately determined.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The expertise of the authors was appropriate. The literature review was extensive. The background information on the space program and data obtained from

the various eras of spaceflight and analog related research were good. Generally, the paper was well structured and easy to read.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The summary provided a good overview of cardiovascular deconditioning with spaceflight. Although the data gathered from short-term spaceflight were extensive, fewer data are available from long- duration missions. The data generally support an initial and rapid decrease in cardiovascular capacity that may be tied more closely to hypovolemia. Thereafter, there is a more gradual decay in cardiovascular performance, with secondary mechanisms related to muscle remodeling (cardiac and skeletal) and several central and peripheral adaptations that appear to be linked and contribute to a decreased aerobic capacity. Although no strong evidence was presented for a gender-related aspect for cardiovascular performance, it was an underlying issue that deserves attention for the future.

As noted in the letter report, the committee found that the topic of this evidence book is a subset of the broader issue of the effects of decrements in work capacity on operational performance. The committee suggests that this risk should be redefined to "*Physiological Limits on Performance and Operations*" to include effects such as cardiovascular, metabolic, strength, and thermal limits that might cause operational tasks to be limited or redefined.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 11
Cardiac Rhythm Problems

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
No. The difficulty with making this assessment is that there is little research on the risk of cardiac arrhythmias during spaceflight. The only supportive evidence comes from observational reports that have shown some evidence of non-life-threatening arrhythmias during or after spaceflight. It is not clear that these did not arise simply by chance. Two potential mechanisms are put forth, prolongation of the QTC and cardiac atrophy. There is little solid research to connect these dots.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
Yes. The text makes it clear that potential cardiac rhythm disturbances could be related to underlying cardiovascular disease, to cardiovascular disease that develops over time and would have developed in the same way if the subjects had remained on Earth, and to effects of prolonged exposure to microgravity that have not yet been defined. It could, however, be strengthened by inserting the main recommendation.

Does the evidence book make the case for the research gaps presented?
No. The statement of required action is "systematic evaluation of cardiac structure and function on the International Space Station." A more straightforward approach might be constant telemetric monitoring of subjects on the International Space Station and a more thorough evaluation of cardiac function and anatomy before the subjects enter space. The evidence book could go much further in suggesting experiments and monitoring that should be done.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. Additional gaps to be considered include:

1. Are astronauts screened for family histories of sudden death?
2. Are astronauts screened for various forms of underlying heart disease, that is, for coronary disease with fast CT for calcium; with echocardiograms or cardiac magnetic resonance imaging (MRI) for cardiomyopathy; or with genomic techniques for genes that have been related to arrhythmias?

Does the evidence book address relevant interactions among risks?
Not directly, although the evidence book does suggest that in persons with underlying occult heart disease, arrhythmias may be precipitated by the stress of working in space or of microgravity.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The literature search is adequate and the overall readability of the evidence book is sufficient. However, it would be strengthened with the addition of experts in myocardial imaging, that is, fast CT for coronary calcium and cardiac MRI as well as additional expertise in clinical electrophysiology.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The paper emphasizes that the risk of cardiac rhythm problems in persons exposed to microgravity for prolonged periods of time is hypothetical. Only a few cases of astronauts developing arrhythmia during or following spaceflight have been reported, and it is not clear if these abnormalities occurred as a result of chance or as a result of some aspect of exposure to a microgravity environment. Key issues deal with the necessity of more rigorous screening of astronauts for occult cardiovascular disease prior to spaceflight and more sophisticated monitoring techniques to determine the prevalence of cardiac arrhythmias in persons exposed to prolonged weightlessness. This should be feasible with contemporary telemetry techniques and is needed to assess the magnitude of the problem.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 12
Inadequate Nutrition

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. The document makes a compelling case for the importance of proper nutrition. Perhaps most important, the opening material documents in considerable detail evidence from prior space missions to indicate that astronauts often experience reduced dietary intake.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
Yes. The authors have described this particular risk quite clearly and succinctly.

Does the evidence book make the case for the research gaps presented?
Yes. In most cases, the evidence is quite clear. This is one area in which substantial data are available from previous missions, and the data are reviewed thoroughly. The arguments are thoughtful. Not all issues are as developed as others. The paper reviews 31 specific nutrients. Most have already been studied

with regard to spaceflight and analog environments, but some have not (e.g., Vitamin A, niacin, pantothenic acid). In the latter cases, the statements with regard to gaps simply say, "This issue should be studied."

Although the document covers evidence regarding 31 nutrients, it does not explain how this list was generated. Therefore it is difficult to know whether these 31 factors were selected from a larger list or if these are all the possible nutrients that could be considered. From the lay perspective, the list would be exhaustive and possibly unnecessary due to the varying levels of strength in the arguments for each. This could be partially clarified by including a review of the current nutritional guidelines used for astronauts and relevant gaps in knowledge associated with each standard.

Are there any additional gaps in knowledge that should be considered for this specific risk?
No. This paper seems to cover all of the relevant ground with regard to nutrition.

Does the evidence book address relevant interactions among risks?
Yes. The paper does raise important issues regarding connections between nutrition and other important risks, such as loss of bone density, radiation, and (to a lesser extent) behavioral health.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The authors have a sufficient level of expertise on the issues and the literature review seems to be completely exhaustive. In fact, the background sections for each of the 31 nutrients might be considered to be too long and detailed. They read a bit like excerpts taken from a textbook on nutrition. The paper is well organized and nicely written, but it is so long and detailed that it is easy to miss the main points.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
This is a thorough and nicely written summary of many important issues related to the possible impact of inadequate nutrition. The primary concern with the

evidence book is that it provides an excessive amount of detail, particularly with regard to background on the 31 nutrients. It also does not explain to a novice why these particular 31 nutrients were selected for inclusion in this report. An enormous amount of evidence is reviewed regarding nutrition and previous spaceflights, and it seems likely that that information could be condensed and summarized.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 13
Crew Adverse Health Event Due to Altered Immune Response

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?

Yes. Evidence provided relative to cellular and humoral immunity alterations associated with spaceflight do make the case that this risk is relevant, though the evidence book appropriately observes that no clear evidence of disease associated with these alterations has yet been observed.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.

No. The short description is clear, but to be more generalizable it would be reasonable to change the wording from "Further research may elucidate whether microgravity exposure impairs the immune system, and whether this change represents a health risk to crews" to "Further research may elucidate whether microgravity exposure or other characteristics of spaceflight impair the immune system, and whether this change represents a health risk to crews."

Does the evidence book make the case for the research gaps presented?

Yes.

Are there any additional gaps in knowledge that should be considered for this specific risk?

Yes. The lack of correlation between observed changes in cell-mediated and humoral immunity and clinically evident disease suggests that an important gap is the ability to assess which changes are functionally significant. Simply doing more in-flight measurements of existing immune tests may not be particularly useful in the absence of predictive biomarkers that have a validated relationship

to clinically overt immune disorders. Identifying such biomarkers might be considered another gap.

Does the evidence book address relevant interactions among risks?
No. A discussion of known effects of different types and doses of radiation would be appropriate.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

Some text in the evidence book is unclear, as follows:

1. Introduction, paragraph 1: "The specific functions of these cell populations can vary widely, and in some cases they are counter regulatory." The meaning of the term "counter regulatory" is unclear. Beginning this Introduction with a brief overview of the components of the immune system (humoral and cellular) may be more useful than starting with an assertion about white cells trafficking around the body.
2. P. 4: "Dysregulation detected individual immune assays may be either hyper-activity or hypo-activity."

Overall, the paper would leave a nonspecialist unable to interpret its detailed observations. It is readable only by a specialist conversant with the meaning of the various (and somewhat arcane) assays of immune function. The addition of an author (or assignment of existing authors) to create an explanatory context for each detailed finding in the evidence book would be helpful, in addition to the creation of an introductory overview on human immune function as noted above.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The evidence for alterations of immune function appears overall to have a somewhat opportunistic gestalt to it, as if measurements were made because it was possible to do a variety of assays and not because of a coherent plan to identify functionally important alterations of immune systems. The majority of data relates to cell-mediated immunity, and little attention is given to antibody

classes and titers—which in theory might have equally important effects on alteration of host defenses—nor to other molecules such as cytokines that modulate immune response.

Similarly, the research gaps seem quite tactical and not strategic, as closing the gaps might still leave NASA without an understanding of the most meaningful and predictive assessments of immune function. A conceptual framework for understanding which parts of the immune system, when altered, have real prognostic significance might emerge from a comparison of the reported findings in the evidence book and the growing terrestrial literature on the molecular biology of disease states of over- and underactive immunity.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 14
Performance Errors Due to Sleep Loss, Circadian Desynchronization, Fatigue, and Work Overload

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?

Yes. The paper makes a strong and clear case that this risk is highly relevant to long-duration space missions. It provides a clear review of the evidence from ground-based studies on the effects of sleep loss, circadian desynchronization, fatigue, and work overload on alertness, cognitive performance, reaction time, and to a lesser extent, motor behavior. There is a clear discussion of the biological and behavioral mechanisms through which each of these factors affect performance, and the relevance of this risk to long-duration space missions. The review of the research findings is informative for short-duration missions, and has applications as well for long-duration missions to the Moon and Mars. The discussion of different light intensities on the Moon and Mars and possible effects on sleep and performance is also informative.

Is the description of the health risk provided in the PRD clear? Provide suggestions of revised wording.

Yes. It is precise and nicely written.

Does the evidence book make the case for the research gaps presented?

Yes. The issues identified are interesting and well presented. They are well defined and clearly lend themselves to further empirical investigation. One con-

cern, however, is the extent to which these research gaps fit into determining overall priorities for research. Some issues to consider include:

1. The research is elegant and thorough; more work can be done and no doubt will be done well. What additional level of precision and types of research are needed to address mission-related sleep and fatigue concerns?
2. How can the importance or potential impact of these risk factors be compared to or balanced against the need for additional research on other behavioral and psychiatric risk factors?
3. The quality of the work in the area of sleep research is clearly superior, but does the benefit justify the relative lack of attention being paid to other important concerns?

Are there any additional gaps in knowledge that should be considered for this specific risk?

Yes. The evidence book states that motor performance has not been affected substantially by sleep loss, fatigue, etc. More information on this point would be interesting because EVA as well as onboard activities require skilled motor functioning.

Does the evidence book address relevant interactions among risks?

Yes. This is a very positive point in the paper, pointing to the interaction of sleep loss, fatigue, etc., on the risk of performance errors.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*

These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The expertise of the authors is very strong. A number are leaders in the field of sleep and performance. The literature search is also sufficient and the table documenting the findings from spaceflights is very helpful. Apparently the authors have covered the available studies in the English- language literature. Where available, it would also be informative to report findings from the Soviet/Russian space program. The text readability is good, but editing would be beneficial to reduce the amount of repetition in the document. The same information and phrases are presented in a number of places throughout the evidence book.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The paper is clear and, on the whole, well written. The review of the literature on different amounts of sleep loss and effects on performance as well as the interaction among sleep loss, circadian desynchronization, fatigue, and effects on performance is informative and well presented. The description of research findings from a range of ground-based laboratory and "real-life" situations, as well as evidence from spaceflights, is also helpful in obtaining a perspective of risk. The designation of research gaps applicable for planning for planetary missions is well thought out and compelling. A highly positive feature of this paper is the discussion of individual differences in the effects of sleep loss and fatigue on human performance. In addition, the description of current research, particularly the development of two different biomathematical models showing the temporal dynamics and effectiveness of cognitive performance as predictors of performance decrement, may prove to be a highly important countermeasure enabling astronauts to self-monitor their performance readiness.

The only major reservation about this evidence book is the difficulty that is involved in comparing efforts devoted to this topic relative to the sparse number of studies devoted to other significant behavioral and psychiatric risks.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

A crosscutting issue is the effect of sleep loss and fatigue on psychosocial adaptation.

Chapter 15
Performance Errors Due to Poor Team Cohesion and Performance, Inadequate Selection/Team Composition, Inadequate Training, and Poor Psychosocial Adaptation

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. The existing evidence is covered in considerable detail. However, in part the case is made based on non-flight information because, unfortunately, empirical evidence from space is extremely sparse and often anecdotal.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
Yes. It is clear and succinct, and again points to the lack of systematic research in this area.

Does the evidence book make the case for the research gaps presented?
In part. Gaps 1 and 2 are based on the literature review and are presented with accompanying information about how JSC personnel and other investigators are attempting to deal with these gaps. Gap 3, regarding methods and tools for selecting and composing crews for optimal team performance, would be strengthened by a fuller prior discussion covering empirical research in this area along with the authors' recommendations.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. The approach of this paper is to focus on how to optimize human performance during long-duration missions, rather than simply how to eliminate errors. A strong case is made that the best way to reduce risk is to achieve optimal performance. This conceptual framework is positive and provides a context for the research that needs to be carried out that ultimately will reduce the risk of performance errors. However, more information is needed based on empirical research in space, and on heterogeneous small groups performing in arduous extreme environments or in simulation chambers. Additional attention should also be given to the definition of teams and of cohesiveness, including potential impacts of the broader "mission team" that includes both astronauts and earth-based support staff. A potential consideration is the distinction between group cohesion and individual morale and how personality, demographic, and situational variables influence the manner in which emotional reactions may affect the individual's and the crew's performance.. More comprehensive research in analog environments with greater fidelity to the space voyage or planetary exploration, including simulations of a space vehicle, will advance information obtained from teams interacting via computer on specific tasks. This program of research will supplement the lesser amount of information that can be obtained studying the relatively small number of flight crews. Further, the issue of leadership is absent, including the interaction between leadership style and situational demands on impact on a mission.

Does the evidence book address relevant interactions among risks?
Yes. The relationship between team performance and individual adaptation is presented. However, there is almost no coverage of the impact of specific behavioral problems such as personality disorders and mood disorders (poor psychosocial adaptation) on team cohesion and performance. This information is relevant to the risk of performance errors, particularly if certain types of behavior problems have a specific impact on various team factors, and in turn performance. Moreover, individual adaptation is relevant to team selection and the development of countermeasures. Finally, additional focus is needed to address the lack of specific criteria that define what constitutes optimal, outstanding, adequate, or inadequate performance and the external validity of analogue tasks (not only analogue environments).

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The literature review on issues such as team cohesion and selection is of interest. A great deal of relevant information is presented, with a summary and recommendations at the end of each section for the type of research that needs to be carried out to mitigate risk. However, the coverage is uneven. At times, the paper does not go beyond a somewhat superficial discussion of the literature, making points that are quite obvious, or not following through with more in-depth analysis. For example, with regard to selection, what are the various options that might be taken for measuring personality or attitudes toward teamwork, and so on? The section on Training (pp. 12-13) mentions previous studies that show different kinds of training have an impact on "performance." But the issues are treated in a very general way. What kind of training? For what kinds of individuals? Conducted by whom? How was performance measured? In addition, the literature on single- and mixed-gender expedition teams as an analog for spaceflight and planetary exploration is not covered, although these studies were specifically designed to inform about individual and team processes in space. A more thorough review of data that originates from international space agencies, including the Shuttle/MIR and ISS studies of team process is also needed. The evidence book could also be strengthened with a review of issues related to extended cohesion, i.e., promoting positive interactions beyond the contexts of selection, training, and flight to the post-flight period.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The paper presents a considerable breadth of topics and research findings. However, greater attention to empirical studies in space and of small groups performing in arduous extreme and simulation environments is needed. Editing is required to clarify some of the comments that are vaguely presented or repeat the obvious. The recommendations for research on selection and countermeasures for dealing with the risk of performance errors due to team performance need to be expanded. Furthermore, coverage of the effects of particular behavior problems on team functioning is lacking.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 16
Behavioral and Psychiatric Conditions

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?

Yes. The case is made, but not in a strong and persuasive fashion. Unfortunately, most of the evidence that is provided is either intuitive or based on anecdotes and personal testimonials. Specific findings from analog environments as well as space missions are presented, including a small amount of information from the Russian space program, primarily the book by one cosmonaut. Numerous statistical analyses are presented projecting behavioral and psychiatric risks based on data primarily from analog environments.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.

No. The writing is clear, but it would be helpful to provide more details regarding the specific types of psychiatric and behavioral conditions that are expected and the impact they might have on the health of the crew and the success of the mission. Information beyond *Safe Passage* (IOM, 2001) should be included, commenting on data from more recent space missions.

Does the evidence book make the case for the research gaps presented? The gaps presented are somewhat vague (e.g., what are the best assessment measures to detect behavioral and psychiatric disorders?). There is an enormous amount of literature on this topic. This evidence book, however, does not connect the existing literature on the assessment of psychopathology to the specific circumstances and special problems involved in spaceflight. The paper moves from this very general issue (assessment of psychopathology) to an extremely specialized and somewhat narrow topic that involves cognitive changes following exposure to isolated, confined, and extreme environments. The report should make this connection more explicitly and further investigate the decline in cognitive performance during long-duration missions, but this is mentioned only in the Gaps section. The risk of behavioral problems due to monotony and boredom should also be considered in depth. The final gap mentioned involves countermeasures to maintain behavioral health (presumably including both psychological and pharmacological interventions). Again, this is a reasonable statement at the most

general level, but it is not connected to a more specific set of goals that might motivate a systematic research program.

Are there any additional gaps in knowledge that should be considered for this specific risk?

Yes. The section on personality factors is extremely sparse and does not cover adequately the many personality studies of personnel in extreme environments including simulation studies, as well as data from astronaut selection. Moreover, the described methodology of the Ursin et al. (1992) paper is imprecise, as their paper is a review article with speculations about long-duration flight.

The comment in the Executive Summary, that the select-in procedures used thus far have not been able to predict "whether an astronaut would be adversely affected by the stresses of spaceflight" (p. 4) and thus countermeasures remain the primary focus of risk mitigation, needs further clarification. NASA has collected a huge body of data via various personality and other assessment measures. NASA should make these data accessible, while taking into consideration informed consent and guarding confidentiality, to retrospectively assess possible predictors of later functioning. In addition, given the limited availability of data, NASA may wish to examine "anecdotal" sources including archival literature, such as astronaut memoirs and the NASA oral history series. Although countermeasures are clearly crucial, there is still much research that could be carried out that would inform about select-in personality traits, and an examination of the predictive effectiveness of different personality assessment instruments. This is a highly important issue because the traits adaptive for long-duration missions may be quite different from those adaptive for shorter missions. Greater attention to selecting out those with personality disorders versus clear Axis I clinical disorder psychopathology is also important. The authors may also wish to make more of a point about how valid different analogues may be—e.g., an Antarctic station where 100-200 people winter over is not all that comparable to a ten-day Shuttle mission with a dozen or fewer, or a 2+-year trip to Mars and back with half a dozen astronauts."

Other gaps that should be considered include outcome research on the most effective countermeasures for training coping skills, etc., preflight; countermeasures for behavioral and psychiatric problems during and after a flight; computer-based counseling; on-board presence of a crewmate trained in counseling; telepsychiatry; and evaluation of the effectiveness of countermeasures for families before, during, and after flight.

Greater research attention is needed to understand the cause and phenomenon of asthenia reported by the Russians as a problem or disorder manifested by an unknown number of cosmonauts during spaceflights. This apparently psychophysiological state would constitute a high risk during long-duration missions.

Does the evidence book address relevant interactions among risks?
Yes. Coverage of sleep problems is informative. However, the review may be strengthened by a consideration of environmental design. For example, the ability to control and vary the environment of the capsule would be important to combat boredom.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The paper is highly readable, although some editing is indicated. Several sections in the paper are redundant. It reads as though it was written in several smaller sections by different authors, and these sections were not carefully integrated.

The reliance on "personal communication" interspersed throughout the paper detracts from its overall scientific quality. It would be helpful to add experts on topics such as the treatment of depression. Will conversations with ground-based professionals be effective, especially given communication delays? Can crew members be trained to help each other with psychosocial interventions? There is little information in this paper on empirical findings from the Russian space program.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The paper makes a strong case for the risk of behavioral problems and psychiatric disorders occurring during long-duration missions. However, there are two primary problems with the content of the paper. One is that the evidence used to develop the argument does not move much beyond statements from previous Institute of Medicine reports, references to unpublished papers, and anecdotes attributed to specific staff members and astronauts. The other problem is that the gaps identified are so general and vague that they do not lend themselves to empirical evaluation.

More attention to personality and behavioral predictors of problems and psychopathology in space or postflight is indicated, as well as potential impact on astronaut families. There is a need for more comprehensive understanding of the

types of disorders experienced in space as reported by the Soviet/Russian space program, based on their considerable experience in long-duration missions. Greater attention needs to be paid to research on the effectiveness of the countermeasures used to deal with the various risks covered, and in particular, the development and evaluation of countermeasures for dealing with postflight problems by astronauts and their families.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

Missing: prevention and treatment of postflight behavior/psychiatric disorders.

Chapter 17
Acute Radiation Syndromes Due to Solar Particle Events

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
No. Replace "atmosphere" with "magnetosphere" or "magnetosphere and earth shadow."

Does the evidence book make the case for the research gaps presented?
Not entirely. The description of the acute gap #1 is confusing both in wording and with respect to intent. The goal would seem to be to develop probabilistic uncertainty distributions for certain acute effects associated with galactic cosmic radiation (GCR) and solar particle events (SPEs); the unspoken assumption is that we now have such information for gamma rays and X-rays (or perhaps, the *only* information we now have pertains to these types of radiation), and need more information about relative biological effectiveness (RBE) of proton and high charge and energy (HZE) nuclei in particular for extrapolating to GCR and SPE. On the other hand, the problem may not be just a matter of RBE. If the mechanisms of tissue damage differ, which is suggested by Figure 20-3 in the radiation carcinogenesis paper, extrapolation from low linear energy transfer (LET) radiation like gamma and X-ray may not be direct.

In general, the discussion in the text should prepare the reader for each of the research gaps; this does not always occur. Acute Gap #5 (which is important) is an example of this.

Acute Gap #11 is somewhat surprising: Fertility and heredity impairment are not usually considered to be acute effects that would damage the mission as laid out in the initial paragraph of the evidence book. Like increased cancer risk, they certainly are matters of concern, but do they belong here? (Of course, technically the effect is "acute" as opposed to "stochastic," but the initial paragraph uses the word in a somewhat different way.)

Are there any additional gaps in knowledge that should be considered for this specific risk?
Some effort might be expended in expanding on the "etc." in Acute Gap #5 (in general, "etc." isn't appropriate for a scientific paper unless one is sure the reader can readily supply the details).

Does the evidence book address relevant interactions among risks?
See comments about Acute Gap #5.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

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- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The evidence book would benefit from a good editor with knowledge of the field. Sometimes the wording is confusing. For example, on p. 17-4: "In contrast to the constant presence of galactic cosmic rays in space, SPE exposures are sporadic *and without sufficient shielding protection.*"

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
Overall, the paper would benefit from editing.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 18
Degenerative Tissue or Other Health Effects from Radiation Exposure

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
Yes.

Does the evidence book make the case for the research gaps presented?
Yes.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. Additional gaps in knowledge to be considered include:

1. Genetic susceptibility and its influence on individual response?
2. ISS currently operates at Earth normal except during prebreathe; however, some Constellation class missions may be operating with elevated oxygen concentrations (30-34 percent). Because response to radiation is in part mediated by generation of oxygen-free radicals, will this potentiate degenerative effects of radiation exposure?
3. Because the CNS effects are of such potential concern, consider briefly listing these here with crossreference to relevant document.

Does the evidence book address relevant interactions among risks?
Yes.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
Appropriate.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

This is an excellent and comprehensive review of the state of knowledge about degenerative tissue effects and the need to improve that state. However, the lack of search information about genetic susceptibility and potential interaction with oxygen concentration should be addressed or dismissed as literature search would reveal.

Small correction: pp. 18-19, line 4: it's an arithmetic (not geometric) average—see NCRP 132, eq. 7.6 (p. 246). Note that geometric averages, although convenient for lognormal model calculations, are biased toward the lesser of risk projections according to two transport models.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The primary concern is a lack of recognition (this is pervasive throughout the evidence books) that individual gene profiles might inform and influence risks. For example, to use a CNS example, genes have been identified that correlate with early-onset Alzheimer's disease; would such mutations render an individual more susceptible to degenerative CNS effects (either acute or late)? A second area of concern is about the interaction with ambient oxygen levels.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

See above.

REFERENCE CITED

Hirsch, D. B., J. H. Williams, S. A. Harper, H. Beeson, and M.D. Pedley. 2007. *Oxygen concentration flammability thresholds of selected aerospace materials considered for the Constellation program*. NASA Technical Report #20070018178, http://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20070018178_2007017304.pdf (accessed April 13, 2008).

Chapter 19
Acute or Late Central Nervous System Effects from Radiation Exposure

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. The paucity of human evidence, the small sizes of relevant animal studies, the apparent lack of studies of nonhuman primates, and the possibility of acute effects that could degrade crew performance make this a potentially serious risk

factor, possibly equal or greater in importance to that of radiation-related cancer risk.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
Yes. The PRD is clear and succinct.

Does the evidence book make the case for the research gaps presented?
Yes. The gaps enumerated are more or less self-evident. There is some urgency because of the possibility of severe consequences to mission performance.

Are there any additional gaps in knowledge that should be considered for this specific risk?
New gaps are likely to emerge as we learn more about the problem.

Does the evidence book address relevant interactions among risks?
Yes.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

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- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The evidence book has the great advantage of information provided by NCRP Report No. 153, which was commissioned by NASA. That report includes a comprehensive literature survey. The expertise provided by the NCRP committee and the senior author of the evidence book is considerable. The evidence book is accessible to a science professional not familiar with the specific area covered, but some effort is required.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The evidence book addresses a possibly serious risk factor for which the epidemiological literature in particular is not very informative because of important differences between the radiation environments inside and outside the Earth's magnetic field. Information from experimental studies and medical case reports

is limited by small numbers. A greatly expanded research program would seem to be required.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 20
Radiation Carcinogenesis

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. The case is an easy one to make, and it is made very well.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
No. The phrase "is likely to increase" risk should be changed to "may increase." because "risk" refers to probabilities and because the case is a strong one. The following change is suggested: "Occupational radiation exposure from the space environment may increase cancer morbidity or mortality in astronauts."

Does the evidence book make the case for the research gaps presented?
Yes. As stated in the PRD, the main conclusion, that we have to find a practicable way to reduce the risk, trumps everything not directly related to that goal.

Are there any additional gaps in knowledge that should be considered for this specific risk?
No. The list of gaps seems comprehensive. It would be helpful if they were prioritized in terms of probable importance for risk and likelihood of achieving useful results in the next decade or two (a kind of cost–benefit analysis for research on identified gaps).

Does the evidence book address relevant interactions among risks?
No. There are many potential for interactions between radiation and other risks that should be considered. One example is the potential interaction between radiation and immune dysfunction incurred during space travel (see Farrell et al., 2000, and accompanying editorial). Also, given that the full program may take decades, NASA should be archiving material for genetic testing related to possible new developments with respect to genetic susceptibility to radiation-related cancer.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
The latency periods are such that any radiation-related cancer would most likely appear after the completion of the mission. On the other hand, predicted lifetime excess cancer risk, which would be uncertain and should be represented by an estimated probability distribution, would provide full information for a decision about acceptability of risk. The approach of Figure 20-2 comes close to that ideal.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

Author expertise is high, especially with respect to understanding of radiation physics, epidemiology, and risk estimation.

Some cited references do not appear in the reference list, suggesting that the document was submitted before it could be fully proofed, but the overall quality of the evidence book is high.

Readers not quantitatively inclined will probably skip the mathematical parts, but they should remain in the paper.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
Overall, the evidence book provides a very good and comprehensive review of the issue of radiation-related cancer associated with space activities.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

This comment is a general one, not limited to the specific evidence book: The approach using separate evidence books could be too compartmentalized, unless the next phase is to integrate them. It would make sense to classify risks and risk factors in terms of (1) effect on ability to successfully complete the mission (e.g., acute effects) and (2) long-term effects on health and well-being following the mission (e.g., cancer risk). The next step would be to carry out quantitative uncertainty analyses, using objective data where available and expert subjective uncertainty information where necessary. The process should be transparent and open. The analyses would be designed to provide estimates of the implications of the various sources of information for the two types of effects, with uncertain-

ties. Such analyses might be expected to identify areas for which more information is most needed because of possible or likely consequences for mission success and long-term health effects.

REFERENCE CITED

Farrell, R. J., Y. Ang, P. Kileen, D. S. O'Briain, D. Kelleher, P. W. Keeling, and D. G. Weir. 2000. Increased incidence of non-Hodgkin's lymphoma in inflammatory bowel disease patients on immunosuppressive therapy but overall risk is low. *Gut* 47(4):514-519; editorial commentary by L. J. Kinlen, pp. 462-463.

Chapter 21
Therapeutic Failure Due to Ineffectiveness of Medication

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. The evidence book makes a convincing case for risks associated with medication use. The title is somewhat misleading, as the evidence book clearly demonstrates that there are risks related to self-medication, and inaccurate recordkeeping in addition to "ineffectiveness of medication." It is striking that the largest indication for self-medication is pain relief, yet debriefings suggest that pain is inadequately addressed in flight. Similarly, the evidence book appropriately warns against the "un-counseled polypharmacy trend of medication use in space." We suggest changing the title to: "Risk of therapeutic failure or adverse effect due to ineffectiveness of medication, medication interaction, or unanticipated idiosyncratic reaction."

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
Yes.

Does the evidence book make the case for the research gaps presented?
Yes. The evidence book is comprehensive, although a bit difficult to read.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. Additional gaps in knowledge to be considered include:

1. How does genetic variation contribute to differences in drug effectiveness and side effects in the space environment?

2. What potential interactions with alcoholic beverages might be anticipated (if the crew is international and if alcohol is allowed in-mission)?
3. How will the natural degradation associated with long storage periods be mitigated for long-duration space travel?
4. What classes of drugs should be taken on a mission, what quantities should be taken, and how can the risk of inability to treat be minimized, especially during long-duration exploration-class mission?
5. The decision on which classes of therapeutic agents and which drugs to take will impact which conditions can be treated. A methodology for decision making should be included.

Does the evidence book address relevant interactions among risks?
Yes.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
Merging is appropriate. No risks appear to have been omitted.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The expertise is appropriate and the literature review is comprehensive. The evidence book is extremely thorough. This will make it a bit difficult for the average "science professional" to wade through. The case for Gap #3 could be improved, including the consideration of technologic solutions. Gap #4, as worded, is overly broad and overarching and Gap #5 is vague.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The evidence book makes a convincing argument for significant gaps in knowledge and need for additional research. It does not appear to adequately address the following issues, listed as gaps above:

1. It is now recognized that genetic polymorphisms influence drug metabolism significantly (e.g., warfarin, tamoxifen, codeine). In clinical practice, testing for known mutations that affect drug metabolism is rapidly becoming part of the standard of care. Ongoing research should include archiving samples for future testing as new genes are identified. Use of drugs may need to be optimized to individual astronauts' genetic profiles.

2. When long-duration exploration-class missions are undertaken, a decision will need to be made about taking alcoholic beverages or not. If alcoholic beverages are to be flown, potential interactions of drugs and alcohol in the space environment must be considered.
3. Because of the duration of exploration-class missions, drugs will need to be stored for considerable time. Degradation occurs with time, even on Earth. Storage periods may exceed current recommendations. Loss of potency and potential for toxicity may result. The time factor needs to be addressed as one of the unique factors in these classes of missions.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 22
Inability to Adequately Treat an Ill or Injured Crew Member

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?

Yes. The synthesis of in-mission experience and incidence of illness derived from analog environments makes a strong case for the importance of autonomous health care capability for exploration-class missions, and the probability that some health emergencies may not be treatable.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.

Yes. The wording conveys the essence of the issue.

Does the evidence book make the case for the research gaps presented?

No. The evidence book states: "Identification of the 'gaps' between anticipated in-mission medical conditions and abilities to mitigate or treat these conditions adequately is currently being conducted." No list of gaps is presented, nor is the basis on which anticipated conditions will be included or excluded.

Are there any additional gaps in knowledge that should be considered for this specific risk?

Yes. A gap exists not only for specific medical conditions identified, but also for a published and widely understood algorithm or method for including or excluding any particular condition for in-mission treatment consideration. An approach

based solely on existing in-mission and analog environment experience is likely to be insufficiently effective, and should be enhanced by best available synthesis of the other health risk categories. For example, although altered immunity has yet to be associated with clinically evident disease, consideration of treatments of conditions that might result from altered immunity, such as disseminated viral reactivation, should be included in planning for long-term missions.

Does the evidence book address relevant interactions among risks?
No. Inability to provide treatment is interlinked with "risk of error due to inadequate information."

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The paper is quite readable and well formulated, with adequate citations to published and unpublished findings. Author expertise appears to be appropriate to the task.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
This evidence book seems to be in an early stage of development. The addition of a detailed list of gaps will do much to illuminate the directions in which research and development will be going within NASA. As written, it describes a necessary, but not sufficient, overall approach to the provisioning of autonomous health care resources and, at least as importantly, the enumeration of conditions that will be left untreated during exploration-class missions.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 23A
Lack of Human-Centered Design: Sub-Risk of Reduced Safety and Efficiency Due to Poor Human Factors Design

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. The case is made largely on the basis of anecdotal incidents that are convincing, but not a thorough scientific evaluation. The numerous examples are compelling, but it would be a stronger case if they were limited to the space accidents rather than the ground-based accidents (e.g., aviation, ship, power plant) as well. It is far more important to demonstrate the problems that exist in long-duration spaceflight and the research required to address those problems than it is to describe the effects of general human accidents in recent history.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
No. Although the case is strong, the description is inadequate. It is filled with jargon and is not specific.

Does the evidence book make the case for the research gaps presented?
Yes.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. Additional gaps in knowledge to be considered include:

1. Manual control
2. Advanced displays
3. Workload assessment
4. Training, both initial and in-mission
5. Use of artificial intelligence for malfunctions
6. Spatial disorientation as it affects performance

Does the evidence book address relevant interactions among risks?
Yes. With human factors, everything is connected to everything else. A fatigued astronaut will need a redundant checklist. A disoriented one will need a more compelling display. Further, the authors may wish to address the potential overlap associated with the impact of environmental design on psychosocial and behavioral adjustment issues, e.g., issues discussed in Chapters 15 and 16.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

The literature should be divided into the specific accounts associated with the Human Factors examples, and the broader references dealing with space experiences and human factors methodology. The expertise and examples are adequate, though not all are directly applicable. The overall readability is poor because of too much jargon and too much repetition. The evidence book list of authors includes many from "inside" the NASA system, and may be improved with additional external academic perspectives.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*

This section is a full and provocative primer on the general issue of dangers associated with the various aspects of human-centered design, and what can happen if the principles are ignored. It suffers from being too long—but especially in not distinguishing between the dangers associated with the failure to follow known procedures, and the absence of information about what procedures to employ for long-duration spaceflight. The first is a matter of training and the second is the subject for NASA's Human Research Program (HRP) research.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*
  1. Manual control
  2. Displays
  3. Spatial disorientation
  4. Fatigue

Chapter 23B
Lack of Human-Centered Design: Sub-Risk of Error Due to Inadequate Information

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?

Yes. As discussed below; however, the case could be made more compelling.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.

Yes. It is clear. but incomplete. "Lack of information can be a problem, but so can too much information if the means of separating the important information are inadequate or poorly designed." A suggested revision follows:

> "Task errors can be due to lack of, or inadequate ability to discern, appropriate information, which in turn may be due to any of the following:
> [(a), (b), (c), (d) as shown]
> (e) excessive information, with unclear or otherwise inadequate demarcation between the information that is important or useful for the situation and the information that is not."

Does the evidence book make the case for the research gaps presented?
Yes. The supporting evidence from spaceflight is very strong, and NASA is certainly one of the world's leading experts. However, the categorization of the spaceflight examples could have been more logically presented in some instances. The ground-based supporting evidence is not adequate. For example, using an occurrence that is nearly 30 years old (the Three Mile Island nuclear accident in Pennsylvania) as an example of inadequate displays and controls certainly raises the question of whether there are more recent examples. If so, these should be cited as examples, and if not, query whether a problem still exists.

In addition, because the risk definition does not adequately address having too much information, none of the examples relates to that issue. There is a large amount of supporting ground-based evidence that is available concerning every category enumerated in the evidence book, involving both inadequate and too much information. The evidence book would be stronger if such issues were also included.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. There are undoubtedly gaps associated with the issue of too much information, which is not adequately discussed in the report.

Does the evidence book address relevant interactions among risks?
Yes.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*

- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

No additional comments.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The paper satisfactorily addresses issues associated with inadequate information, but the paper should also address issues associated with too much information, which can also lead to undesirable outcomes.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 23C
Lack of Human-Centered Design: Sub-Risk Associated with Poor Task Design

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes. As discussed below, however, the case could be more compelling.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
Yes. It is clear but incomplete. Focusing solely on reducing operator error is politically popular, but can result in serious inefficiencies when applied in actual operation. Moreover, the issue relates to all tasks, not just critical tasks. A suggested revision to the second sentence follows: "All tasks, especially critical tasks, must be designed to minimize human error in a way that improves efficiency as much as possible, or at least minimally degrades efficiency."

Does the evidence book make the case for the research gaps presented?
Yes. Similar to Chapter 23B: Inadequate Information, the supporting evidence from spaceflight is very strong, and NASA is certainly one of the world's leading experts. However, the categorization of the spaceflight examples could have been more logically presented in some instances. The ground-based supporting evidence is not adequate. For example, using an occurrence that is more than 60 years old (a cargo ship explosion in 1947) as an example of which cargo compartments should and should not be adjacent to each other (not to mention the

issue of why this is an example of poor task design) certainly raises the question of whether there are better and more recent examples. If so, why aren't more recent examples cited, and if not, query whether this is still a problem.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. There are gaps associated with determining the impact on efficiency of an error-reducing task design.

Does the evidence book address relevant interactions among risks?
No. The design of tasks that necessitate EVA must consider the physical and other limitations created by the EVA suit.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

No additional comments.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The paper should address not only the error potential of task designs, but also the impact on efficiency. In addition, task design of activities that involve EVA must also consider the physical and other limitations of the EVA suit.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 24
Inadequate Food System

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
Yes.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.
No. The last sentence suggests that an allocation of resources for food has already been made, which is unlikely at this early stage. The following is a suggested replacement for the last sentence: "Furthermore, careful attention must be paid to the resources allocated to creating a satisfactory food system in order to avoid unduly depriving other systems of needed resources."

Does the evidence book make the case for the research gaps presented?
Yes.

Are there any additional gaps in knowledge that should be considered for this specific risk?
Yes. One gap that is not mentioned is whether acceptable food will grow on Mars, the Moon, or enroute, given the reduced gravity, reduced sunlight, available water, radiation, and other aspects of the growing environment. This uncertainty may necessitate carrying enough on-board food to provide adequate and acceptable nutrition in case biogeneration is not successful. If enough on-board nutrition has to be carried, as a contingency, a potential query is whether biogeneration should be part of the overall nutrition plan.

Does the evidence book address relevant interactions among risks?
No. The paper addresses several interactions, most notably the relation between adequate and acceptable food and the crew's physical and mental well-being, but at least one risk interaction is missing. The evidence book on central nervous system effects from radiation exposure mentions some dietary countermeasures, but there is no indication in this food system paper regarding giving any special consideration to those dietary items.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*
These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

No additional comments.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
The paper provides a good description and analysis of the many difficult issues involved.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.

Chapter 25
Adverse Health Effects from Lunar Dust Exposure

Does the evidence book make the case (sufficient evidence) that this risk is relevant to long-term space missions?
No.

1. The evidence book would be strengthened by the addition of a systematic introduction to the toxicology of airborne particulates, so that the reader would have a set of benchmarks against which the evidence regarding lunar dust can be considered. As a related consequence, the document jumps from one topic to another, including some examples (e.g., Hawks Nest tunnel disaster) that have little relevance for the task at hand. It makes the assumption that activation/passivation is the key issue, but does not adequately justify this. The draft does not do an adequate job of presenting and discussing the potential health effects of dust exposure. These would include at least fibrogenicity, carcinogenicity, allergic sensitization, and respiratory/dermal irritant properties.
2. This evidence book should include a more complete and systematic presentation concerning what is known about the characteristics of lunar dust in order to consider adequately the potential health risks. This is another prerequisite for an evaluation of risk and gaps. The human health risks from airborne dust exposure vary according to chemical composition, particle size, physical characteristics (e.g., crystalline structure, particle shape, fibrous character), and a variety of human factors (e.g., pre-existing illness, respiratory rate). As an example, the draft paper seems to presume that lunar dust is respirable (see first sentence of executive summary), but there is no discussion about the particle size distribution of lunar dust and not all evidence supports this assumption. More attention is necessary for this important issue.
3. Similarly, the current draft fails to consider potential allergic/immune consequences of lunar dust. Indeed, terms such as “airborne allergen” and “IgE” never appear, and the word “immune” (or related) appears only once. This is despite the evidence that two individuals who were

exposed to lunar dust reported allergic symptoms or findings. The first, an Apollo astronaut, described his response as "hay fever" (i.e., pollen allergy); the second, a ground-based physician-scientist, described an "allergic-type" reaction, apparently supported by changes in basophil and eosinophil counts. This oversight should be considered and addressed to ensure the development of effective countermeasures.

4. The draft offers two Earth-based analogs (silicosis among miners and volcanic ash exposure) without convincingly explaining how these compare with possible lunar dust exposures. It fails to explore another body of evidence that may be relevant—environmental exposure to PM10 particulate dust (10μM-diameter particulate matter) and its effect on respiratory and cardiovascular function.

Is the text of the short description of the health risk provided in the PRD clear (it should be Section I of the evidence book)? Provide suggestions of revised wording.

No. The text is not an affirmative statement describing the problem. Rather it is simply a critique of the risk statement in the PRD. It is suggested that it be rewritten, not just revised.

Does the evidence book make the case for the research gaps presented?

Yes. Most of the gaps identified seem reasonable; however, the paper may be strengthened if it begins to establish relative importance to each.

Are there any additional gaps in knowledge that should be considered for this specific risk?

Yes. Additional gaps in knowledge to be considered include:

1. Respiratory dynamics under conditions of reduced gravity or weightlessness. Does particle distribution and deposition in the respiratory tract differ from Earth-based conditions?
2. Effectiveness of available control methods to reduce exposure.
3. Role of lunar dust as a possible airborne allergen.
4. Countermeasure development, ranging from physical to pharmaceutical, to deal with the airborne allergen potential.

Does the evidence book address relevant interactions among risks?

No. Only EVA suits are mentioned. Other topics for consideration include impact of prolonged exercise, poor human factors design, and cognitive errors.

Comment if relevant to the specific evidence book: *Is the merging of some risks in the Bioastronautics Roadmap into a single risk appropriate? Is the omission of some risks in the Bioastronautics Roadmap appropriate?*

These are not relevant to this evidence book.

Comment on other issues regarding the evidence book, including:

- *Is the author expertise sufficient? Other disciplines needed?*
- *Literature search: Is the breadth of the search sufficient? Is information on the search strategy needed?*
- *Overall readability: Is it appropriate for a "science professional" who is not familiar with the specific area covered?*

See comments above regarding the literature base. The authors seem highly skilled and knowledgeable in a variety of areas, but the draft suggests the need for more input from the clinical, epidemiological, and environmental health scientists who are familiar with the occupational and environmental health risks of long-term, low-level exposures to a variety of airborne particulates.

Overarching comments on the evidence book: *Provide a short paragraph summary of the key issues raised in your review of the paper.*
No additional comments.

Please note:

- *Crosscutting issues and ideas for broader recommendations*
- *Additional risks that should be added to the list (missing risks)*

No additional comments.