How Do We Get from Cell and Animal Data to Risks for Humans from Space Radiations?†

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After four decades of human exploration in space, many scientists consider the medical consequences from radiation exposures to be the major biological risk associated with long-term missions. This conclusion is based upon results from a research program that has evolved over the past thirty years. Despite the diversity in both opinions and approaches that necessarily arise in research endeavors such as this, a commonality has emerged from our community. We need epidemiological data for humans, animal data in areas where no human data exist, and data on mechanisms to get from animal to humans. We need a programmatic infrastructure that addresses specific goals as well as basic research. These concepts might be deemed overly simplistic and even tautologous were it not for the fact that they are frequently underutilized and even ignored. This article examines the goals, premises, and infrastructures proposed by expert panels and agencies to address radiation risks in space. It is proposed that the required level of effort and the resources available demand a unified, focused international effort that is, at the same time, subjected to rigorous peer review if it is to be successful. There is a plan; let us implement it.

“I suppose we shall soon travel by air-vessels, make air-instead of sea-voyages, and at length find our way to the moon; in spite of the want of atmosphere.” George Gordon [Lord] Byron, 1788–1824.

INTRODUCTION

The story of Phaethon and Helios in Greek mythology about Phaethon’s abortive attempt to orbit the Earth might be interpreted as an example of early awareness on the part of our ancestors of the intrinsic risks associated with space travel. Similarly, the misfortune of Icarus when he ignored the risk limits set by Daedalus for flying toward the sun (not too high and not too low) might be one of the first written theses about the potential dangers from solar radiation in space. Today, after decades of relatively frequent shuttle trips and orbital missions, and the realization that interplanetary missions “toward a human presence in space” are technologically feasible, radiation has emerged as a major hazard, perhaps the major health hazard, for personnel in space. Nevertheless, despite an increasing concern about the potential health consequences and following decades of research, the uncertainties in those risks remain too high1). Moreover, there frequently appears to be a dichotomy between the types of information we purport to need to determine these risks in space and the types of biological data being sought. With continuous human presence in space but decreasing resources, it is imperative that we examine whether we are being as effective and as efficient as possible in determining the health risks from radiations in space.

At The 1st International Workshop on Space Radiation Research in Arona, Italy, the opening speakers searched for solutions. Dr. Juergen Kiefer2) questioned whether the procedures for radiation protection on Earth are necessarily the best systems to be applied in space. Dr. Eric Hall3) noted that cancer risks are not detectable at low doses through epidemiological investigations and proposed that mechanistic studies can lead us to the means to extrapolate appropriate data to that low-dose region. Dr. Francis Cucinotta4) suggested that experimental models could lead to testable
theories that ultimately could allow accurate risk projections. Dr. Gerhard Kraft\textsuperscript{5)} presented an example of such a theoretical model currently being used successfully in radiotherapy.

To define more precisely the means for moving from experimental cell and animal data to risk in humans in a space radiation environment, we briefly review expert opinions of what those potential risks are, how they might be best determined, and how the research outcomes compare with the proposed needs. Finally, we conclude with specific recommendations.

WHAT ARE THE RISKS?

It is difficult to ascertain exactly when radiation in space was recognized as a serious health hazard. Certainly, there was a strong interest in examining space radiations unattenuated by the Earth’s atmosphere even before the space program for purposes of particle physics, astronomy and astrophysics. Radiation doses, however, were not monitored until the fifth Mercury mission\textsuperscript{6}). Nevertheless, by the mid 1960s, the potential consequences of radiation were recognized as a problem to the extent that NASA and the National Research Council of the U.S. National Academy of Sciences reported on the radiobiological factors associated with human flights\textsuperscript{7,8}). The level of concern has oscillated significantly during the last four decades as public and governmental interest in human presence in space has varied and as new information has been forthcoming. In 1989, the National Council on Radiation Protection and Measurements\textsuperscript{9)} evaluated radiation received in space activities. The group was relatively conservative in its evaluation of the risk, concluding only that it was expected that exposures in space would be greater than those for terrestrial radiation workers. Two recent NRC/NAS reports\textsuperscript{10,11)} led to the conclusion that radiation beyond low Earth orbit (LEO) potentially poses serious health effects that must be controlled before long-term missions are initiated. Most recently, we seem to be reaching unanimity that radiation is one of the major hazards in space, possibly the major unresolved biomedical issue. NASA’s Critical Path Roadmap (CPR)\textsuperscript{12)} lists four type-I severe risks, its most severe classification. Two of these, Human Behavior and Clinical Capability, address the ability of crews to respond to changes in performance or acute medical problems rather than specific hazards or diseases. The remaining two, Radiation and Bone Loss, have direct and perhaps synergistic clinical consequences.

In the case of radiation, the major risk according to NASA’s CPR is the increased likelihood of cancer, with the additional possibilities of damage to the central nervous system, synergistic effects with other hazards, acute responses to exposures, and effects on fertility, sterility, and heredity.

The NCRP/NAS Space Studies Board strategy for research in space biology and medicine\textsuperscript{10,11)} enumerates seven higher priority recommendations with regard to risks from radiation and, again, carcinogenesis is the first item. Their higher priorities also include determining cell killing and chromosomal aberrations, better methods for extrapolation from rodents to humans, better error analyses, better designs for space vehicles, and better means of predicting solar events, as well as five lower priority recommendations.

The NASA-sponsored report on modeling human risks\textsuperscript{13)} infers from the existing literature that space radiation can cause cancers and organ damage. The report of the NCRP on radiation protection guidance for space activities\textsuperscript{9)} concluded that the major concerns about radiation in space are cancer and genetic effects. The more recent NCRP report on radiation protection for low Earth orbits\textsuperscript{14)} likewise concludes that the concern about radiation exposure is the possibility of late effects, the most important of which is cancer.

There is a consensus, then, that cancer is the number one issue to be resolved with regard to radiation exposures in space, with CNS damage, synergistic effects, and a few other key issues to be evaluated as well for their relevancy. Radiation is likely to be the major cause of long-term complications. Shorter-term bone loss and other acute responses may be enhanced in a radiation field, although little data are available to evaluate the risk.

It is appropriate at this point to quote the words from NCRP Report 98\textsuperscript{9)} in reference to the early NAS/NRC reports, namely, “It should be recalled that, with the other attendant and much greater risks involved in space activities, it seemed inappropriate to be unduly restrictive about radiation exposures.” It is our inability to address in a satisfactory manner what appears to be a potentially manageable risk despite the dedicated efforts of our colleagues that suggests that we should reexamine the modus operandi. If cancer or CNS damage or other diseases pose a potential risk great enough to seriously jeopardize either crews or missions, how can we determine sufficiently the level of risk and evaluate potential countermeasures that might reduce the risk?

WHAT INFORMATION DO WE NEED?

Although there is general agreement that radiation is a major hazard, there would appear to be less agreement on what research is needed to obtain adequate risk values with
acceptable uncertainties for low doses of radiations in space. Human epidemiological studies provide the most direct and, in principle, the most reliable information. For the case at hand, the human population exposed in space is small and the likelihood of observing radiation induced cancers or other diseases above background levels even over long periods of time is likewise small and encompassed with large uncertainties. Moreover, such confounding factors as microgravity, changes in diets, or changes in sleep cycles contribute to the risks for these diseases, making it necessary to infer that fraction of the total risk arising from radiation, increasing the uncertainties even further. There are basically three other sources of experimental data: epidemiological data for humans exposed in other scenarios (such as survivors of atomic-bomb or reactor incidents, patients given radiation therapy, or radiation workers), animal studies, and cellular or subcellular studies. The human data that we have obtained is generally for photons not protons or energetic heavy ions and at acute rather than protected exposures. Although these data are essential for establishing absolute risks, they nevertheless must be extrapolated to the radiations and conditions in space. It is that extrapolation that introduces major uncertainties in the final results\(^1\). Recently, there is an emphasis on genetic and cytogenetic biomarkers in-vitro, which are more easily obtained and more easily quantified. Relevant genetic information is essential for developing mechanistic models, and mechanistic models, we claim, are essential for determining risk. Such data have already been useful in establishing relative susceptibilities of sub-populations with specific genetic characteristics\(^15,16\). However, relative susceptibility and risk, while related, are not the same. It has been considerably more difficult to correlate observed genetic changes, particularly between those in vitro, with cancer rates in animal models. In fact, recent data suggest that in-vitro genetic changes do not correspond directly to those observed in cells in vivo\(^17\).

For decades, in-vivo studies have served as the mainstay for evaluating risks arising from environmental modifying factors. Over two decades ago, Fry\(^18\) observed that “The existing human data cannot alone provide estimates of risk of exposures to very low doses...” further noting “the fact that some model for the dose-response relationships must be used makes it imperative to design animal experiments in order to test the model.”

We draw two important inferences from Fry’s paper. The first is that we need animal experiments to measure relevant endpoints such as cancer to determine risks. The second is that we need theoretical models to establish dose response relations from the animal results in order to apply them (extrapolate) to humans. In practice, however, little work is being done to measure carcinogenesis or other diseases in vivo, and there is little direct support from agencies for developing theoretical biology models.

In view of the major advances in genetic and molecular biology, we might question whether Fry’s approach is necessary or even applicable to today’s situations. The importance of such research is poignantly summarized in the National Academies’ review of NASA’s Biomedical Research Program\(^19\), which concluded that “There is a good balance between dosimetry and molecular and cellular radiobiology. However, more emphasis should be placed on carcinogenesis and CNS end points, using animal models. Such experiments must be carried out in ground-based facilities so as to estimate the risks to astronauts of exposure to HZE particles and develop guidelines for limits on exposure to these particles.”

[Boldface in reference. The dearth of such experiments was dramatically summarized in “The First Biennial Space Biomedical Investigators’ Workshop (January 1999) which included descriptions (abstracts) of 23 relevant projects, of which only three dealt with research on vertebrates-one on mutations of an exogenously incorporated gene in mice; one on behavioral effects of HZE particles on rats; and one on the induction of breast cancer in rats by HZE particles and gamma rays”\(^19\). There was a similar distribution for the 10th Annual Space Radiation Health Investigators’ Workshop (1999)\(^20\). These statistics are not much different than those for The Second International Workshop on Space Radiation Research in Nara, Japan, 2002.

Despite the repeatedly expressed consensus that animal-based studies of carcinogenesis are necessary to obtain the needed risk factors, my conclusion is that little such research has been taking place. Further, if we accept the premise that we need carcinogenesis, CNS damage, and other relevant endpoints in animal models, the question remains how we would use those data.

**IS THERE AN ACCEPTED PROCEDURE THAT WILL GET US TO RISKS IN SPACE?**

Despite the legitimate criticisms against indiscriminately extrapolating animal results to humans, animal research has been uniquely successful for determining risks from radiation and drugs as well as for evaluating countermeasures and treatments. In 1997, a NASA-sponsored panel\(^13\) did an excellent job of reviewing the status of cell and animal research and the procedures for applying these types of data.
Their general conclusion was that “neither existing in vitro and culture models nor theoretical and computational biology can substitute for in vivo studies...” Equally important, they have summarized succinctly and precisely the process needed to go from cells to humans. We present a variation of that procedure in Figure 1modified for the present application.

The important underlying premise is that a mechanistic-based theoretical model of sufficient accuracy must be developed with which to calculate risks for cancer, CNS damage, or other diseases. The key point is that it is the theoretical model, not the experimental data, not even the human epidemiological data that is used to determine risk in humans.

Genetic and molecular data are used to establish what important cellular and subcellular mechanisms must be incorporated into the model. However, care must be exercised to establish that the processes apply to the in-vivo case. For that, we need in-vivo genetic and molecular data to establish relative and absolute levels of importance of the different pathways and to establish what epigenetic, absco- pal, and exogenic factors modify the cellular pathways and endpoints and, therefore, also must be incorporated into the model.

Changes in both the cellular processes and clinical endpoints with radiation type, energy, and dose rate must be both measured in biological systems and modeled.

Potential synergisms between different radiations and radiation and other factors such as bone loss, tissue atrophy, or nutritional changes must be examined and incorporated into the model, if they are significant.

Finally, the model must be benchmarked with existing human data to establish the absolute magnitude of the risks.

In summary, a theoretical model or models must be constructed that can model cellular and subcellular processes leading to clinically relevant endpoints for protons and HZE particles. The cellular component of this model is tested by using it to model clinical endpoints including cancer and CNS damage in relevant animal models, iterating the process until sufficient accuracy is established for the calculations. That model is also used to calculate cellular responses for relevant human cells in vitro, compared with measurements, and again tuned for accuracy. In all cases, changes in responses, if any, with particle types, energies, and dose rates must be established. The model is then used to calculate expected clinical responses for humans for relevant situations where we have data for subcellular responses and for cancer and other clinical endpoints. Throughout the

![Diagram](https://academic.oup.com/jrr/article-abstract/43/Suppl/S1/1107915/1107915)

A matrix representation of a process for assessing risks in humans with theoretical models and cell and animal data.

Adapted from LBNL Report 40278, Modeling Human Risk: Cell & Molecular Biology in Context, (13).
entire process, realistic error analyses must be carried out to provide the level of confidence for situations where there are no benchmarking data. Then, the model can be used to establish risks and risk uncertainties for humans in space where we have no data.

Obviously, this is a time-consuming program requiring a high degree of organization and coordination. However, in the long run, only a focused programmatic effort is likely to yield meaningful results in a reasonable period of time. National coordination and international cooperation are certainly already present, but there is room for improvement. There are obvious recommendations to be made, to remind us of the goal and to refocus the successful programs, and to question research endeavors that do not appear to fulfill the criteria.

**RECOMMENDATIONS**

Before stating the overall conclusion, I have five recommendations to make, each of equal importance, so the order of presentation is not meant as an indication of relative significance. These five recommendations are:

1. We must support low-dose, in-vivo studies of carcinogenesis and tumorigenesis as a function of dose rate. As costly and time-consuming as they are, without such data, we will almost certainly not achieve a scientifically meaningful conclusion.

2. We must support the development of relevant theoretical models. These models are necessary tools for determining risks in humans where there are no human data. We must be careful to differentiate between theoretical modeling, which uses existing models to interpret or interpolate experimental data, and the development of new theoretical models, which allow better and more accurate modeling.

3. We should reexamine the human epidemiological data in terms of low dose responses, both in terms of cancer and other diseases, but also in terms of genetic and molecular changes. This requires a correlation of specific responses with individuals and individual characteristics rather than global representations, a level of examination yet to be done.

4. There should be a small international cooperative group coordinating animal studies, particularly those for carcinogenesis, tumorigenesis, and neurotoxicity, to maximize resources, quality, and productivity. A good model for effective organizations of this type might be the cooperative groups organized to run clinical trials in medicine, such as the Quality Assurance Review Center (QARC), Children’s Oncology Group (COG), the Eastern Cooperative Group (ECOG), or the American College of Surgeons Cooperative group (ACOSOC).

5. There should be an independent review by scientists, overseen by a neutral organization such as a national academy of science or a council for radiation protection, of the types of in-vivo carcinogenesis and CNS studies that should be carried out. This report should be the basis for a programmatic, peer-reviewed research program.

Finally, we have a well-defined problem with a well-defined goal. That is, we have a radiation environment in space with an uncertain risk, uncertain both in terms of the nature of those risks and their magnitudes. We need to determine the types and levels of risk adequately and develop countermeasures to assure an acceptable level of risk for personnel in space. The methods for determining radiation risks have been developed and refined over the years and are well known to the scientific community, albeit resource and time intensive. We can hope for serendipitous alternatives that might solve the problem in a quick and simple way, but we must focus on a strategic, programmatic effort. An internationally coordinated goal-oriented, peer-reviewed program should be formed that supports large, focused research projects for risk assessments and countermeasures, commonly called a top-down approach. In parallel, we should continue with the more typical investigator-initiated research, the bottom-up approach, to stimulate innovative ideas and to search for better methods.

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