2014 Advanced Environmental Health/Advanced Food Technology Standing Review Panel

Status Review for:

The Risk of Adverse Health Effects Due to Alterations in Host-Microorganism Interactions,
The Risk of Adverse Health Effects of Exposure to Dust and Volatiles During Exploration of Celestial Bodies, and
The Risk of Performance Decrement and Crew Illness Due to an Inadequate Food System

Comments to the Human Research Program, Chief Scientist

2014 Advanced Environmental Health/Advanced Food Technology (AEH/AFT) Standing Review Panel (SRP) Status Review WebEx/teleconference Participants:

SRP Members:
Howard Kipen, M.D., M.P.H. (Chair) –Rutgers – Robert Wood Johnson Medical School
Harriet Burge, Ph.D. – EMLab P&K
Terry Gordon, Ph.D. – New York University School of Medicine
Janice Harte, Ph.D. – Michigan State University
Dennis Heldman, Ph.D. – The Ohio State University
Jeffrey Laskin, Ph.D. – Rutgers – Robert Wood Johnson Medical School
C. Glen Mayhall, M.D. – University of Texas Medical Branch, Galveston
James Pestka, Ph.D. – Michigan State University
Anna Shvedova, Ph.D. – National Institute of Occupational Safety and Health
Art Teixeira, Ph.D. – University of Florida

NASA Johnson Space Center (JSC):
Erin Connell, Ph.D
Grace Douglas, Ph.D.
Mark Ott, Ph.D.
Heather Paul
Michele Perchonok, Ph.D.
Jennifer Rochlis, Ph.D.
Mark Shelhamer, Sc.D.
Scott Smith, Ph.D.
Susan Steinberg, Ph.D.
Mihriban Whitmore, Ph.D.

National Space Biomedical Research Institute (NSBRI):
Graham Scott, Ph.D.

NASA Headquarters (HQ):
Bruce Hather, Ph.D.
Steve Davison, Ph.D.

NASA Research and Education Support Services (NRESS):
Tiffin Ross-Shepard

On December 10, 2014, the AEH/AFT SRP, participants from the JSC, HQ, the NSBRI, and NRESS participated in a WebEx/teleconference. The purpose of the call (as stated in the Statement of Task) was to allow the SRP members to:

1. Receive an update by the Human Research Program (HRP) Chief Scientist or Deputy Chief Scientist on the status of NASA's current and future exploration plans and the impact these will have on the HRP.
2. Receive an update on any changes within the HRP since the 2013 SRP meeting.
3. Receive an update by the Element or Project Scientist(s) on progress since the 2013 SRP meeting.
4. Participate in a discussion with the HRP Chief Scientist, Deputy Chief Scientist, and the Element regarding possible topics to be addressed at the next SRP meeting.

Based on the presentations and the discussion during the WebEx/teleconference, the SRP would like to relay the following information to Dr. Shelhamer, the HRP Chief Scientist.

General Comments:

1. The SRP thought the WebEx/teleconference was very informative and appreciated the presentations from Dr. Shelhamer, Dr. Rochlis, Dr. Ott, and Dr. Douglas.

Comments specific to AEH Risk:

1. During the WebEx/teleconference, an issue was brought up as to the use of C. elegans as a model for evaluating microbial-host interactions, especially with reference to its applicability to humans. Although C. elegans is a useful model to identify genes regulating many biological process including cell growth and development, the SRP thinks its use in understanding complex processes regulating the interaction with microbes and humans is very limited. The biological systems important in understanding how microbes interact with human tissues are not the same as with C. elegans. For example, extracellular matrix of the host is crucial for microbial host interactions. While humans have approximately 30 collagens, C. elegans have hundreds in just the cuticle alone. This would argue for a more well thought out plan developing an understanding of microbial-host interactions that impact on human health either in a microgravity environment or during celestial space travel.

2. The SRP wants to remind the AEH portfolio scientists that the human microbiome works in close association with a virome. The human virome is very active with respect to mutations and may be even more active than the bacteria in the microbiome. That raises the question as to whether the virome may be even more susceptible than the bacteria to radiation in deep space. Some SRP members think this should be considered a "Gap" requiring research to determine whether or not the human virome may undergo such mutations as to seriously disrupt the microbiome, whereas other members felt that there was not a mature enough data base on which to base an active gap research program. The SRP would be pleased to revisit this question at greater length at its next in-person meeting.

Comments specific to AFT Risk:

1. Overall, the SRP thinks the tasks being pursued by the AFT portfolio seem to be moving in the right direction. Outcomes from many or most of the tasks should assist to achieving the 5-year shelf-life goal.

2. One of the key observations discussed during the WebEx/teleconference was the need to take advantage of the combined impacts of thermal treatment, moisture content, and storage temperature to obtain the desired outcomes. Then, there is the additional step of fortification to ensure that key nutrients are at desired levels 5 years later.

3. Probiotic Lactobacillus acidophilus (ATCC 4356) is being used for current studies, but the SRP wonders if any effort has been made to look at additional types of probiotic microorganisms following the initial work with L. acidophilus? A mixture of these may have an increased benefit.

4. For the study of functional foods baseline and requirements analysis, the SRP thinks the principal investigator should consider looking into the bioavailability of these after different processing and storage conditions, etc.

5. The SRP has brought up the cold storage issue during the last couple of SRP review cycles. One member has provided detailed suggestions for the HRP's consideration. To further address these issues see the detailed addendum. The SRP would like to request that engineers be included as part of the 2015 review and that this meeting be an in-person meeting. Some issues the SRP would like to discuss with the engineers and the AFT portfolio are:
    a. What is the current plan for keeping food on Mars if shipped ahead of human flights? What type of storage units? What types of precautions are possible? Will radiation be controlled or prevented? Will temperature be controlled in any way?
    b. Will there be fluctuating temperatures for the food stored on Mars? If so will that change related to the exposure to the sun? How long is daylight? Is the temperature fluctuation 70 to -80^{0}F (some comments on the conference call seemed to mention those temperatures)? Would a solar heating system or some other system help absorb temperatures from the daylight hours to modify the cold temperatures later?
    c. Will the packaging withstand the -80^{0}F temperatures? It seems that delamination occurred with these low temperatures? Would it be possible to put out a RFP to companies to develop prototype films/ packages that would protect the food and be stable to very cold temperatures and fluctuating temperatures? Maybe better adhesives for the laminates or films could be produced in other ways?

6. The impacts of low temperature storage (specifically frozen) cannot be evaluated without considering the temperature history during cooling to the storage temperature. If these conditions are not considered, it will definitely lead to unacceptable conclusions.

7. The current tasks include only one sub-freezing temperature condition. The SRP thinks these results cannot be used to suggest that the outcomes would be similar at all other sub-freezing temperatures. The same is true for refrigerated storage temperatures, although the temperature range is not as broad. The SRP also thinks that the combined impacts of storage temperature and moisture content deserve more attention than indicated in current projects.

8. During the WebEx/teleconference Dr. Douglas indicated that the current pouches would expand because of residual oxygen in the pouches (0.5 to 1 %?). Since CO_2 is the primary gas, if any of that migrates into the pouches it shouldn't affect food quality (oxidation reactions) negatively. Would the food have to be protected from radiation, dust storms, rocks, dust, etc. in some sort of unit? Would this be buried below the surface, if possible?

<u>Response to the Addendum Questions:</u>

1. Recent lunar dust studies evaluated this dust to determine a Permissible Exposure Limit (PEL) for an 8 hour work day. Should future studies of lunar and other celestial dusts include (a) evaluation of the cardiovascular risks associated with the inhalation of these dusts and (b) the determination of the maximum acute exposure limit?

    - The establishment of an 8 hour PEL of 0.3 mg/m3 for lunar dust, based on Scully et al (2013) seems appropriate for respiratory health protection and is endorsed by the SRP with the caveat that the SRP has not had an opportunity to review and discuss as a group the Scully risk assessment methodology.

    - Another caveat is concern as to whether an 8 hour standard is appropriate given that the astronauts may have longer exposures if their habitat becomes contaminated. The SRP recommends a short term or 24 hour PEL.

    - The SRP noted that the PEL values listed in the addendum text and Human Research Roadmap are different. It says 0.3 in one document and 0.5 to 1 mg/m3 in the paper and 5 mg/m3 lunar dust inhalation somewhere else.

    - As the addendum question outlines, there is also a basis for concern about acute effects of higher concentrations of dust. In general the SRP feels that acute exposures are very important, both for physiology and for symptoms, and that derivation of an appropriate ceiling value (concentration) should be pursued, with recognition of possible variability in the dust composition.

    - The SRP also discussed whether the PEL is appropriately designed. Considerations should also be brought up as to where exposures of astronauts are expected to occur (e.g., inside the space suits, putting on or taking off a space suit or other articles of clothing, in the space living environment, etc.). The efficacy of the air/surface cleaning systems and protocols in reducing particle exposures needs to be better considered.

- The SRP thinks additional experts should be consulted who can provide better insight into exposure assessment issues, especially during long term celestial missions. There was concern that the PEL was not developed by an unbiased group of scientists and risk assessment experts. It would be preferred to have independent risk assessment scientists validate the decisions of the researchers who did the inhalation studies.

- The experts that suggested the PEL may also be using the terms for respirable incorrectly. If eye/nose irritation is an important consideration, then the 'inhalable' descriptor term should be used to cover the larger size particles too.

- Over the past 15 years, there has been accumulating epidemiologically-based recognition that increases in ambient particulate matter (largely combustion derived), in conjunction with exposure to air pollution gases (NOx, CO, SOx) is associated with increased risk for adverse cardiac events over time courses of possibly hours (triggering MI and stroke), and certainly days or years (promoting atherosclerosis). There is a substantial literature that provides mechanistic underpinning (biomarker change) for these epidemiologic associations, and as the addendum question points out these views are widely held. That said, it is a widely held view that much, if not all of the risk of adverse cardiac events, occurs in the very young, the elderly, and those with underlying susceptibility (although biomarker changes do occur in healthy individuals).

- Cardiovascular stress/risk is an important consideration, but more information is needed on expected exposure scenarios and confounding variables. While the consideration of evaluating the potential for cardiovascular disease is important in terms of inhaled environmental and occupational airborne particles, the SRP thinks the risk in healthy and very fit astronauts would be low. Therefore, the SRP would not recommend adding CVD testing as a research gap. If it is considered, then retrieval and analysis of heart rate/ECG data for heart rate variability and related outcomes from the astronauts should be the first step. The SRP recommends that a comprehensive review of available environmental and occupational literature be undertaken, including heart rate variability studies, with an assessment of their applicability to the astronaut workforce.

2. Technological advances have provided new methodologies for tissue culture based evaluation of toxicological compounds (e.g., Wyss Institute Organs-on-a-Chip). Guidance is requested from the SRP as to whether this type of technology is mature enough to be investigated as a screening tool to gain a preliminary evaluation of dust toxicity for initial designs for future NASA spacecraft life support systems.

    - The SRP thinks this type of technology is not mature and validated enough to be used as a screening tool to gain a preliminary evaluation of dust toxicity for initial designs for future NASA spacecraft life support systems. Too much work needs to be done on these "Organs-on-a-chip" systems to sustain the hypothesis that they truly mimic

human organ systems or their responses to materials such as particles and dust. They are created under conditions where they have not been convincingly demonstrated to represent significant drug/toxin metabolism and there is often only minimal consideration of the role of the immune system and its role in toxicity in their construction. Questions have not been addressed as to the best way to insert immune cells or even the type of immune cells to insert. One should be cautious as to what the end-points of toxicity testing are really showing. Their efficacy with standard toxicants and controls has not been validated. It is strongly recommended against using such model until they are much better developed.

SRP Addendum on Food Risk:

This comment elaborates further on recommendations made during the Web/Ex Teleconference of December 10 to consider food storage in deep space or planetary surface environment external to crew habitat. Rationale for this concept stems from several points of consideration, as follows:

1. Current Challenge:

The challenge seems to be lack of technology to develop a food system capable of supporting a crew of six persons on a three-year round trip to Mars. Current effort is focused on achieving 5-year shelf life of packaged food items stored within a closed environment suitable for crew habitat (ambient temperatures and oxygen). Under these conditions, chemical and biochemical reactions may proceed slowly supported by free moisture in the food and eventual oxygen permeation through packaging material, limiting shelf life to little more than one or two years under these conditions. Moreover, even if the shelf-life problem were to be solved, the quantity of packaged food required to support six astronauts for three years would be in the order of 6,500kg (6.5 metric tons) taking up nearly ten cubic meters of volume. It is unrealistic to expect a space craft to lift off from earth's surface carrying this mass and volume.

2. Proposed Alternative Approach
   (Food Storage External to Crew Habitat)

   a. Food Storage Stability:
   This alternative approach would consider packaged food storage in oxygen-free pressure-tight containers exposed to the oxygen-free near cryogenic temperatures of deep space, as well as on the Martian surface. Under these conditions, no chemical or biochemical reactions could take place to limit food shelf life. Therefore, currently available food packaging and thermal processing technology would suffice to achieve long term stability under these storage conditions. Instead, the challenge to be faced by the AFT program would be one of product development to develop thermo-stabilized packaged food menu items that would retain acceptable physical texture properties during the brief freeze-thaw cycles expected to occur during the three-year storage and handling conditions. These would likely be food menu items prepared as casserole dishes.

b. Transport to Mars:

The mass and volume of food required for the three-year mission (10m3 weighing 6.5kg) would likely require two or three unmanned missions to place food containers on the Martian surface for a 28-month supply prior to the last 8-month supply needed to be on board with the crew (external to the crew habitat) on the manned out-bound trip. This would require that each of two unmanned mission would need to lift off and transport a 14-month supply equal to 2.5 metric tons or a 9-month supply of 1.6 metric tons if three unmanned missions were required. Admittedly, at three years elapsed time per mission, the unmanned transport missions would need to begin at least nine years prior to the final manned mission with crew on board, along with the 8-month food supply for the out-bound mission.