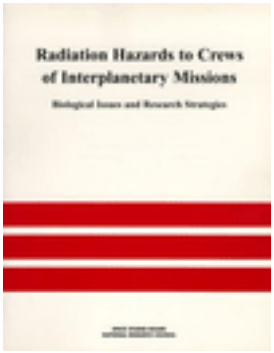

Radiation Hazards to Crews of Interplanetary Missions: Biological Issues and Research Strategies

Task Group on the Biological Effects of Space Radiation, National Research Council

ISBN: 0-309-52429-6, 88 pages, 8.5 x 11, (1996)

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Biological Issues and Research Strategies

Task Group on the Biological Effects of Space Radiation
Space Studies Board
Commission on Physical Sciences, Mathematics, and Applications
National Research Council

NATIONAL ACADEMY PRESS
Washington, D.C. 1996

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Support for this project was provided by Contract NASW 4627 and Contract NASW 96013 between the National Academy of Sciences and the National Aeronautics and Space Administration.

Copies of this report are available from

Space Studies Board
National Research Council
2101 Constitution Avenue, N.W.
Washington, D.C. 20418

Printed in the United States of America

TASK GROUP ON THE BIOLOGICAL EFFECTS OF SPACE RADIATION

RICHARD SETLOW, Brookhaven National Laboratory, *Chair*
JOHN F. DICELLO, Johns Hopkins University School of Medicine
R.J. MICHAEL FRY, Oak Ridge National Laboratory
JOHN B. LITTLE, Harvard University School of Public Health
R. JULIAN PRESTON, Chemical Industry Institute of Toxicology
JAMES B. SMATHERS, University of California, Los Angeles
ROBERT L. ULLRICH, University of Texas Medical Branch, Galveston

SANDRA J. GRAHAM, Study Director
SHOBITA PARTHASARATHY, Research Assistant
VICTORIA P. FRIEDENSEN, Former Senior Program Assistant
CATHY GRUBER, Senior Program Assistant

* Former member.

Foreword

Astronauts who venture beyond the protection of Earth's atmosphere and magnetosphere risk exposure to levels of radiation far exceeding those on Earth. Of all the risks they face, this one is probably the most straightforward to control—by providing adequate shielding. However, because shielding adds weight, cost, and complexity to space vehicles, it is very important for designers to have a good, quantitative understanding of the true risk and its degree of certainty.

This report assesses our understanding of radiation hazards in space. It also considers the additional research needed to reduce the areas of uncertainty, research that must be completed prior to undertaking the detailed design of a vehicle carrying crew members into space for periods of extended exposure. The report finds that it will take more than a decade of research to answer even the narrowest set of key questions, although happily the needed studies can all be conducted on the ground rather than in space.

The nation has backed away from a specific timetable for human exploration of the moon and Mars. Yet it seems plausible that such expeditions will be mounted sometime in the first quarter of the 21st century, especially given the recent resurgence of interest in possible life on Mars from the study of meteorites. It becomes clear, when the lengthy time scale of the research is also taken into account, that the present report is indeed timely and should receive prompt consideration by NASA planners.

Claude R. Canizares, *Chair*
Space Studies Board

Preface

The study that is the subject of this report was initiated as a result of a series of discussions between the leaders of NASA's Office of Life and Microgravity Sciences and Applications (OLMSA), NASA's Life and Biomedical Sciences Division (LBSAD), and the Space Studies Board's Committee on Space Biology and Medicine (CSBM). In order to address concerns within NASA and CSBM regarding the many uncertainties in the understanding of radiation hazards to the crew of long-duration missions in space, CSBM formed an expert task group on radiation biology and physics whose members had no direct involvement with NASA's radiation programs. A CSBM member with the appropriate expertise was appointed to lead the group.

The Task Group on the Biological Effects of Space Radiation (TGBESR) was asked to review current knowledge on the effects of long-term exposure to radiation in a space environment and to consider NASA radiation shielding requirements for orbital and interplanetary spacecraft. The task group was charged with assessing the adequacy of NASA planning for the protection of humans from radiation in those environments and with making recommendations regarding needed research and/or new shielding requirements. Where feasible, the task group would also provide NASA with radiation safety guidelines.

Early in the study the task group was informed by NASA that plans for the international space station were at such an advanced stage that any recommendations affecting shielding of orbital craft could not be implemented by the agency. The task group therefore decided to concentrate on the radiation hazards of interplanetary missions. Further, at the urging of NASA, the task group has attempted to provide reasonable estimates of time lines for completing the radiation research it has recommended.

Although the recommendations of the task group are published here as a separate and independent report of TGBESR, it is the intent of CSBM that this report will also form the basis of a section in a space life sciences strategy report being prepared by CSBM for publication at a later date.

During the course of this study the task group was briefed extensively by representatives of OLMSA and LBSAD regarding NASA's planning for deep-space missions and projections for radiation shielding. The task group also received in-depth technical briefings on the status of NASA's radiation research and the agency's current understanding of radiation hazards, and it consulted a wide range of technical documentation. When verification or additional details of prior research were needed, task group members made direct queries to the pertinent investigators in the radiation research community.

A number of individuals who assisted the task group by supplying information deserve special thanks for their contributions: Harry Holloway, Frank Sulzman, and Walter Schimmerling of NASA headquarters; John Wilson of NASA Langley Research Center; Amy Kronenberg of Lawrence Berkeley National Laboratory; and Gregory Nelson of the Jet Propulsion Laboratory.

Contents

Executive Summary

NASA's long-range plans include possible human exploratory missions to the moon and Mars within the next quarter century. Such missions beyond low Earth orbit will expose crews to transient radiation from solar particle events as well as continuous high-energy galactic cosmic rays ranging from energetic protons with low mean linear energy transfer (LET) to nuclei with high atomic numbers, high energies, and high LET. Because the radiation levels in space are high and the missions long, adequate shielding is needed to minimize the deleterious health effects of exposure to radiation.

The knowledge base needed to design shielding involves two sets of factors, each with quantitative uncertainty—the radiation spectra and doses present behind different types of shielding, and the effects of the doses on relevant biological systems. It is only prudent to design shielding that will protect the crew of spacecraft exposed to predicted high, but uncertain, levels of radiation and biological effects. Because of the uncertainties regarding the degree and type of radiation protection needed, a requirement for shielding to protect against large deleterious, but uncertain, biological effects may be imposed, which in turn could result in an unacceptable cost to a mission. It therefore is of interest to reduce these uncertainties in biological effects and shielding requirements for reasons of mission feasibility, safety, and cost.

This report of the Task Group on the Biological Effects of Space Radiation summarizes current knowledge of the types and levels of radiation to which crews will be exposed in space and discusses the range of possible human health effects that need to be protected against (Chapters 1 and 2). It points out that recent reductions in facilities for radiation research raise concerns about how best to acquire needed new knowledge. The report goes on to suggest other steps to be taken and the types of experiments needed to reduce significantly the level of uncertainty regarding health risks to human crews in space (Chapter 3). In Chapter 4 the task group recommends priorities for research from which NASA can obtain the information needed to evaluate the biological risks faced by humans exposed to radiation in space and to mitigate such risks. It outlines, in general terms, the commitment of resources that NASA should make to carrying out these experiments in order to design effective shielding in time for a possible mission launch to Mars by 2018, which would allow for energetically favorable flight trajectories. Chapter 5 addresses additional issues pertinent to carrying out studies on the effects of radiation, and the appendixes provide additional details and clarification as appropriate.

Summarized below are the task group's conclusions, its recommendations for future experiments, and its estimates of the time needed to carry out these experiments. The data from these experiments should permit NASA to design cost-effective shielding to protect astronauts from the deleterious effects of radiation in space.

1. The principal risks of suffering early effects as a result of exposure to radiation in space arise from solar particle events (SPEs). It is not too difficult a task to provide appropriate shielding or storm shelters to protect against exposure during SPEs, but surveillance methods to predict and detect solar particle events from *both* sides of the sun relative to a spacecraft must be improved.

2. The kinds of biological effects resulting from exposure to the ionizing radiation encountered in deep space do not differ from those resulting from exposure to x rays. However, the quantitative difference between the risks posed by x rays (low-LET radiation) and by heavy high-energy nuclei (high-LET radiation) may be large, and the magnitude of the human biological effects is largely unknown. An understanding of these effects—including cancer induction, central nervous system changes, cataract formation, heritable effects, and early effects on body organs and function—as well as of the shielding necessary to mitigate these effects for crew members, is essential for the rational design of space vehicles built for interplanetary missions.

3. The task group members generally agreed that the potential late effects of radiation are the major concern in estimating risks to crew members. Of the known late effects, cancer is currently considered to be the most important. However, experimental data suggest that exposure to high-atomic-number and high-energy (HZE) particles may also pose a risk of damage to the central nervous system (CNS). Since it is estimated that during a 1-year interplanetary flight each 100-μm^2 cell nucleus will be traversed by a primary energetic particle of atomic number greater than 4,[1] further experimentation is essential to determine if CNS damage is a significant risk.

4. To estimate the cancer risk posed by exposure of humans to radiation such as HZE particles, for which no human data are available, it is necessary to use data on the Japanese atomic bomb survivors exposed to acute low-LET radiation and then extrapolate, based on experimental data, to estimate the risks posed by high-LET radiation. At present, the only comparative data for cancer are for studies on the induction of Harderian gland tumors in mice. Additional research is required to reduce the uncertainties of the assumptions inherent in this approach. To calculate risks associated with exposure to low-fluence-rate HZE particles, it is assumed, based on cell and animal studies, that there is not a large dose-rate effect.

5. Biophysical models and data for cell killing and mutagenesis indicate that as the LET increases, the biological effect of the radiation increases to a maximum near a LET of 100 keV/μm and then decreases at higher LET. (See, for example, NCRP Report No. 98.[2]) However, no such decrease was observed in the one animal tumor for which data were obtained using a number of heavy ions with increasing LET.[3] This discrepancy creates uncertainties in estimates of risks associated with exposure to particles at these higher LETs. To resolve these uncertainties, additional systematic studies are needed on the induction in animals of other radiobiologically well characterized cancers, such as leukemia and breast cancer. From a practical point of view, sufficiently accurate data can only be obtained from ground-based experiments using acute doses.

6. The background frequencies of the heritable changes in humans, which might be increased by exposure to radiation, range from ~ 10^{-5} to 3×10^{-3} per genetic locus.[4] The minimum chronic dose that would double these values is ~ 4 Sv,[5] a value greater than that given in NASA's current lifetime exposure guidelines. Hence, the genetic risk—the absolute increase in the frequencies of heritable changes—to an astronaut will be low. The risk to the gene pool of the overall human population will of course be far lower due to the relatively small number of space-faring humans.

7. The doses of radiation to which crews are exposed in space are not expected to induce early deterministic effects, with the possible exception of skin damage and a temporary reduction in fertility. Skin damage is likely only following exposure at high doses outside the spacecraft. Experimental studies in dogs indicate that any reduction in fertility per unit dose of radiation may be greater for low-dose-rate, protracted exposure than for acute exposure.[6]

8. The space vehicles used for missions of short duration in low Earth orbit have required minimal optimization of radiation shielding for crew protection purposes. In contrast, optimization of shielding for prolonged interplanetary trips will be a major factor in the design and cost of space vehicles. It will be

necessary to know, for protons and HZE particles, the basic nuclear cross sections for interactions and fragmentation in shielding. Such data will be used to calculate the particle distributions and energies present behind different types of shielding as a result of the incident radiation passing through the shield material. Such transport calculations must be verified by ground-based experiments.

9. A knowledge of the particle types and energies present behind types of shielding should be used, with appropriate risk models, to calculate biological effects—cell killing, mutations, chromosomal changes, and tumor induction—in animals exposed to radiation. NASA investigators should also obtain parallel experimental data for the same radiation types and energies and compare these to the results calculated with models. This research is best accomplished at ground-based facilities.

10. Microgravity has little effect on the responses of simple cellular systems to radiation,[7] and uncertainties about the effects of microgravity seem negligible compared with the other uncertainties regarding risk (see 11 below). Doing cell biology and cancer induction experiments in space is costly and difficult and would require that a source of radiation be carried in the spacecraft. Because only a limited number of animals could be investigated, the results would not be statistically significant. Hence, for the study of living systems, radiation experiments in space should have a very low priority compared with ground-based research.

11. The estimated overall uncertainty in the risks of radiation-induced biological effects ranges from a factor of 4- to 15-fold greater to a factor of 4- to 15-fold smaller than our present estimates because of uncertainties both in the way HZE particles and their spallation products penetrate shielding (particle transport) and in the quantitative way in which these types of radiation affect biological functions.[8] In the absence of precise data and calculations, the shielding would have to protect crew members against the higher, but uncertain, estimated risk. The cost of this possibly unnecessary shielding has been estimated by NASA researchers to be in the range of $10 billion to $30 billion.[9] In comparison, the cost of a ground-based, dedicated HZE particle research accelerator is estimated (in 1996) to be $18.7 million, with an annual operating cost of about $4 million for 2000 operating hours per year.[10,11] The disparity between the excess cost of additional shielding and the annual NASA budget for biology and space radiation physics indicates the need for a significant increase in the research budget for these areas.

12. Major radiation facilities—including both specialized radiation sources and animal colonies—have been shut down in recent years. At present, there are severe limits on the availability of radiation particle types and particle energies for HZE particle research. NASA can no longer rely on the Department of Energy and the Department of Defense for expertise, research, and facilities. If the necessary facilities, expertise, and funding were available now, it would take approximately 10 years to provide data that NASA needs to assess the best way to provide appropriate safeguards for its spaceflight crews.

13. Unless NASA obtains access to a reliable source of HZE particles with an appropriate support staff for a significant fraction of each year, it will take well over 10 years, perhaps over 20 years, depending on the level of effort, to reduce the present large uncertainties in particle transport behavior and in the biological response functions for cancer induction. Such a delay will postpone the design of necessary shielding or may result in the use of excess shielding (at a higher cost) and possibly delay any planned Mars mission beyond the next quarter century.

14. In Chapter 4, the task group outlines its recommendations for research priorities that NASA should follow to obtain the information needed to evaluate the biological risks faced by humans exposed to radiation in space and to mitigate such risks. The research priorities recommended by the task group include extensive physical and biological experiments, including animal studies using light and heavy nuclei up to 1 GeV/nucleon. Such experiments could take more than 20 years at NASA's present utilization rate of approximately 100 hr/yr of accelerator time at Brookhaven National Laboratory's Alternating Gradient Synchrotron (AGS), the only source for HZE particles supported by NASA.

15. To carry out needed research expeditiously, NASA should explore a number of possibilities, including international collaborations, so as to increase the research time available for experiments with HZE

particles and protons at energies over 250 MeV. Such possibilities include a combination of more running time at the AGS and at lower-energy accelerators, expansion of existing facilities (see Appendix C), the commissioning of new beam lines at existing facilities, and the construction of a new facility. A 1992 National Research Council letter report (Appendix D) emphasized the need for a dedicated HZE particle facility.

The fact that the present report reaches conclusions similar to those in the 1989 report of the National Council of Radiation Protection[12] underscores the need for additional resources and facilities in order to understand quantitatively the radiation biology associated with interplanetary flights.

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1

Introduction

The long-range plans of NASA include possible human exploratory missions to the moon and Mars within the next 25 years. There are three potentially serious health effects for crew members that need to be controlled or mitigated before such relatively long-term missions beyond low Earth orbit can be initiated:[1] (1) the effects of microgravity on human physiology and the effects, if any, on cell biology and biochemistry; (2) the psychosocial aspects of long-duration confinement in microgravity with no escape possible; and (3) the biological effects of exposure to radiation in space. The last concern is a serious one because the levels of radiation in space are high enough and the missions are long enough that adequate shielding is necessary to minimize carcinogenic, cataractogenic, and possible neurologic effects for crew members. A question still to be answered is what will provide the necessary protection, for the extent of a mission, against the biological effects of high-energy galactic cosmic ray particles ranging from energetic protons with low mean linear energy transfer (LET) to nuclei of high atomic number and very high energies (HZE) with high LET, and against the effects of transient radiation in solar particle events.*

This report summarizes current knowledge of the types and levels of radiation to which crews will be exposed in space and discusses the range of possible human health effects that need to be protected against (Chapters 1 and 2). It points out that recent reductions in facilities for radiation research raise concerns about how best to acquire needed new knowledge. The report goes on to suggest other steps to be taken and the types of experiments needed to reduce significantly the level of uncertainty regarding health risks to human crews in space (Chapter 3). In Chapter 4 the task group recommends priorities for research from which NASA can obtain the information needed to evaluate the biological risks faced by humans exposed to radiation in space and to mitigate such risks. It outlines, in general terms, the commitment of resources that NASA should make to carrying out these experiments in order to accomplish an effective shielding design in time for a possible mission launch to Mars in 2018, a year allowing for energetically favorable flight trajectories. The final chapter of the report addresses additional issues pertinent to carrying out studies on the effects of radiation, and the report appendixes provide additional details and clarification as appropriate.

STATEMENT OF PROBLEM

The knowledge needed to design adequate shielding has both physical and biological components. Knowledge is needed of the distribution and energies of radiation particles present behind a given shielding material as a

*For example, with substantial uncertainty, the annual estimated equivalent dose behind ~7.5 cm of aluminum for galactic cosmic rays during the 1977 solar minimum (high fluence level of galactic cosmic rays) would have exceeded the current equivalent dose limit of 0.5 Sv/yr.

result of the shield being struck by a given type and level of incident radiation. Equally important is knowledge of the effects of a given dose on relevant biological systems for different radiation types. Each of these components involves significant uncertainty that must be reduced to permit effective design of shielding, given that the level of uncertainty governs the amount of shielding. It is only prudent to design shielding that will protect space crew members from the predicted, but uncertain, high levels of biological effects from their exposure to radiation. At the same time, excess shielding, based on current cost estimates, would impose an excess expenditure at the level of tens of billions of dollars.[2]

An understanding of the scope of needed biological and physical data requires an explanation of certain aspects of radiation behavior and the biological impact. HZE particles impinging on shielding, or on human tissue, result in very dense ionization tracks (high LET) with numerous fragments that produce a spectrum of other energetic nuclei, protons, neutrons, and heavy fragments. The numbers of these other nuclei depend on the nature of the shielding and its mass per unit area. The energy loss of the individual particles depends on their types and energies. Thus each particle contributes to the radiation dose and biological response, which are dependent on the number of particles, their types, and their energies. The theoretical calculations of doses per particle type obtained thus far for relevant shielding materials must be verified by ground-based experiments, because the radiation field rate in space is too complex for sufficient experimental analysis. At the present time, the uncertainties in these measurements amount to a factor of ~2 or more (see "Estimates of Uncertainty in Radiation Risk Factors," Chapter 2).

Ionizing radiation either directly affects cellular macromolecules or reacts with water to produce free radicals that affect these macromolecules by so-called indirect effects. These effects are mitigated somewhat by the presence of free radical scavengers in the surrounding medium. The scavengers are useful in reducing the effects of low-LET radiation but do not seem to result in any significant decrease in the damage caused by high-LET radiation.

The biological effects of fast charged particles depend on the nature of the particle (its charge and velocity) and on the specific biological end point under observation (e.g., cell killing, mutation at a specific genetic locus, chromosomal alterations, cell transformation in vitro, and tumor induction). The relative biological effectiveness (RBE) is taken as the ratio of the dose of gamma rays required to produce a specific effect to the dose of particle radiation required to produce the same level of effect. The RBE depends on the type of particle and the biological effect under consideration and may vary with the magnitude of the biological effect. More importantly, RBE varies greatly with the LET of the particle. For example, high-energy protons may have an RBE value approaching 1.0, whereas high-energy iron nuclei may have an RBE value approaching 40. For tumor induction in animals exposed at lower doses, the relationship between RBE and LET is known for only one tumor site—the Harderian gland in mice. As there are no equivalent data for tumor induction in humans for different LET values, it is necessary to extrapolate from cell and scanty mouse data to evaluate human risk.

Human radiation risk data, still being collected, are available from the analysis of cancer induction in the Japanese individuals exposed to acute doses of radiation resulting from the atomic bombs.[3] These doses are not known precisely. As this radiation was primarily low LET, in order to estimate risks to humans in spaceflight conditions one must extrapolate from the RBE vs. LET data for cells in culture and small mammals to humans. In addition, one must extrapolate from the risks from acute exposures of humans to the low-dose-rate chronic exposures involved in space missions (except for the relatively acute exposures from solar particle events). As a general rule, as the dose rate decreases, the biological effect from a given dose also decreases. This dose reduction, in going from acute to chronic exposure, also depends on the biological system and may range from a factor of 2 to 10.[4] The dose rate reduction factor for HZE particles is not well known but is probably closer to 1.[5] Two other factors that must be considered, but whose impacts are currently unknown, are the effects of biochemical or cellular repair reactions following exposure to HZE particles and the effects of microgravity on such reactions. Thus, in estimating the risks to humans exposed to radiation in space, the uncertain factors are the radiation fields behind the shielding and the extrapolation, via cell culture and animal experiments, from the uncertain risks posed by acute low-LET exposure to risks posed by chronic high-LET exposure.

To quote Curtis, Nealy, and Wilson, "Uncertainties in these numbers are difficult to estimate but a rough analysis leads to a 10-15% uncertainty in the initial charged particle spectra, a 50% uncertainty in the radiation transport calculation, a factor of 2-3 uncertainty in the risk coefficients for low-LET radiation (most of which is due to uncertainty in the dose and dose rate effectiveness factor) and perhaps a factor of 2-5 uncertainty in the risk cross sections at high-LET. Thus, an overall uncertainty in the risk of radiation-induced cancer of a factor of 4-15 for a space crew in the galactic cosmic ray environment appears to exist at the present state of our knowledge."[6] Obviously, these uncertainties have, themselves, large uncertainties.

CONTRIBUTIONS AND USE OF PAST RADIATION RESEARCH

In 1961, an ad hoc working group was appointed by the Space Science Board of the National Research Council (NRC) to provide scientific advice on the radiation environment in space associated with a manned lunar landing. A report was prepared for NASA and the Department of Defense (DOD).[7] In 1964, this group, known as the Space Radiation Study Panel, was reconstituted with the charge to (1) establish a scientific and philosophical basis for determining radiation-protection criteria for manned spaceflight operations; (2) identify the biological responses in humans relevant to mission success or failure and determine their relative order of importance; (3) propose, where possible, interim estimates of dose-response relationships for those responses of greatest importance to missions of up to 3 years' duration; and (4) recommend research programs required to fill gaps representing deficiencies in current knowledge relative to accomplishment of the above objectives. The panel's report, *Radiobiological Factors in Manned Space Flight*, was published in 1967 and still remains an essential reference.[8] It was the main source of information for the guidelines recommended in 1970 by the NRC to NASA[9] for establishing radiation exposure limits for space crew members. The recommendation was that the career limit for whole-body exposure to radiation be 4 Sv.[10] Additional limits were suggested to prevent or limit the effects of radiation on the skin (12 Sv), the testes (2 Sv), and the lens of the eye (6 Sv).[11] These recommendations were the basis of NASA's radiation protection program for the next 20 years.

In the 1967 report it was concluded that "the present knowledge of man's responses to radiation, particularly under the conditions anticipated in space, does not permit establishment of dose-effect relationships to the degree of accuracy desired for spacecraft design and operational planning" (p. 267).[12] The panel predicted correctly that it would take many decades before such accuracy would be achieved. On a more hopeful note, it surmised that observations on humans and radiobiological research would result in a better assessment of radiation risks in space.

In succeeding years, considerable progress has been made toward improved understanding of the risks posed by exposure of humans to ionizing radiation. Most of this information has been gained from studies of the effects of radiation in general and not from investigations aimed directly at answering questions about the effects of radiation in space. For example, the 1970 NRC-recommended radiation protection exposure limit of 4 Sv to the whole body was based on estimates for the risk of excess leukemia because there were no adequate risk estimates for solid cancers.[13]

In the late 1980s it was clear that a reexamination of the radiation exposure limits was required. Both the missions and the makeup of the astronaut corps were changing, and perhaps most importantly, there were more data about radiation risks. In 1989, the National Council on Radiation Protection and Measurements (NCRP) issued its report *Guidance on Radiation Received in Space Activities*, which had been requested by NASA.[14] This report introduced different career limits depending on gender and the age of onset of exposure in space. The career equivalent dose limits that were recommended were based on a lifetime excess risk of cancer mortality of 3×10^{-2} per 1 Gy of low-LET, acute radiation.[15] The report's scope was limited to low-Earth-orbit missions, although it considered the radiation environment in deep space and the biological effects of high-Z high-energy (HZE) particles. Recommendations for protection against deterministic effects were also made in 1989. The career limit of 12 Sv recommended in 1979 by the NRC for skin was reduced by the NCRP in 1989 to 6 Sv, and the limit for the lens of the eye was reduced from 6 Sv to 4 Sv.[16] Since 1989, the estimates of cancer risk based on studies of atomic bomb survivors have been increased significantly, and the NCRP will issue new recommendations in the near future.

CURRENT UNDERSTANDING OF BIOLOGICAL EFFECTS OF RADIATION

Types of Effects

For settling radiation protection standards, the division of biological effects that are important for human health into stochastic and deterministic effects has been useful.

Stochastic effects are considered to be due to radiation-induced changes randomly distributed in the DNA of single cells that may lead to cancer or genetically transmissible effects, depending on the target cells. Cancer occurs after a long latent period: after 2 or more years in the case of leukemia and, in the case of solid cancers, within a period ranging from 2 years to decades. It is assumed that the frequency of such effects increases with dose without a threshold and that the severity of the effect is independent of dose. Stochastic effects are the most important consideration in setting protection limits for human populations exposed to radiation at low doses. It is important to note that factors such as radiation weighting factors or quality factors apply only to stochastic effects in the dose range pertinent to radiation protection. Based on studies of atomic bomb survivors at Hiroshima who were exposed to acute levels of mainly gamma rays but also fission neutrons at very high dose rates, estimates for the risk of contracting leukemia have been refined,[17] and there are also data on mortality and the incidence of solid cancers at more than 20 sites in the human body.[18,19] (The precise contribution of the fission neutrons to the total dose at Hiroshima is poorly known but is not considered to be a major contributor to the risk of cancer to those exposed at Hiroshima.) In 1991, the International Commission on Radiological Protection (ICRP)[20] included leukemia and eight specific sites of solid cancers in its estimates of the probability of an individual contracting a fatal cancer after whole-body exposure to low-LET radiation at 1 Gy and at a high dose rate. The estimated probabilities were 7.12×10^{-2} per person based on a multiplicative projection model and 4.16×10^{-2} per person using an additive model.[21]

Deterministic effects, previously termed nonstochastic effects, occur only after exposure to relatively high doses and affect cell populations to the detriment of specific organs or whole organisms. These effects can range from acute radiation sickness to hair loss or nausea. In contrast to stochastic effects, deterministic effects are dose dependent in both frequency and severity. Deterministic effects may occur early, in a matter of hours or days, or late, after many months or even later. Radiation protection standards are set to prevent deterministic effects, whereas standards to protect against stochastic effects are selected to limit effects to an "acceptable" level.

Effects Induced by Protons

While the estimated risks of adverse biological effects calculated from the data on atomic bomb survivors are the basis for current radiation protection limits, the types of radiation received by the atomic bomb survivors differ markedly from the types of radiation to which space crews would potentially be exposed. In deep space, the radiation environment consists mainly of galactic cosmic radiation (GCR) at a low fluence rate. In the energy range from 100 MeV per nucleon to 10 GeV per nucleon, the GCR consists of 87 percent protons, 12 percent helium ions, and 1 percent heavier ions.[22]

Protons are also the major component of solar particle events (SPEs), with a smaller contribution by helium and heavier ions emitted from the sun. A major difference between SPE radiation and the GCR is the much greater transient fluence in SPE radiation, which in very large SPEs can be 10^{10} protons cm^{-2} with energies greater than 10 MeV.[23]

No data are available for most of the deterministic effects induced in humans by exposure to protons, and very limited data are available from studies done on animals. One such study was carried out from 1963 to 1969 by the U.S. Air Force (USAF) and NASA to determine the RBE of various types of radiation found in space.[24] About 2000 rhesus monkeys and 5000 mice were irradiated with protons of energies ranging from 32 to 2300 MeV obtained using cyclotrons at various institutions. An attempt to simulate exposure to SPEs was made using 10 MeV plus 110 MeV protons at NASA's Space Radiation Effects Laboratory synchrocyclotron at Langley Research Center. Exposures to electrons and x rays were also carried out to enable comparison of the effects of radiation of different qualities. The study showed that the biological effects of the higher-energy and penetrating protons (>138 MeV) were similar to those caused by 2-MeV x rays and ^{60}Co gamma

rays. The RBE for acute mortality was about 1.0 to 1.1. Other studies on the acute biological effects of high-energy protons suggest an RBE of about 1 compared with that for x rays. In the case of 160-MeV protons, Urano et al. found RBE values ranging between 0.8 and 1.3 for killing of jejunal crypt cells, skin damage, and effects on the lens of the eye in exposed mice.[25] An exception to these RBE values of about 1 was the indirect finding by Storer et al. of higher RBE values, namely 2.4 and 4.9 for 30-day lethality and testicular atrophy, respectively, in mice.[26]

In the treatment of human cancer with irradiation by protons, an RBE of 1.1 has been used for planning purposes, and this value does not appear to underestimate the effectiveness of the protons.

A subpopulation of the primates studied in the USAF/NASA project has been monitored for almost 30 years for late effects such as cancer, cataracts, and shortening of life. The follow-up of these animals has been especially important in assessing the risk of cataractogenesis, because no estimates exist of the risk of cataract induction in humans following proton irradiation. Significant lenticular opacifications have occurred in monkeys about 20 to 24 years after exposure to 55-MeV protons at 1.25 Gy and higher levels.[27] Results obtained from these experiments suggest that the dose-response relationship for induction of cataracts by protons are similar to that seen with low-LET radiation.

In the case of stochastic effects, there are no data for cancer induction in humans exposed to protons. The USAF/NASA study of primates discussed above has found life shortening and cancer induction to be dependent on dose but not on proton energy.[28] In the groups exposed to 138 to 2300 MeV protons, leukemia was not a major cause of death. In males, solid cancers were the major cause of life shortening. The dose-response relationships that could be derived were consistent with those found in other experimental studies of the effects of low-LET radiation, namely curvilinear. In females, endometriosis was a major effect that contributed to radiation-induced life shortening. Another finding of note was the increased incidence of malignant brain tumors in the group exposed at 55 MeV.[29] The increase can be attributed to the unusual dose distribution in the brain that resulted from the rotation of the monkeys during exposure, the limited penetration of protons with this level of energy, and probably the young age of the animals. There is no reason to believe that the finding of increased brain tumors is associated with the types or energies of the radiation, but it is related to the doses incurred. In a study of the induction of tumors in mice exposed to 60-MeV protons, Clapp et al. found no RBE values greater than about 1.0.[30] Burns et al. reported an RBE of about 3 for the induction of skin tumors in rats exposed to 10-MeV protons compared with electrons.[31]

When considering astronaut safety it should be remembered that the studies discussed above were carried out with single high-dose-rate exposures that are very different from the exposures occurring in space. Burns et al. noted a reduction in the tumorogenic effect with the increasing fractionation of 10-MeV proton irradiation, an indication of recovery.[32] Furthermore, the curvilinear response to single doses was similar to the response to low-LET radiation, indicating that the protons have attributes of both low-LET radiation and, because the RBE is ~3, of high-LET radiation. Obviously, more data, using protons of several energy ranges, are needed to estimate human cancer risks from galactic protons.

Effects Induced by Heavy Ions

The deterministic effects of exposure to heavy ions have been studied in experimental animals. The RBE of various ions was determined for effects that result from cell killing in the gut, testes, and bone marrow, and in vitro systems.[33] As Figure 1.1 indicates, the RBE increases with increasing LET, reaches a maximum between 100 and 200 keV/μm, and decreases rapidly at higher LET values. The maximum RBE values for effects involving cell killing have been found to be between 2.0 and 3.0.[34] In the case of cataract induction, which is discussed in Chapter 2, the RBE values obtained for rats and mice by Merriam[35] suggest much higher RBE values, 40 to 50 at low doses. Although the work of Lett and coworkers and of Worgul and coworkers suggests that it may be possible, with further data, to extrapolate across species to obtain RBE values for cataract induction, current data do not allow reliable estimation of the risk of cataract induction occurring in humans as a result of exposure to radiation in deep space.[36,37]

Observations on radiotherapy patients indicate that very high doses of low-LET radiation give rise to deterministic-type damage. HZE particles produce high-dose ionization tracks and kill the cells they traverse. The concern about such microlesions in the central nervous system resulting from traversal of cells by heavy

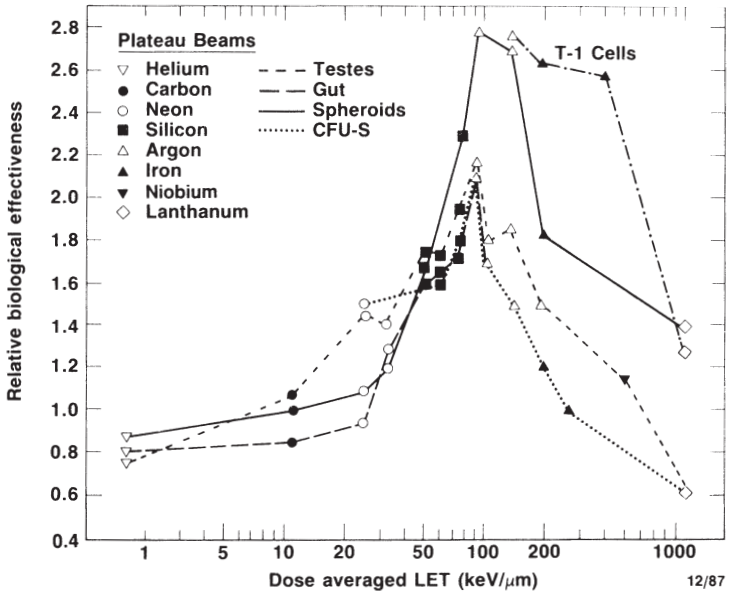

FIGURE 1.1 RBE-LET relationship for inactivation of CFU-S, intestinal crypt clonogenic cells, cells in spheroids, human T-1 cells, and the loss of testis weight. SOURCE: National Council on Radiation Protection and Measurements (NCRP). 1989. Guidance on Radiation Received in Space Activities. Recommendations of the National Council on Radiation Protection and Measurements. NCRP Report No. 98. National Council on Radiation Protection and Measurements, Bethesda, Md. Reprinted by permission.

charged particles, such as iron, has not been eliminated, nor has any evidence been produced to show that the concern is justified. The question of the effects of heavy ions on the central nervous system is discussed in detail in Chapter 2.

The main concern about stochastic effects is the risk of cancer induction. It is agreed that the RBE for carcinogenesis increases with the increasing LET of the radiation. The evidence comes largely from animal experiments with fission neutrons but also from data on induction of lung tumors in humans exposed to alpha particles from radon.[38] There has been only one systematic study of the relationship between the LET of heavy ions and the RBE values of the ions for tumor induction, which was carried out on the Harderian gland of mice.[39] Although this gland is a suitable epithelial system, it is the *only* tumor model that has been examined over the range of LET values encountered in space. Hence, it is not possible to generalize on the basis of these data about RBE values for induction of cancer in important sites of the human body such as the breast, lung, and bone marrow. The data on the Harderian gland tumors show a rise in RBE with increasing LET, reaching a maximum and a plateau of about 30 at about 100 to 200 keV/μm.[40] However, unlike the case of the RBE-LET relationship for cell killing and mutation,[41] there is no evidence of a rapid decrease in RBE at higher LET values. This fact raises an important question, because radiation protection standards are based on dose equivalents described by the quality factor Q as a function of LET, such that dose equivalent = Q × dose. The function Q is established by consensus and is restricted to stochastic effects. The latest consensus Q-LET relationship, adopted by the ICRP in 1991, conforms to the data for cell killing, but it is not yet clear that the relationship holds for the induction of tumors.[42] Similar data, namely, those showing the initial slopes of the dose-response curves for cancer induction in relevant tissues as a result of exposure to representative heavy ions, are required for application of the method suggested by Curtis[43] for estimating of the risks to humans. Furthermore, the proton irradiations associated with those data were performed with a (slightly) different animal model, adding to the level of uncertainty about the biological effects of the heavier ions relative to the effects of protons. The data for induction of skin tumors by argon ions[44] support the expectation of a high RBE for induction of tumors by heavy ions but do not allow any more precise estimate of what

quality factor should be used in estimates of the risk of cancer induction in humans. Because of the importance of establishing the precise Q-LET relationship for cancer induction, more experimental studies are required.

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2

Issues of Concern to NASA: Discussion and Conclusions

In attempting to assess and mitigate the health risks posed to spacecraft crews by radiation in space, numerous issues must be addressed and the physical and biological systems involved are complex. This chapter describes some of these issues and systems and discusses the most relevant problems associated with exposure to radiation in space. Where appropriate, some sections include a discussion of the general areas of research needed to characterize or reduce the health risks posed by space radiation. For clarity, risk is defined here as the likelihood of the occurrence of harmful effects resulting from exposure to radiation.

The potential risks to crew members' offspring as a consequence of crews' exposure to radiation in space are not large compared to the natural background mutation rate, and so the potential risk to the total human genetic pool is very small (see "Heritable Effects" below). However, crew members should be counseled about possible genetic effects of space travel. Although the possibility of catastrophic solar events, which could have short-term debilitating consequences despite the best countermeasures, cannot be excluded, observed solar events have not been in that category. Possible effects of exposure to radiation in space also include opacifications of the lens of the eye, and synergistic effects arising from the microgravity environment cannot be excluded, but there is no evidence that these types of biological effects represent risks comparable with that of carcinogenesis.

The most likely deleterious biological effect resulting from irradiation during interplanetary missions is late-occurring cancers. While other possible effects cannot be excluded, research for several decades has not produced evidence of a comparable risk from other biological sources or comparable risks from synergistic effects. The fundamental problem to be addressed in protecting against radiation is assessing the level of risk, specifically, determining the cancer types and the probability of their induction as a result of irradiation during a specific mission. Under the assumption that the biological information will exist, or can be modeled, what is needed in addition is adequate knowledge of the physical characteristics (the type of particles and their energies behind shielding) that can cause the risk to vary and of how the cancer types and induction probabilities vary as a function of these physical characteristics. Three sets of physical factors contribute to the variability of the risk itself and thus to uncertainty in determining risk: (1) the types of particles and their energies (radiation quality); (2) the amount of radiation; and (3) the extent and timing of exposure, i.e., acute exposure, protracted exposure, or a combination of both. (In fact, these three factors correspond to one probability distribution at the relevant biological sites as a function of particle type, energy, and time at the relevant biological sites.) A quantitative description of each of these three factors is already available to some degree—it is the variability of the distributions that remain in question.

TYPES OF PARTICLES AND THEIR ENERGIES

The two primary types of radiation, galactic cosmic rays (Figures 2.1 and 2.2) and solar radiation (Figure 2.3) vary according to their source and the event producing them. Both are altered substantially in particle type and energy as the primary galactic cosmic and solar particles traverse Earth's atmosphere and the primaries and secondaries are trapped in its magnetosphere as shown in Figure 2.4. The radiation quality likewise changes as the primary and secondary radiation particles traverse the spacecraft or the crew members themselves.[1] Figure 2.5 shows the estimated change in the dose equivalent at various depths in different shielding materials in comparison to its value at zero shield thickness. The large changes as a function of depth and material arise because the primary particles not only are attenuated but also produce secondary particles with a range of types of energy. As a result, the radiation quality is modified and so is the equivalent dose. It is the combination of primary particles, attenuated primaries, and secondary particles at the biologically relevant site that determines the biological effects, not the primary spectrum per se.

Galactic Cosmic Rays

The major components of galactic cosmic radiation (GCR) are energetic protons and heavier ions with even atomic numbers, which are more abundant than those with odd numbers (see Figure 2.1). The relative abundance of each particle type generally decreases with increasing atomic number, although a significant increase occurs at iron-56 followed by a sharp decrease at higher numbers. There is a broad but consistent distribution in the energy per nucleon, with a peak in abundance in the vicinity of 1 GeV/nucleon (see Figure 2.2).

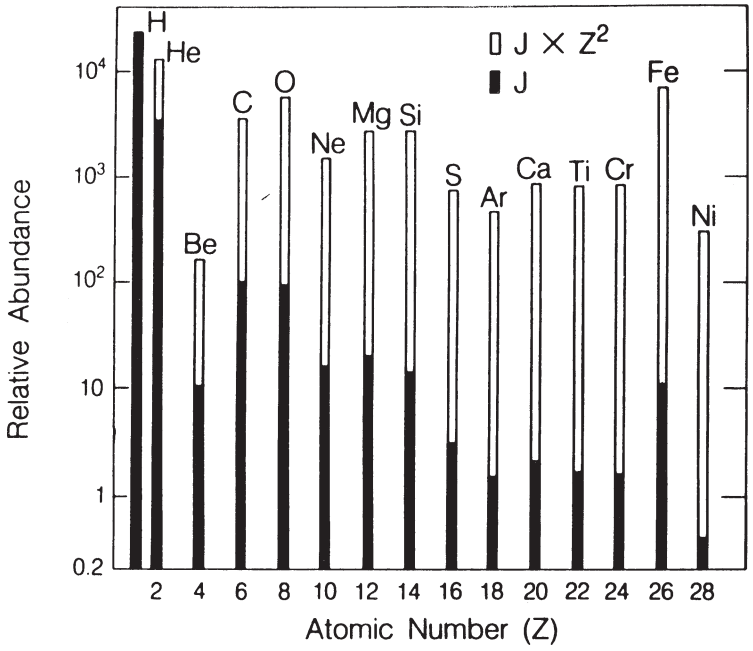

FIGURE 2.1 Histogram showing the relative abundances of the even-numbered galactic cosmic ray nuclei (solid bars) compared to their abundances weighted by the square of the particle's charge to give a measure of the "ionizing power" of each element (open bars). SOURCE: Wefel, J.P. 1979. Instrumentation for radiation measurement in space. Pp. 117-183 in: Proceedings of the Workshop on the Radiation Environment of the Satellite Power System (SPS). (W. Schimmerling, and S.B. Curtis, eds.). U.S. DOE Report CONF-7809164. National Technical Information Service, Springfield, Va.

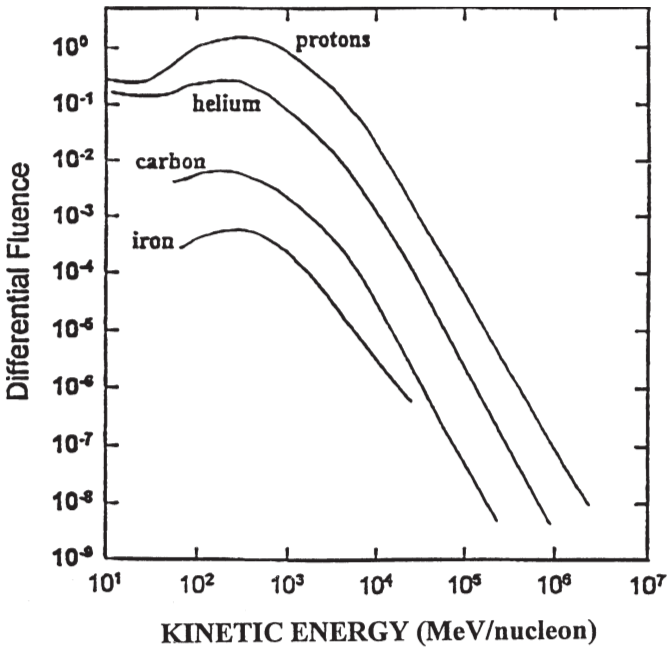

FIGURE 2.2 A representative fluence distribution as a function of the kinetic energy per nucleon. SOURCE: Simpson, J.A. 1983. Elemental and Isotopic Composition of the Galactic Cosmic Rays. Figure 5a in: Annual Review of Nuclear and Particle Science 33: 323-381. Reproduced, with permission, from the Annual Review of Nuclear and Particle Science, Volume 33, © 1983 by Annual Reviews Inc.

Galactic cosmic rays are relatively constant in terms of distribution of particle types and energies over time, but they do decrease in intensity by roughly a factor of 10 during solar events because the increased energy emitted from the sun produces an increased interplanetary magnetic field that deflects a large fraction of the galactic cosmic rays. This change in intensity is a variation with time and does not reflect uncertainty in our knowledge of the spectrum. The uncertainty lies in our ability to predict the intensity over appropriate periods of time. The variability of the instantaneous galactic cosmic ray intensity is approximately a factor of 10, but the average variability is much less because solar events occur over a small fraction of time. Moreover, the probability of solar events occurring varies cyclically with the periodicity of the 11-year solar cycle, and thus planetary missions would be less exposed to galactic cosmic rays during solar maximum. Therefore, depending on when missions are flown, variation in cosmic ray intensity may not be a major factor in the uncertainty of risk estimates for radiation exposure. Nevertheless, the uncertainty in the absolute amount of particles and their energies is significant to factors of 2 to 4 at the modal energies, but with larger uncertainties at the lower particle energies.

Solar Particles

Solar particle events (SPEs) produce substantial intensifications of the most energetic particles (including protons, heavier ions and electrons) emanating from the sun. The risk of harmful effects to space crews is generally assumed to be primarily from the protons and, to a lesser extent, the heavier particles, which are relatively less abundant than in the case of cosmic rays. The proton distributions as a function of energy have been measured extensively, and so the uncertainty in the distribution is small, but the intensity may vary by

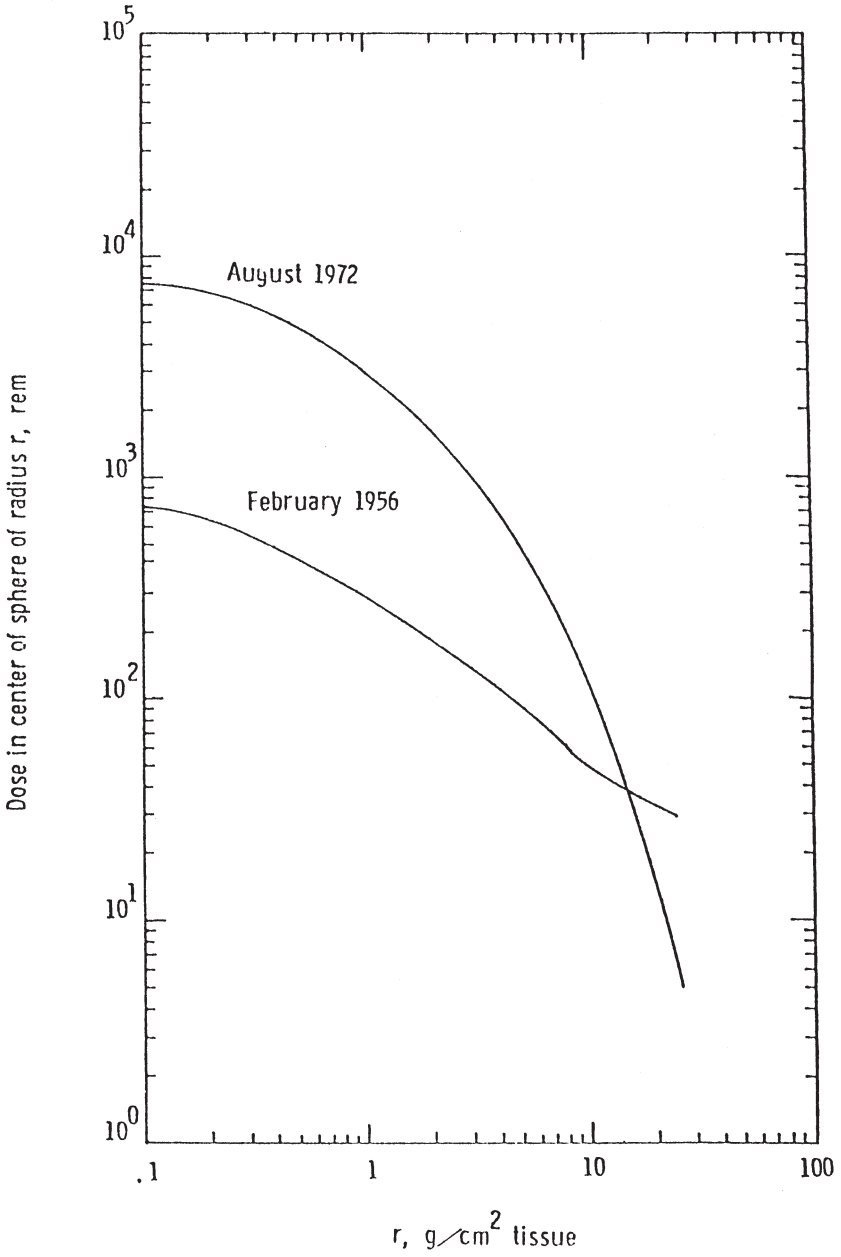

FIGURE 2.3 Dose Equivalent from two major solar events. SOURCE: Wilson, J.W., Townsend, L.W., Schimmerling, W., Khandelwald, G.S., Kahn, F., Nealy, J.E., Cucinotta, F.A., Simonsen, L.C., Shinn, J.L., and Norbury, J.W. 1991. Transport Methods and Interactions for Space Radiations. National Aeronautics and Space Administration Publication 1257. Available from the National Technical Information Service, Springfield, Va.

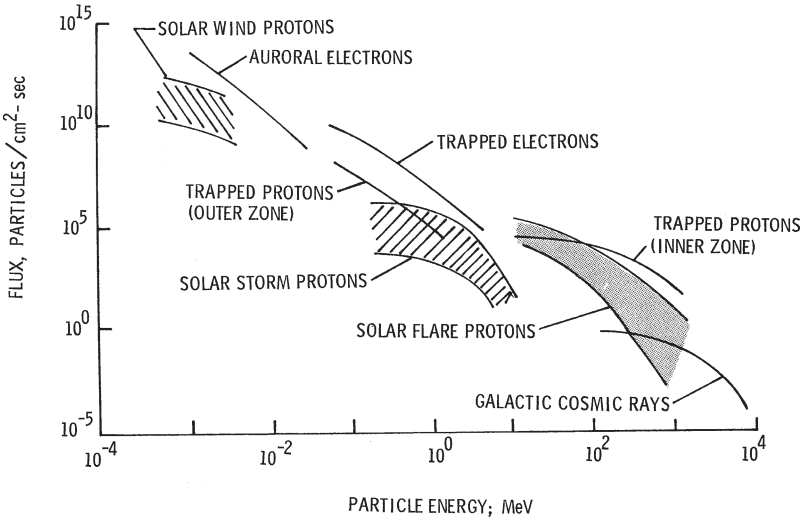

FIGURE 2.4 Space radiation environment. SOURCE: Wilson, J.W., Townsend, L.W., Schimmerling, W., Khandelwald, G.S., Kahn, F., Nealy, J.E., Cucinotta, F.A., Simonsen, L.C., Shinn, J.L., and Norbury, J.W. 1991. Transport Methods and Interactions for Space Radiations. National Aeronautics and Space Administration Publication 1257. Available from the National Technical Information Service, Springfield, Va.

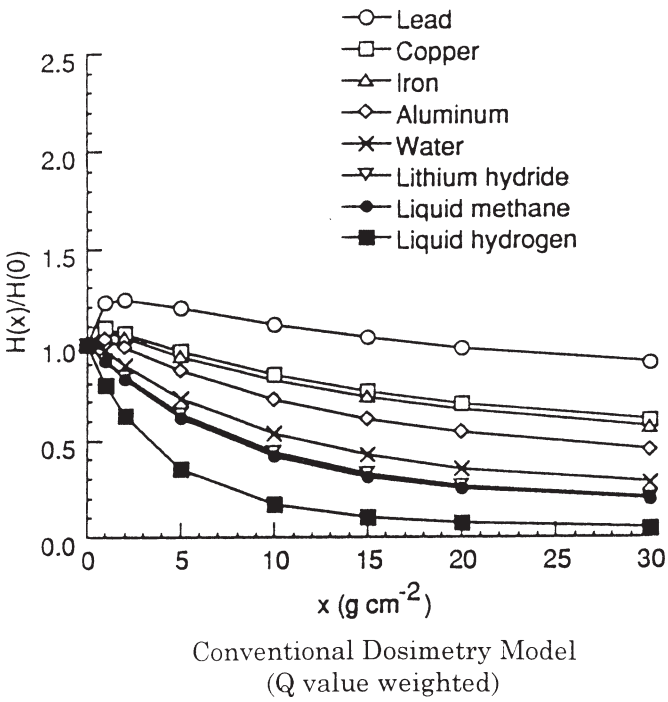

FIGURE 2.5 Calculated effect of shield material on the dose equivalent using the program NUCFRG2. Attenuation of dose equivalent in one-year exposure behind several shield materials. H(x)/H(0) is the normalized dose equivalent behind several shield materials. H(x) is the Sievert dose at a shield density x. H(0) is the Sievert dose without shielding (at the surface). SOURCE: Wilson, J.W., Kim, M., Schimmerling, W., Badavi, F.F., Thibeault, S.A., Cucinotta, F.A., Shinn, J.L., Kiefer, R. 1995. Issues in space radiation protection: Galactic cosmic rays. Health Phys. 68: 50-58. Reproduced from the journal *Health Physics* with permission from the Health Physics Society.

several orders of magnitude. This variability in intensity translates to a significant uncertainty in risk, although that risk is reduced during solar minima. Conversely, the number of SPEs increase around solar maxima, increasing overall risk.

Simonsen et al. estimated the radiation doses and dose equivalents from the October 1989 SPE for various human organs as a function of thickness of water shielding.[2] The doses to the skin, intestine, and bone marrow at water thickness of 0.5 cm were 7.21, 0.56, and 0.8 Gy, respectively, corresponding to 11.32, 0.75, and 1.07 Sv. At a water thickness of 10 cm, these values decreased to 0.35, 0.13, and 0.15 Gy or 0.46, 0.17, and 0.20 Sv, respectively. NASA's current lifetime limit for radiation exposure is 1 to 4 Sv, depending on age and gender.

Secondary Particles

The broad distribution of the primary background radiation in space by particle type and energy has significant uncertainties at the lower energies, and significant variability is contributed by the uncertainty in the timing and intensity of solar events. However, a major uncertainty in estimating space radiation's harmful effects for space crews is the uncertainty of the actual particle distribution at the point of exposure of crew members inside a spacecraft, inside a space suit for crew members conducting extravehicular activities, or actually at the sites of specific organs of crew members. The human body has an equivalent thickness of approximately 20 cm of unit density tissue for isotropically distributed high-atomic-number, high-energy (HZE) particles; the skin, although on the surface of the body, will be irradiated by a significant fraction of primary particles and the resultant secondary particles which have passed through the body. As the primary particles pass through the spacecraft and the bodies of the people themselves, secondary particles, including heavy secondaries and nuclear recoils, photons, electrons, neutrons, and even pions and muons, are produced in abundance. After only a centimeter or less of shielding material is traversed, the number of these secondary particles exceeds the number of the primary particles. Some of the secondaries, such as the low-energy nuclear recoils and secondaries, have linear energy transfers (LETs) greater than do most of the primary HZE particles. At the same time, the secondary electrons form a low-LET radiation background that also may have some biological significance for intracellular effects such as DNA damage and subsequently produced mutations.

Estimates of Uncertainty in Radiation Risk Factors

There are no rigorous estimates of the uncertainties associated with assessing health risks to crews in a radiation space environment. Curtis et al.[3] provide estimates of the errors associated with values for the major contributors to a calculation of the risk from high-LET radiation, and these are shown below:

1. 10 to 15% uncertainty in the initial charged-particle spectra;
2. 50% uncertainty in the radiation transport calculation;
3. 200 to 300% uncertainty in the risk coefficients for low-LET radiation;
4. 200 to 500% uncertainty in the risk coefficients for high-LET radiation; and
5. 400 to 1500% uncertainty in the overall risk.

Little information is provided to substantiate the values, and no comparisons are made with experimental data. As noted by the authors, the values should be treated as rough estimates.

Conclusions

- Current models of the GCR spectra may have reached a 10% root mean square accuracy.[4] The enhancements needed in the models are the statistical uncertainties to be expected in the spectra due to the solar cycle and, for verification purposes, an accurate representation of the even-odd isotope abundance ratio. Distributions in energy and type of fragmentation products from particles with energies representing GCR

need to be calculated at different times in the solar cycle and compared with subsequent laboratory measurements.

- Superficially, it appears that intensive research, both theoretical and experimental, ground- and space-based, over the last decade has altered by only about 25% the calculated distribution of primary particles as a function of their type and intensity. A review is needed to compare the physical data and theoretical methods available approximately one decade ago with those currently available in the three major areas (types of particles, their energies, and their quantity) specified in this report to see if the ~ 25% number is correct.
- Experimental measurements of particles emanating from a thick laminated shield need to be compared with calculations to benchmark the computer codes (modeling programs) and reduce the uncertainty in the shielding calculations. Once the cross section codes have been validated, the transport code itself must be validated. These measurements must include a "broad beam" geometry to assure that secondary particle products are fully accounted for.
- The risk of experiencing adverse biological effects in space depends on the length of a mission, not only because the dose received from GCR depends on mission length, but also because the probability of SPEs occurring increases with time as well. Specifically, it is necessary to know how much solar events contribute to total proton fluence over the period of the shortest anticipated mission. A better estimate is needed of the risk posed by a minimum-length mission compared to that by a 460-day mission.

BIOLOGICAL EFFECTS OF RADIATION

There is extensive literature on what is currently known about the biological effects of radiation as summarized, for example, in the published deliberations of the NRC's Committee on the Biological Effects of Ionizing Radiations (BEIR) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). This section introduces the various end points of concern for risk assessment and describes the potential magnitude of any radiation risks to crews during extended spaceflight. Based on proposed mechanisms of origin, the adverse health outcomes associated with exposure to radiation are considered under two broad categories: early and late effects, the former mostly deterministic, the latter mostly stochastic.

Early Effects

General Considerations

Deterministic Effects The acute somatic effects of ionizing radiation are by nature deterministic (formerly known as nonstochastic) effects. They are mass phenomena involving depletion of cells in a given organ system or tissue; only after a significant number of cells have been killed is any clinical effect apparent. Thus, the dose-response relationship shows a threshold, with the threshold dose for most acute effects on the order of 1 Gy or more. (By contrast, stochastic effects, such as genetic alteration and cancer, can potentially arise from damage to single cells.) Thus, significant risks for experiencing early effects occur only with very high radiation fluences.

Radiation Environment Because of the deterministic nature of early effects, it is likely that radiation arising from HZE particles and background cosmic radiation would pose no significant risk of early deleterious biological effects for spacecraft crew members. The number of cells damaged by individual HZE particles would be too small to significantly affect organ function, and the doses arising from penetrating background cosmic radiation would be too low.

As previously discussed, the principal risk for experiencing early effects would thus be derived primarily from SPEs, which are associated with the release of high fluences of protons of varying energies. The doses of radiation associated with such events may be sufficiently high to produce acute effects. The primary danger would be to crew members who were outside the shielding afforded by the spacecraft for a sufficient length of time during one of these SPEs.

Relative Biological Effectiveness of Protons Studies conducted with a relatively broad range of proton energies indicate that the values for relative biological effectiveness (RBE) for acute effects are similar to those for 250-keV x rays;[5] thus the risk per unit dose of early effects arising from exposure to protons from SPEs should be similar to that for effects arising from low-LET radiation such as electrons and gamma rays. Thus the risk estimates described below are derived from rather extensive data on effects of low-LET radiation, given that very few data are available on the incidence of such early effects following whole-body proton irradiation. It should be noted that there has been no evidence for new or qualitatively different early effects arising from proton irradiation per se that would lead to uncertainty in the prediction of early biological effects in space.

Early Systemic Effects

Prodromal Radiation Sickness Early prodromal effects of irradiation occur within a few hours of acute exposure and are characterized primarily by nausea and vomiting.[6] The latter in particular can have serious consequences in space, particularly for individuals wearing helmets and space suits. The whole-body dose at which vomiting occurs in approximately 50% of individuals is in the range of 1.5 to 2.0 Gy for acute exposures.[7] Nausea and perhaps vomiting may occur in a few individuals exposed to radiation at doses in the range of 0.5 to 1.0 Gy, but such symptoms would likely be mild and occur only 12 hours or longer after irradiation.[8] On the other hand, nausea and vomiting would be expected in virtually all individuals receiving doses of 2.5 to 3.0 Gy, the severity increasing with the dose.[9] These prodromal effects of radiation, which occur within 1 to 2 days after exposure and then subside,[10] can be minimized by use of antinausea medications.

Total Body Irradiation—Acute Radiation Syndrome The clinical effects of acute, whole-body exposure to radiation involve primarily the hematopoietic system and are due in particular to depletion of circulating white blood cells (granulocytes) and platelets.[11] Again, the threshold for the production of significant clinical effects is in the range of 1.5 to 2.0 Gy, although changes in white blood cell counts can be detected after exposure at substantially lower doses.[12] The clinical effects occur 2 to 4 weeks after exposure when the granulocyte and platelet counts reach a minimum, and are characterized by infections and bleeding.[13] If only minimal supportive care is available, mortality may occur following exposure at doses in the range of 3.0 to 4.0 Gy.[14] Significantly higher doses would be required to produce the above effects if exposure to radiation were extended beyond one day.

Conclusion The probability that radiation fluxes within a spacecraft would be sufficient to cause early systemic effects is extremely low. The principal potential risk of these effects would be to crew members working outside the spacecraft for a prolonged period of time during an SPE.

Skin

Skin damage could be a potential problem for crew members working outside a space vehicle, where the skin would receive the highest dose of any organ system. The acute radiation dose necessary to produce erythema is of the order of 6.0 Gy, whereas that for moist desquamation is in the range of 15 to 20 Gy.[15] The doses required to produce these effects will increase by a factor of 2 or more for protracted exposure.[16] Such single exposures would occur only in association with major SPEs. Transient epilation may also occur following acute doses of the order of 6.0 Gy, but hair regrowth always occurs after such doses.[17]

Impairment of the normal healing of soft tissue injuries may occur following exposure to radiation. Studies with mice and rats indicate that the doses required for impairment of wound healing are high, 5.0 Gy or more, and thus within the range sufficient to produce erythema or skin damage.[18] One study found that a reduction occurred in the rate of healing as measured by tensile strength, but the overall healing time and the final strength of the healed wound were not affected.[19] Proper care of wounds to prevent infections and bleeding is essential.

Fertility

Two primary consequences of gonadal irradiation are (1) reduced fertility or transient or temporary sterility, which may last from several months to several years, and (2) permanent sterility. The nature of these effects and the doses required to produce them vary in males and females. For the male, the doses reported to cause temporary sterility generally fall in the range of 0.5 to 4.0 Gy for single acute exposures to low-LET radiation, although the threshold dose may be lower.[20] A single acute dose as low as 0.15 Sv, about 0.15 Gy, has been reported to produce a decrease of the sperm count in some normal men.[21] The duration of temporary sterility is dose-dependent and may last from 8 to 10 months up to several years.[22] Permanent sterility has been reported following doses in the range of 2.5 to 4.0 Gy. An unresolved question involves the effect of dose rate on male fertility. Some data from canine experiments suggest that, as a consequence of the cyclic process of spermatogenesis, susceptibility to radiation-induced infertility may be enhanced by low-dose-rate, protracted exposure.[23] Under conditions of space travel (assuming crews stay within NASA's present lifetime limit of 1 to 4 Sv), it is expected that the acute exposure of crew members (male and female) will be low enough so that any reduction in fertility should be minor and transient. Figure 2.3 gives doses (assuming little shielding) from an SPE. If a crew member were outside the spacecraft during a flare, there could be some early systemic effects as outlined above.

Doses of radiation necessary to sterilize most females fall in the range of 6.0 to 20 Gy, although a small percentage of women may be permanently sterilized by exposure at lower doses. Temporary sterility or reduced fertility may occur at doses as low as 1.25 Gy.[24,25] Doses of 2 to 6.5 Gy are required to sterilize 5 percent of women for more than 5 years; protraction of exposure appears to reduce this effect.[26]

Other Organ Systems

Damage to the epithelium of the gastrointestinal tract, particularly the small intestine and distal stomach, occurs in individuals receiving 4.0 to 5.0 Gy or more of whole-body radiation.[27] These doses are presumed to be significantly higher than those that might be received by crew members during space travel.[28] At doses below 4 Gy, however, transient early symptoms of nausea may occur within a few hours of irradiation.[29] These symptoms can be expected to subside within 1 to 2 days, but their severity increases with dose. Individuals receiving doses of whole-body radiation sufficiently high to cause even mild intestinal damage (4.0 to 5.0 Gy) most likely will have incurred life-threatening damage to their hematopoietic systems.

Conclusions

Early effects of radiation in the major organ systems occur only following relatively high doses of radiation. Thus, with the possible exception of skin damage and a transient reduction in fertility, the early effects of irradiation are not likely to be a significant risk to spacecraft personnel. Skin damage would occur only in crew members working outside the spacecraft during an SPE.

Late Effects

General Considerations

Potentially important late effects following exposure to radiation during spaceflight include induction of cancer and damage to the central nervous system (CNS). Uncertainties concerning the risk of cancer induction are related mainly to the quantification of these risks. With respect to assessing the potential for CNS damage, it is first necessary to establish, prior to conducting research directed toward quantitation, whether CNS damage is likely to occur. It is also necessary to consider the potential for an increased risk of cataract formation and to determine if there will be increased heritable effects leading to increases in the rates of mutation in the human population. The uncertainties in risk estimates are large (see above, "Estimates of Uncertainty in Radiation Risk Factors") for the many reasons discussed below.

Cancer and Uncertainty in Estimates of Its Induction

As pointed out above, induction of cancer is generally considered the most significant deleterious biological effect of exposure to radiation in a space environment. Estimates of the risk of developing cancer as a result of spaceflight and the uncertainties in these estimates have been discussed in considerable detail in NCRP Report No. 98, *Guidance on Radiation Received in Space Activities*.[30] Current understanding of the risk to humans of contracting cancer following exposure to radiation—whether in the terrestrial environment or in deep space—is founded on data from studies of atomic bomb survivors. Based on these data, risk estimates have been developed for both the incidence and mortality of leukemia and solid tumors in a number of organ sites[31] following low-LET irradiation. Uncertainties in these estimates derive from several sources. First, because this is an ongoing study of a population, approximately 40% of which is still living, estimates are highly dependent on whether the models used to project lifetime risks are appropriate. Second, because the atomic bomb survivors in Japan were exposed at an acute high dose rate, principally to gamma rays, with a relatively minor component of the dose coming from fission neutrons, uncertainty in estimating the level of risk is increased when radiation is delivered at low dose rates or when the total dose delivered is protracted over a period from weeks to months. To correct for these differences, current risk estimates have incorporated a dose rate effectiveness factor (DREF) that reduces by a factor of 2 the estimated risk of contracting certain neoplasms under conditions of low dose rate or protracted exposure.[32,33] The DREF is based on current models for mechanisms of radiation-induced carcinogenesis and on results derived from experimental studies.[34,35] A third area of uncertainty in using existing data to assess risks from exposure to radiation in spaceflight is related to models used to extrapolate from risks estimated from a Japanese population irradiated in 1945, with specific and unique patterns of cancer incidence rates and age-specific mortality rates, to modern Western populations.

These sources of uncertainty in estimating the risk of cancer are generic to consideration of risk estimates in any exposed population. In addition, there are unique aspects of risks that are specific to radiation exposure in deep space. As described above (in the section titled "Types of Particles and Their Energies"), the radiation environment in deep space consists principally of galactic cosmic rays composed of protons, helium ions, and, to a lesser extent, heavy ions rather than the mainly low-LET radiation to which atomic bomb survivors were exposed. For the most part, radiation in space occurs at a low fluence rate. However, additional risks are associated with the higher dose and dose rate exposures from SPEs, the most important component of which is protons from a risk standpoint.

Since there are no epidemiological studies of humans exposed to the kinds of radiation that will be encountered in space, estimates of risks for biological effects induced by high-LET radiation are based on the risk estimates for exposure to low-LET radiation multiplied by weighting factors that express the effectiveness of an absorbed dose of such radiation in terms of equivalent doses (Table 2.1). The radiation weighting factor W_R is used in radiation protection to weight the absorbed dose averaged over an organ to obtain the equivalent dose to that organ for the radiation quality of interest. The W_R values, as well as derivation of the related quality factors (Q), are based on many experimental RBE values for stochastic effects, including those for cancer induction in animals and cancer-related end points such as mutations and chromosomal aberrations, and are selected by advisory groups such as the International Commission on Radiological Protection (ICRP).[36] While more direct estimates of such risks would be preferred, use of these factors is state of the art, given current understanding of the mechanisms of cancer development and the role played by radiation in inducing carcinogenesis.

Reducing the uncertainties associated with the values of quality factors is necessary to improve risk estimates associated with space travel. Clearly, uncertainties in these quality factors translate directly to uncertainties in risk. These values are highly dependent on an improved understanding of RBE as a function of particle type and energy transferred for tumor induction over a range of LETs. Such an understanding is crucial to the development of appropriate quality factors for the range of radiation types encountered in deep space.

An additional source of uncertainty in risk that must be addressed relates to dose-response relationships for cancer induction and the influence of dose rate for protons such as encountered in deep space. Such information is required to derive estimates of risk at the low fluences that will exist in space. For the low

TABLE 2.1 Radiation Weighting Factors (W_R)

Radiation Type and Energy Range	W_R
Photons, all energies	1
Electrons and muons, all energies[a]	1
Neutrons, energy < 10 keV	5
10 keV to 100 keV	10
100 keV to 2 MeV	20
2 MeV to 20 MeV	10
20 MeV	5
Protons, other than recoil protons, energy > 2 MeV	2[b]
Alpha particles, fission fragments, heavy nuclei	20

NOTE: All values relate to the radiation incident on the body or, for internal sources, emitted from the source.

[a] Excluding auger electrons emitted from nuclei bound to DNA.

[b] ICRP recommends a W_R of 5 for protons, other than recoil protons, with energy >2 MeV (see International Commission on Radiological Protection. 1991. 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Annals of the ICRP 21. Pergamon Press, Elmsford, N.Y.).

SOURCE: National Council on Radiation Protection and Measurements (NCRP). 1993. Limitation of Exposure to Ionizing Radiation. NCRP Report No. 116. National Council on Radiation Protection and Measurements, Bethesda, Md.

dose rates expected from heavy ions, dose rate considerations should not be as important because the probability that two different heavy ions will traverse the same human cell is small.

Because essentially no data from human populations are available to allow investigators to make direct estimates of risk from exposure to these types of radiation, or which address the factors influencing sources of uncertainty in risk estimation, such estimates are heavily dependent on data from other studies. Hence, both an adequate understanding of the relationships between RBE and particle type and energy, as well as information on dose response and dose rate effects derived from experimental studies are essential to understanding the cancer risks associated with deep-space travel. Existing experimental data are inadequate.

Even in animal systems, data on tumor induction following exposure to protons and heavy ions are sparse. Critical data on cellular responses to irradiation, required to support the use of laboratory animal tumor data for estimating risks to humans, are also lacking in many instances. Cell survival studies, while not directly applicable to estimation of cancer risks, do permit comparisons of the effectiveness of different types and levels of radiation and determination of the repairability of induced DNA damage. Cellular studies of the induction of somatic mutations and chromosomal aberrations provide data that can be linked fairly directly to carcinogenic effects. Such studies, particularly in human cell systems, are important for understanding possible mechanisms of carcinogenicity and in the appropriate application of animal data to the estimation of risks to humans.

As described in Chapter 1, data for tumor induction following proton irradiation are available for only a few tumor types following acute exposure. The limited dose-response data that can be obtained from these studies suggest similarities to responses that would be seen after gamma ray irradiation.[37-39] Only one study found evidence to support an RBE of greater than 1.[40] Additional support for similarities in effects from exposure to proton and to low-LET radiation comes from the work of Burns et al., who have reported a curvilinear dose response for rat skin tumor induction similar to that occurring after exposure to electrons and a reduction in the carcinogenic effects of exposure to protons.[41]

Cellular studies have been conducted using protons of different energies to examine cell survival and induction of chromosomal aberrations.[42-45] Although the range of energies used is lower than that encountered in the space environment, these data also suggest similarities in effects between protons, gamma rays, and x rays. The dose responses tend to be linear/quadratic, and there is clear evidence for repair of proton-induced DNA damage.

While most data tend to support the view that the risks for carcinogenic effects, as a result of irradiation by high-energy protons, will be similar to those for low-LET radiation, additional studies of protons in the

range of energies relevant to those encountered in space, 0.1 GeV and higher (see Figure 2.2), could strengthen this conclusion considerably. The purpose of such experiments would be to determine whether biological effects of exposure to these higher-energy protons are qualitatively similar to those seen with exposure to low-LET radiation and to determine whether repair of proton-induced DNA damage can be observed.

Information on tumor induction following exposure to heavy ions is also limited. Burns et al. have conducted experiments on skin tumor induction in rats following argon irradiation (Figure 2.6).[46] These data provide evidence of a linear dose response for tumor induction with this high-LET radiation and support the expectation of a relatively high RBE. However, because of the dominance of the dose-squared term (concave upward) in the low-LET dose response, the data do not allow for the estimation of a single RBE value that could be used in the determination of an appropriate weighting factor that is independent of dose. As stated previously, the determination of appropriate quality factors requires information on the relationship between LET and RBE for tumor induction. The only systematic study of such relationships was conducted for the Harderian gland in mice.[47] The data show a rise in RBE with LET that peaks at an RBE of 30 in the 100- to 200-keV/μm range. Importantly, there was no clear-cut evidence of a decrease in RBE at LET of up to about 400 keV/μm as predicted by biophysical models and as observed for cell killing and mutation. Because the quality factor-versus-LET relationships adopted by ICRP incorporate a decrease at LET greater than 100 keV/μm, these Harderian gland data suggest possible important discrepancies that need to be explored with other tumor-induction models. Studies of Harderian gland tumorigenesis also suggest that the RBE values for fission spectrum neutrons are similar to those for 100- to 200-keV/μm heavy ions.[48] If this is the case, there are dose-response and dose rate data for the induction of several tumors in mice after neutron irradiation that could be used in support of establishing a reliable quality factor for heavy ions in this energy range.[49]

While not able to be used directly for the derivation of quality factors, studies of cells have provided evidence that for high-LET radiation, linear dose-response relationships are only slightly influenced by fractionation or protraction.[50-52] In addition, studies of mutagenesis and induction of chromosomal aberrations suggest possible qualitative as well as quantitative differences between high- and low-LET radiation and different particle types of the same LET that need to be examined further for their applicability to understanding cancer risks.[53,54] Of these, it is important to note the recent observations of high-LET radiation effects on chromosome instability and the induction of delayed radiation damage leading to expression of damage in the progeny of surviving irradiated cells.[55]

Conclusions The present state of knowledge regarding cancer induction by irradiation, as described above, requires that additional research be directed in two areas. First, a pragmatic set of studies is needed to provide data necessary for the determination of appropriate quality factors that should be used in making risk calculations. These should be systematic studies of RBE as a function of particle type and energy for a select number of heavy ions and for protons using well-defined animal models for tumorigenesis. In addition, information on dose rate and fractionation effects for protons is also needed. Improvements in risk estimates beyond those attainable with these data require a more complete understanding of the mechanisms of tumor induction and of principles that will aid in using data, from experimental systems subjected to relatively high radiation doses, to estimate effects on humans exposed to low, protracted doses and in estimating risks across populations. These kinds of studies will require the development and exploration of new model systems and the application of developing technologies in cell and molecular biology.

Central Nervous System

Outside Earth's magnetic field, the fluence rates of the GCR are at the maximum during solar minimum: about 4 protons per cm^{-2} s^{-1}, 0.4 helium ions per cm^{-2} s^{-1}, and 0.04 HZE particles per cm^{-2} s^{-1}. The number of particles traversing cell nuclei depends, of course, on the size of the nucleus (Figure 2.7),[56] which in the CNS can vary from the small nuclei of microglia to the very large nuclei of motor neurons. Assuming a nuclear area of 100 μm^2, Curtis et al. estimated that each cell nucleus in the body would be hit by a proton once every 3 days, by a helium ion once per month, and by higher weight atomic particles once per year.[57,58] Estimates for strikes by the heavier particles, in particular, are strongly influenced by the degree of particle fragmentation occurring as the radiation traverses the shielding of the spacecraft.

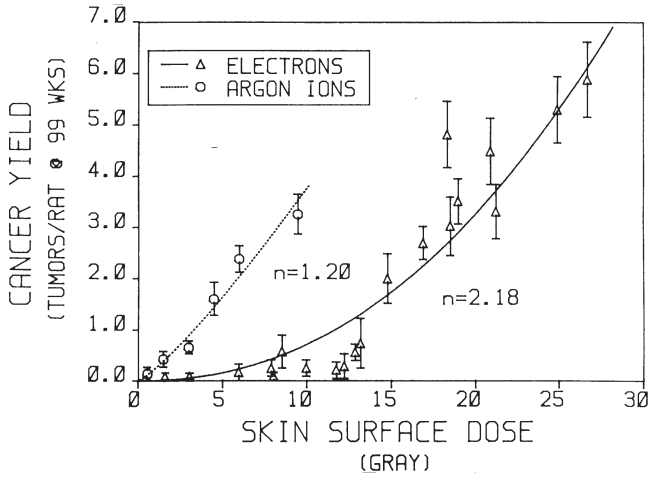

FIGURE 2.6 Cancer yield in rat skin as a function of surface dose (single dose, 3 to 5 Gy/ min; 300 to 500 rad/ min) in rats exposed at 28 to 58 days of age. Errors are estimated from total number of tumors. The curves are least fit to the power function $y = b^n$, where n = exponent of quadratic, y = y axis, and b = x axis. SOURCE: Burns, F.J., Hoselet, S., and Garte, S.J. 1989. Extrapolations of rat skin tumor incidence: Dose, fractionation and linear energy transfer. Pp. 571-582 in: Low Dose Radiation: Biological Basis of Risk Assessment (K.E. Baverstock and J.W. Stather, eds.). Taylor and Francis, London. Reprinted with permission from Taylor and Francis.

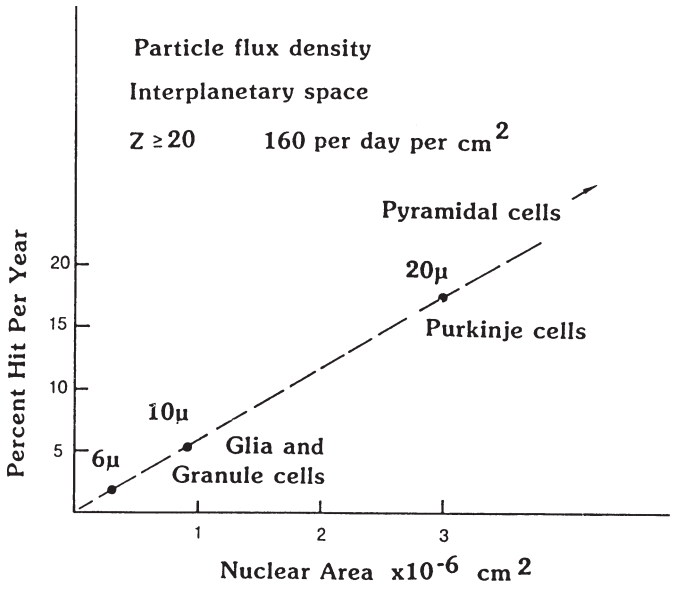

FIGURE 2.7 The dependence of size of the nuclei of neurons on the probability of traversal of heavy charged particles in space. SOURCE: Gauger, G.E., Tobias, C.A., Yang, T., and Whitney, M. 1986. The effect of space radiation on the nervous system. Adv. Space Res. 6: 243-249. Reprinted from *Advances in Space Research* with kind permission from Elsevier Science Ltd., The Boulevard, Langford Lane, Kidlington OX5 1GB, UK.

It is probable that most of the damage done to the CNS by protons is repairable by DNA repair and regrowth of cells. Certainly, animals in experiments have been exposed to higher fluence rates than are likely to be encountered in space—and have not shown clinically detectable changes in the CNS. The main concern, however, is about HZE particles, particularly iron ions. The axons and dendrites of neurons are very radioresistant, and the cell nuclei, which do not undergo division in adult life, appear to be very resistant as well. They are not lost after irradiation in mitosis, as is usually the case with proliferating cells. What is inadequately known is whether any functional capability is diminished and, in particular, whether effects such as decreased DNA repair occur late in life long after exposure.

Lack of Data for Estimating Risks The reason for concern regarding the CNS is due to the fact that it cannot be stated with confidence what late effects, if any, might occur in the CNS of humans exposed to the various types of radiation in space such as heavy ions and secondaries of the more prevalent protons. There is evidence that in photoreceptors iron ions cause an increased loss of DNA.[59] Whether a significant interaction occurs between aging and radiation-damaged cells (which is suggested by at least one investigator[60]) is also not known. Before investigators can conclude that the risks of late effects to the CNS are so improbable that they are not of concern, there have to be some data for relevant end points and doses.

Effects of HZE Particles The concern about HZE particles is that the energy deposition may be significantly different from that of radiation qualities for which we have some radiobiological understanding. One particle of very high Z and energy can traverse a number of contiguous cells. There is very dense ionization in the inner part or core of the particle track, with secondary particles and delta rays extending to neighboring cells. Although this pattern of potential damage raised concerns many years ago about the possibility of microlesions, the concerns have not yet been answered satisfactorily. While the lack of a solution to these concerns may seem surprising, the existence of the HZE particle component has been known only since 1948, and biological research using heavy ions has been restricted to a very small number of centers in the world with suitable accelerators. Furthermore, the critical experiments have proven difficult to carry out.

The effects of HZE particles on the CNS include (1) cellular effects, including biochemical changes; (2) functional changes; and (3) late effects, especially DNA repair deficiencies.

Cellular Effects High doses of low-LET radiation cause cellular changes and degeneration in neuronal tissues. Heavy ions are more effective in causing cellular damage, and the effects appear earlier than those appearing after exposure to low-LET radiation. In studies of the forebrain of rabbits, damage could be detected after exposure to 0.5 Gy of neon ions.[61] Studies indicate that in the brains of fruit flies, swelling of neurons and changes in membranes could be detected with fluences that resulted in an average of less than one traversal per cell body by an argon particle.[62] Dose-response data are lacking for clearly defined damage at either the cellular level or in specific areas of the brain. For example, what is the effect of various radiation fluences on the centers in the floor of the fourth ventricle, the site of a number of centers including the cardiac and respiratory centers, in which there are closely packed neuron cell bodies? If traversal of neurons by the various HZE particles in the GCR does in fact result in early- or late-occurring damage, the fourth ventricle is an area of the brain that could be at risk (there are also others). This example indicates how little we know about the potential effects of radiation on the CNS. Without such information it is impossible to assess the potential risk of clinically important damage to the CNS that might result from crew members' exposure to radiation during long-duration missions in deep space.

Functional Effects A number of studies have been carried out on the effect of HZE particles on the function of the CNS in rats and mice. Doses in the range of 0.5 Gy appear to impair the function of the neural networks involved in motor performance.[63] Aging and exposure to radiation affect the CNS in similar ways and it is sometimes difficult to isolate the cause for affected functions, such as balance. Taste aversion has long been used as a test of behavioral and other changes induced by irradiation, and studies indicate that iron ions are more effective than lower-LET radiation in altering this particular type of behavior.[64]

Late Effects, Especially Repair Deficiencies Because many of the experiments concerning heavy ions have been associated with end points relevant to radiotherapy, questions about the effects on nonrenewing cell systems, especially the CNS, have remained unanswered. Differentiated cells such as those in the CNS or the liver can incur relatively large doses of radiation of different qualities and still retain their function. What is not known is whether untoward effects may appear later. The integrity of the transcribing regions of the genome must be reserved to ensure the fidelity of the RNA transcripts and also of the proteins, translated from RNA, that are necessary for the correct functioning of cells.

Changes with age in the retinal DNA of rabbits after irradiation have been studied by Lett and his coworkers.[65-67] With both low-LET radiation and heavy ions, the evidence suggests that the initial radiation-induced DNA damage is repaired but that a subsequent breakdown of DNA occurs with age. The age at which secondary changes in the DNA of the photoreceptor occurred decreased with an increase in the LET of the radiation. The secondary changes in the DNA occurred earlier and were more marked with iron ions than with other heavy charged particles or with photons. Significant effects were noted after exposure at 2 to 3 Gy of iron ion radiation.

If it is assumed that the photoreceptors are a reasonable surrogate for neurons in the CNS, then the above results suggest that it is necessary to obtain adequate dose-response data using the most sensitive techniques for detecting DNA damage. Furthermore, it is mandatory to determine whether or not breakdown of DNA, which is an indication of impending cell death, occurs many years after exposure to radiation.

Conclusion Existing studies suggest that HZE particles may induce damage in the CNS. As yet, there are no complete data for RBE-LET relationships for the relevant end points for assessing the risk of radiation-induced damage. The results of studies with HZE particles suggest that it is not possible to predict the risk of CNS damage accurately from the effects of low-LET radiation.

Cataracts

Cataracts are considered a hazard of exposure to radiation, and limits for exposure are set for terrestrial workers who deal with radiation sources. The limits are based on estimates from studies of humans exposed to low-LET radiation. There is considered to be a threshold dose below which lenticular opacities of clinical importance do not occur. For this reason, cataract induction is considered a deterministic effect. However, the threshold is more a matter of the level of detection capable of detecting the beginning of cataractogenesis, and the most likely mechanism is consistent with a stochastic effect.

Assessing the risk of cataractogenesis from irradiation in space, in particular in deep-space missions, requires a knowledge of the associated RBE values of the various types of radiation. There are no data for induction of cataracts in humans exposed to HZE particles, and only sparse data for induction by protons. Thus, reliance on data from animal experiments is necessary.

The sensitivity of the lens of different species varies by more than an order of magnitude, decreasing with increasing size. In humans, a threshold dose for low-LET radiation of about 2.0 Gy has been considered reasonable. For the atomic bomb survivors, a somewhat lower threshold dose, 1.0 to 1.5 Gy, was derived by Otake and Schull.[68] Since these results pertain to high-dose-rate exposures, it is important to know the reduction in effect that may result from fractionation or from lowering of the dose rate. Data from patients receiving radiotherapy or irradiation prior to bone marrow transplantation suggest a significant decrease, perhaps on the order of fivefold, in cataractogenic effects compared with the number induced by single high-dose-rate exposures. On the basis of experiments with rats,[69] no such sparing would be predicted for the effects of exposure to very high LET radiation. Evidence from studies on monkeys indicates that the cataractogenic effect of protons will not be very different from that of gamma rays.[70] Therefore, exposure to protons on a Mars mission, unless there is an unexpectedly high exposure during SPEs, should not cause clinically significant opacities. The estimates of the risk of cataract induction from exposure to heavy ions are somewhat disparate,[71,72] and until more definitive estimates are in hand, relatively high RBE values should be used in calculating the equivalent doses for estimating risk.

Heritable Effects

The great majority of data on the assessment of genetic or heritable effects in human populations following exposure to radiation has come from studies of the atomic bomb survivors. The following end points have been assessed: untoward pregnancy outcomes (major congenital malformation, stillbirth, neonatal death); sex of child; tumors with onset prior to the age of 20; death of liveborn infants through an average age of 26.2 years, exclusive of death from malignancy; growth and development of liveborn infants; cytogenetic abnormalities; and mutations altering the electrophoretic behavior or function of a selected battery of erythrocyte and blood plasma proteins. There were no significant increases in any of these indicators from a combined parental gonadal equivalent dose of 0.4 to 0.5 Sv. [73]

A recent study by Kodaira et al. examined variations in size of six minisatellite regions (see glossary) in the DNA of 64 children from 50 families in which one or both parents were exposed to the atomic bomb explosion and in 60 children from families in which neither parent was exposed.[74] There was no difference in the frequency of change in the two groups. A similar result was reported by Satoh et al. for mutations detected by the denaturing gradient-gel electrophoretic method.[75]

UNSCEAR[76] made estimates of the (unirradiated) background incidence of mutational effects per generation for the end points studied on the acutely exposed Japanese population. The values ranged from approximately 10^{-5} per locus for loci encoding proteins to 3×10^{-3} per locus for untoward pregnancy outcomes. UNSCEAR also estimated the acute dose that would, on average, double the background incidence—the doubling dose—as 1.7 to 2.2 Sv. Allowing for chronic exposure, a gonadal dose reduction factor was applied to give a minimal estimated doubling dose of 4 Sv for genetic effects. A complete description of the approach used may be found in UNSCEAR[77] and in Neel and Schull.[78] The present lifetime exposure limit for astronauts is ≤ 4 Sv. Hence the actual increase above background in heritable effects per locus, depending on the particular locus, and the risk of heritable effects to individuals engaged in extended space travel will be low. In addition, because the number of individuals who might be exposed to ionizing radiation during long-range spaceflight will represent a very small fraction of the population, any genetic risk to the human gene pool would be negligible.

Variation in Susceptibility to Radiation Across Subject Types

The rapid increase in knowledge of the mechanisms of tumor induction and heritable effects has led to a clear appreciation of the potential for a genetic predisposition to the induction of cancer by exogenous agents and endogenous processes and to induction of heritable changes. Such a predisposition might be specific for a single agent such as ionizing radiation (e.g., predisposition in ataxia telangiectasia heterozygotes) or it might involve sensitivity to a wide range of exogenous agents and endogenous processes (e.g., Li-Fraumeni syndrome (p53 heterozygosity)). Given that within the normal human population a range of risk exists for induction of cancer, it is difficult at this time to assign a value for increased risk owing to a single genetic susceptibility. In general, most of the genetic susceptibility or sensitivity factors that are common in the population tend to increase relative risk by small amounts. Those conferring high relative risk are present at a low frequency. The latter is particularly true for susceptibility for which background frequencies of cancer are high.

It has become increasingly apparent that the sensitivity of cells to radiation is controlled in part by the relationship of DNA repair kinetics to cell cycle progression. The quintessential example is the gene p53, which is involved in cell cycle control at the G_1 checkpoint, the time point in the cell cycle at which DNA synthesis begins, and in the repair of DNA damage either directly or indirectly.[79] A deficiency in p53 can both affect the efficiency of DNA repair and abrogate the G_1 checkpoint, both of which can increase sensitivity to the induction of mutations and chromosomal aberrations. At G_2, which is the time between the end of DNA synthesis and mitosis (the G_2/M checkpoint), p53 appears to function in the direct repair of DNA damage, and not in control at the G_2/M checkpoint.[80] Mice that are homozygous or heterozygous for a knockout of the p53 gene are more susceptible to both spontaneous tumor formation, and tumor formation following exposure to a range of chemicals.[81]

The question of interest then is, What kinds of genotypes might elicit increases in sensitivity to radiation? For example, it is apparent that control of the cell cycle is a very complex process involving in part the interactions of cyclins, cyclin-dependent kinases, and cyclin-dependent kinase inhibitors. Alterations in any of these components could lead to abrogation in the cell cycle control, which would lead to abnormal responses to DNA damage and an increased sensitivity to genetic alteration. It remains of considerable importance to understand the mechanisms of genetic instability arising from abrogation of control at checkpoints in the cell cycle, and to determine the effects these mechanisms can have on radiosensitivity. Work in this area by the wider community of cancer investigators would lead to understanding of the role of genetic instability in cancer predisposition, and to development of assays for detecting individuals at increased risk.

While there will be a range of genotypes among individuals selected for long-range spaceflight, there is a very low probability that there will be highly sensitive individuals in the group. Very specific genotypes, such as those giving rise to ataxia telangiectasia and Li-Fraumeni syndrome, are obvious phenotypically, and such individuals would not constitute part of the selection pool. More subtle individual differences in sensitivity to ionizing radiation would not be detectable phenotypically. It could be argued that a radiosensitivity assay (G_2 sensitivity) such as that described by Scott et al.[82] and Jones et al.[83] could be conducted on lymphocyte samples from potential crew members. However, such an assay is not, at present, directly predictive of an increased sensitivity to an adverse health outcome. Hence, it is appreciated by cancer investigators that a more complete assessment of the G_2 sensitivity assay needs to be conducted in order to establish its range of sensitivity and possible predictive capability for cancer or heritable effects.

DNA Repair

The repair mechanisms utilized by the human body after exposure to radiation are an important part of any discussion of radiation effects, and the repair of damage to DNA is of obvious interest when considering late effects such as cancer. It has been known for a number of years that sophisticated and complex cellular processes exist for repairing all types of DNA damage: single-strand breaks, double-strand breaks, and a wide variety of types of base damage, all of which can result from exposure to radiation. It was also appreciated that the cell would be further protected if such repairs were completed prior to entry of the cell into the S-phase or mitosis/meiosis. If repair occurred at a later time, then there would be an increased probability of induction of point mutations and chromosomal aberrations from errors of replication on a damaged DNA template, errors of segregation, and/or loss of unrejoined chromosomal fragments. In the past 5 years, the repair processes for handling DNA damage have been largely characterized at the molecular level, and their complexity has been established. It is interesting to note that several of the repair processes are modifications of the functions of other cellular housekeeping proteins, such as transcription complexes or cell cycle control genes. For example, the nucleotide excision repair (NER) pathway involves at least 16 proteins, a number of which are components of the TFIIH/BTF2 complex that is a component of the RNA polymerase II transcription initiation complex. The very specific incisions required for removal of DNA damage are produced by enzymes of this complex. Reviews by Wood et al.[84] and Sancar[85] provide details of NER and the effect that mutations in this pathway can have, as illustrated by xeroderma pigmentosum, Cockayne's syndrome, and trichothiodystrophy. While the actual process of excising damaged nucleotides by NER is quite well worked out, the cellular control and damage recognition processes are still the subject of extensive research efforts.

Repair of Oxidative Damage and Double-Strand Breaks

More recently, an understanding of repair of DNA damage induced by ionizing radiation has emerged. Two recent reviews, one on the repair of oxidative damage[86] and a second on double-strand break repair,[87] describe the current level of knowledge. The enzymology of repair of some damaged bases and sugars has been quite thoroughly described in bacterial systems and to a lesser extent in *S. cerevisiae,* and is mostly inferred for mammalian systems.[88] Although there is a very broad range of base damage, it appears that several of the repair activities recognize a range of substrates, thereby leading to the requirement for rela-

tively few enzymes to repair the bulk of DNA and sugar lesions. In broad terms, the process of base and sugar damage repair involves damage recognition, base excision of purine or pyrimidines, site incision, and fragment release. Clearly, variations in efficiency among cell types or species, or within a population, can occur at any one of these steps, each of which is under genetic control. At this time, however, no human syndrome has been identified that results in a sensitivity to ionizing radiation attributable to a deficiency in the repair of oxidative damage.

The understanding of the mechanism of repair of DNA double-strand breaks has taken several significant steps forward recently. Studies have demonstrated that there is a close association between the repair of site-specific double-strand breaks introduced during V(D)J recombination and those generated by DNA-damaging agents.[89] V(D)J recombination allows for the creation of the diversity in immunoglobulin and T cell receptor genes by reassorting variable (V), joining (J), and diversity (D) elements into single exons by recombination.[90] In addition, a range of mammalian cell mutants that are sensitive to low-LET radiation are deficient in V(D)J recombination. This association was shown to be through the DNA-dependent protein kinase (DNA-PK) that is involved in the rejoining of double-strand breaks. The significant activity of DNA-PK in this regard is that it binds to, and is activated by, DNA double-stranded ends.

DNA-PK consists of two polypeptides, Ku80 and Ku70, with the former being a DNA binding protein and the latter having an unknown function, and DNA-$PK_{cs,}$ a catalytic subunit that contains a serine-threonine kinase domain.[91] The kinase activity is limited to the situation when DNA-PK is bound to DNA. DNA-PK can phosphorylate a number of DNA binding proteins in vitro, including transcription factors such as Sp1, c-Jun, and p53. It appears that DNA-PK enters the DNA at one end and can move along the molecule.

It has been shown that several radiosensitive mammalian mutants are defective in Ku80, that cells from severe combined immunodeficient (*scid*) mice have a DNA repair defect, and that additional radiosensitive cell lines have a deficiency in DNA-PK_{cs}.[92] Thus, it appears that repair of ionizing radiation-induced double-strand breaks is performed in part by DNA-PK. It has been suggested that there could be a link between double-strand break repair machinery and transcription, as has been described for NER.[93] A preferential repair of ionizing radiation-induced DNA damage on the transcribed strand has recently been described,[94] and DNA-PK is a potent inhibitor of transcription by RNA polymerase I.[95] On the basis of these mechanistic studies, it is predicted that there will be a range of individual sensitivities to ionizing radiation that is, in part, dependent on the efficiency of the repair processes for double-strand breaks. To date, no human syndromes that are characterized by defects in DNA-PK have been identified, although the DNA-PK_{cs} gene maps to the same human chromosome region as the one for the human gene that complements *scid*.[96]

Other Studies

A good deal has been learned about repair mechanisms by studying the human syndrome ataxia telangiectasia (AT), which is characterized by a sensitivity to cell killing and mutation induction in cells in vitro as a result of exposure to low-LET x rays, and, in some cases, by a loss of x-ray-induced inhibition of initiation of DNA synthesis. It was presumed by investigators that these phenotypes were the consequence of a DNA repair defect, and that different steps or components were controlled by genes in the four different complementation groups, all of which map to a single chromosome region. However, the recent cloning of the AT mutated gene (ATM)[97] and additional characterization of homologous genes in yeast[98,99] have shown that the defect in AT cells is not the result of a repair defect but results from an altered cell cycle control, and perhaps an inability to activate damage-inducible DNA repair.[100] All four complementation groups appear to involve the same ATM gene.

The radiosensitivity and cancer susceptibility of ATM homozygotes are well established and very clear-cut. On the other hand, whether or not there is increased sensitivity in ATM heterozygotes is less clear. It has been reported that there is an increased breast cancer risk for ATM heterozygotes,[101] although this remains equivocal. Recently, Scott et al.[102] demonstrated that lymphocytes from obligate AT heterozygotes had an increased sensitivity to x-ray-induced chromosomal aberrations in G_2. In addition, they showed that about 42% of women with breast cancer showed a sensitivity that was similar to that of obligate AT heterozy-

gotes.[103] This does not mean that these persons were all AT heterozygotes, or that AT heterozygosity predisposes to breast cancer, but rather that altered DNA damage-processing (including repair) genes are more likely to be present in breast cancer patients, and could be partially causative. Thus, heterozygosity for DNA repair genes, where the phenotype is not immediately apparent, could be a marker for susceptibility to cancer, particularly following exposure to ionizing radiation. It is expected that screening for ATM heterozygosity will soon be possible based on recent reports of the genomic organization and gene sequence.[104,105]

Conclusion

A growing understanding of the various mechanisms of repair of ionizing radiation-induced DNA damage, and of the effects of mutations in genes involved in the repair itself or in its control, is likely to greatly aid in predicting the risk of adverse biological effects arising from exposure to radiation, and eventually in identifying individuals at increased risk.

LOSS OF RESEARCH PROGRAMS

Over many years, NASA maintained only a very small radiation health program because of the responsibility, mandated to the Department of Energy (DOE) and its predecessors, for radiation studies. Recently, the funding for NASA radiation research has increased. However, although the percentage increase in funding has been large, the budget in years past was small. Moreover, DOE has significantly reduced its funding for radiation studies in the last few years. Major radiation and animal facilities have been closed, including the high-LET radiation sources for experimental studies at Oak Ridge and Argonne national laboratories. DOE funding of the important facility at Columbia University has been terminated, and the future of the radiation facilities at the Armed Forces Radiobiology Research Institute is now threatened. BEVALAC, the only facility in the United States that was producing beams of heavy ion spectra of energy and LET suitable for cellular and animal studies, as well as for investigations of fragmentation and aspects important for dosimetry, was closed by DOE in 1993. As noted by several previous advisory groups (see, for example, Appendix D), this closure has had very serious consequences for efforts to estimate risks from exposure to radiation in deep space.

Two accelerators, one in Germany and one in Japan, have been developed for heavy ion radiotherapy (see Appendix C) and could be of use in the NASA program. There is no question that international collaboration involving accelerators (with guarantees of appropriate particles and beam time), personnel (to operate and use the facilities), and the necessary financial commitments would be of help in carrying out the priority experiments outlined in Chapter 4.

Although sources of heavy ions exist in the United States and other countries (Appendix C), it is essential to have not only facilities that provide beams for the required range of ions of various energies up to 1 GeV/nucleon, but also laboratory and animal facilities that are readily accessible to U.S. investigators. The present U.S. source of 1 GeV/nucleon heavy ions, the Brookhaven Alternating Gradient Synchrotron, is now used by NASA for only about 100 hours per year. At this rate of utilization, it would take more than 20 years to obtain the physical and biological data needed to make rational decisions about the shielding needed to protect space crews from the biological effects of radiation in space (see Chapter 4).

Collaborative efforts cannot involve transfer of animals among international sites because of strict national quarantine restrictions aimed at reducing the spread of potentially hazardous microorganisms and viruses. Moreover, the travel of animals over a number of time zones would force a resetting of their biological clocks, during which time they would be physiologically and psychologically altered and not useful for controlled experiments. Hence, a requirement for international efforts is the establishment of identical animal colonies at international sites so as to eliminate scientific and legalistic impediments and any effects of biological variability in experimental results. All animal colonies, for example, would have to conform to international accreditation standards, and animal experiments would have to be approved by local institutional review boards and by the board of a collaborating investigator's institution.

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3

How to Reduce Risk and the Uncertainty in Risk Estimates

SHIELDING

Recommendations for Research to Better Determine Shielding Requirements

When compared with concerns about other physiological issues and about vehicle reliability, there was initially minimal appreciation of the hazards of exposure to radiation in low Earth orbit. The lone exception involved the trapped radiation belts, which reached a maximum intensity in the South Atlantic Anomaly, but with judiciously chosen flight paths, even this exposure was kept to acceptable levels.

The relative risks posed by exposure to radiation will be substantially different for the establishment of a moon station or for a crewed mission to Mars. For instance, the protective effects of Earth's geomagnetic field will no longer apply, and consequently the spectra and abundance of particles composing the radiation source term will differ from that observed in low Earth orbit.

While minimal shield optimization was required in the initial low-Earth-orbit vehicles, optimization will and should be a major factor in the design of vehicles for prolonged solar system travel. Research areas that should be addressed are as follows:

1. Characterization of the radiations in space and their uncertainties for galactic cosmic radiation and solar particle events (SPEs);
2. Basic cross sections for primary particle interactions and formation of fragmentation products;
3. Experimental validation of transport and fragmentation shielding computer modeling codes; and
4. Complete reassessment of shielding materials and radiation risk models.

Knowledge Base Development

Current studies indicate that the particle distribution and energies that occur behind the various potential shield materials are critically dependent on the fragmentation and secondary particle production that occurs when spacecraft shielding is struck by radiation. Even cross sections for protons, which have been studied extensively both experimentally and theoretically in the most heavily supported computer modeling codes, show disagreements by a factor of 2^1 between the values calculated from models and measurements in energy regions for which there previously were no data. To reduce the uncertainties in any transport code (i.e., computer modeling programs used to calculate the transport of primary radiation and secondary particles through materials) being used for such calculations, precise measurements of interaction cross sections (relative probabilities) are required against which to benchmark the code.

The total amount of beam time purchased by NASA for research with ions heavier than protons is currently 100 hours per year. This includes the time not only for the physics experiments referred to above, but also for the biological irradiations and the dosimetry for biological experiments, which may take as much time as the biological irradiations themselves. This amount of beam time compares with about 400 hours per year previously available for similar research studies at the now-closed Berkeley BEVALAC. From the predicted cross sections for the secondary particles and the maximum count rates of the most sensitive detectors to detect these particles in the apparatus, it is possible to estimate typical time periods necessary to accumulate a sufficient number of counts at a specified beam rate, so that the random error in total counts is minimized. A reasonable estimate for measurements of secondary particle spectra is about 1 hour of beam on target for each data point, i.e., one incident particle type at one energy level for one target composition at one thickness. Each shield material would need to be tested with at least three particle types, not including protons. Each particle type would need to be accelerated to about five different levels of energy, and five shielding thicknesses should be tested at each energy. Including the time needed for setting up experiments and testing equipment (which may equal the time needed to accumulate data), the task group estimated that about 100 hours are needed for each shielding material examined with one particle type for data collected along the primary beam axis, with the beam time increasing geometrically with scattering angle. (A semipermanent or dedicated facility could drastically reduce set-up times, since equipment may be left in place between experiments.) If collection of off-axis data is also considered, a conservative estimate of the time needed for obtaining data on particle types, numbers, and energies is about 300 hours for each particle for each shielding material, or about 900 hours for three materials. This amount of time would increase by a factor of 2 or more if data were collected at off-axis scattering angles and could correspond to about 1 or 2 equivalent chronological years of dedicated research at most DOE accelerators.

The composition of the GCR particle spectra dictates a focus on iron as the highest-atomic-number (Z) particle of critical interest. Studies with additional ions are required, however, to benchmark the theoretical cross section code against the Z range of interest. Because the uncertainty in the calculated cross sections is reflected in the uncertainty in the level of required shielding, reduction in the uncertainty of these data values will have major cost reduction implications.

Needed in addition to validation of the cross section calculation codes is validation of the transport code itself. Experimental measurements of particles emanating from a thick laminated shield need to be compared with theoretical calculations to benchmark the transport codes and reduce the uncertainty in the calculation of the amount of shielding needed. The laminate shields should be chosen carefully to reflect the full scope of materials that might be used; SiC, ^{6}LiH, Al, regolith and other hydrogen-containing materials that show promise.

Shielding Approaches

As indicated above, radiation has not been considered a serious hazard in low-Earth-orbit missions of relatively short duration at low inclinations, given that the doses within spacecraft have been well within NCRP guidelines.[2] For the mission to Mars, however, loss of the shielding benefits of Earth's magnetic field and the longer time periods over which dose is accumulated require that the shielding design be reevaluated. The concept of "just add a little more aluminum" is not a satisfactory solution.

Two options can be considered for shielding in space: active or passive shielding. The passive approach of bulk shielding was chosen for the NASA low-Earth-orbit missions and resulted in a reliable system at reasonable cost. An active system would require the use of very large magnetic field strengths to deflect charged particles away from the spacecraft. Minimizing energy requirements would entail the use of superconducting systems and would involve the associated complexity of such systems. Since cosmic radiation is essentially isotropic, a fully encompassing magnetic shield would be desirable but from a practical point of view would be very difficult to achieve. Thus, the construction of a satisfactory active shield is questionable. NASA has chosen to not pursue design of an active shielding system primarily because of doubts about its reliability and this report focuses on the requirements for a passive shielding system.

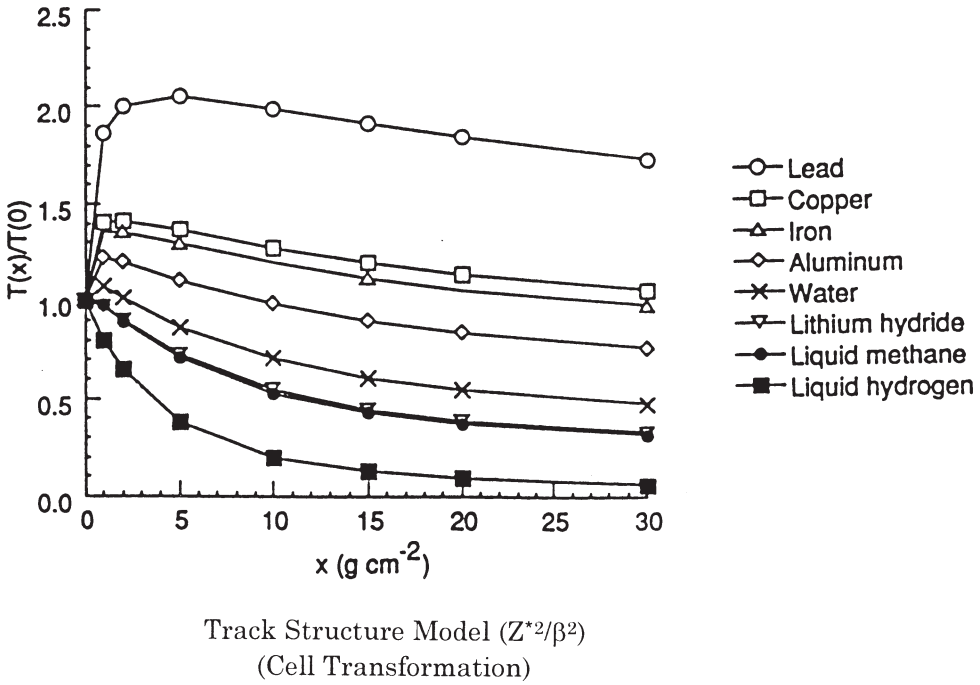

FIGURE 3.1 Calculated effect of shield material on cell transformation using the program NUCFRG2. Attenuation of cell transformation in one-year exposure behind several shield materials. T(x)/T(0) is the relative radiation-induced transformation as a function of shield thickness x. T(x) is the number of transformations at depth (x). T(0) is the number of transformations at the surface. SOURCE: Wilson, J.W., Kim, M., Schimmerling, W., Badavi, F.F., Thibeault, S.A., Cucinotta, F.A., Shinn, J.L., and Kiefer, R. 1995. Issues in space radiation protection: Galactic cosmic rays. Health Phys. 68: 50-58. Reproduced from the journal *Health Physics* with permission from the Health Physics Society.

At a recent space shielding workshop, liquid hydrogen was identified as the optimum shield material.[3] Accepting this fact, metal hydrides—i.e., lithium hydride—would appear to be prime candidates for consideration as potential shield materials.

Current calculations with the HZETRN/NUCFRG2, a transport code utilized by Langley Research Center investigators, indicate that the production of fragments and secondary particles is such that increasing the thickness of aluminum shielding has conflicting effects depending on the risk model in use. When evaluated by the dose-equivalent model (see Figure 2.5) or the model for transformation of cells in vitro (Figure 3.1), a substantial buildup in radiation damage occurs with increasing aluminum thickness. However, when evaluated using the conventional quality-factor LET model, a smaller increase is observed. When the results of the two models are compared using lithium hydride as the shield material, an increase in risk with increasing shield thickness is not predicted by either model. Clearly, the risk model chosen will have a substantial impact on material selection and the design of the spacecraft and thus must be determined with care and "frozen" early in the time line of the project.

Some data[4] exist for questioning the use of the terrestrially developed quality factor as a function of the LET model (discussed in Chapter 1), currently incorporated in radiation safety standards, for evaluating the hazards of exposure to radiation in space. Of note is the variation in cross section for transformation with particles at a constant LET of about 18 keV/μm. A theory of doubly restricted stopping power has been proposed by Grusell[5] that suggests such a variation but does not accurately predict the observed magnitude of the difference. Additional effort is needed to determine the viability of the doubly restricted stopping power theory. This work should be complemented by biological studies in a series of cell types to confirm the variation in biological damage with particle mass at a constant LET.

Cost of Research vs. Cost of Excess Shielding

The process of designing a shielded environment for prolonged space travel is a difficult task even when given accurate known information on the space radiation source spectra and accurate nuclear and atomic reaction models. However, the current state of knowledge is such that accurate source spectra, interaction cross sections, fragmentation cross sections, and biological response functions to radiation exposure are not available. Much of this information can be obtained through a focused, primarily ground-based, research program. The costs of such a program, in time and money, have to be compared with the costs of using currently incomplete and inaccurate databases and radiation shielding models and then allowing for excess shielding in the spacecraft design to compensate for the maximum uncertainty associated with the poorly known parameters. Using the Apollo mission experience as a guide, Wilson has estimated that at an overall uncertainty factor of 3 for the risk posed by exposure to HZE particles, the increased costs of compensating for that uncertainty by using excess shielding in the spacecraft for the Mars mission are about $10 billion; at an overall uncertainty factor of 6, the value is close to $30 billion.[6] These figures far exceed NASA's annual research budget for particle physics and biology research of approximately $4.5 million per year.[7]

Accepting increased costs as being associated with increased uncertainty, the question then arises: What are the sources of uncertainty in the current shielding design information? By one estimate the uncertainty factor for HZE ion transport is 2 to 3[8] and for biological response to HZE particles is 5 to 10,[9] corresponding to an overall uncertainty factor as large as 10 to 30. The disparity between the cost of the excess shielding required to compensate for these large uncertainties, and current NASA expenditures cited above, indicate the need for a significant increase in the research budget for space radiation physics and biology if NASA intends to pursue deep-space missions with human crews. This would be true even if the research determined that the actual risks were somewhat higher than currently estimated. The task group concluded that the savings to be obtained by reducing the current level of uncertainty in estimating the risks of exposure to radiation in space far outweigh the cost of obtaining the necessary information through an enhanced ground-based NASA research effort.

RADIOPROTECTIVE AND CHEMOPROTECTIVE DRUGS AND DIET

It is well known that nausea and vomiting are common after exposure to moderate to high doses of radiation, and the use of antiemetic agents is a clinically accepted practice in radiation medicine. However, it is unlikely that radiation-induced nausea will be a major concern for the Mars mission. Rather, the development of nausea is likely to be a concern only in the case of a crew member working outside a vehicle during an SPE. In anticipation of such an occurrence, an antiemetic might be taken as a routine precaution prior to participation in any extravehicular activity.

The development of drugs that can be used to protect personnel from adverse health effects of radiation is one possible approach to reducing acute effects following exposure to radiation from SPEs that might be encountered outside the spacecraft. This is the only scenario for which strategies employing radioprotective agents are warranted, as day-to-day exposure inside a spacecraft is unlikely to be sufficient to result in such acute effects. A large battery of radioprotective compounds developed as part of a program at the Walter Reed Army Institute of Research includes WR-2721, a compound that has been shown in experimental studies to be effective in reducing a number of deterministic effects associated with exposure to radiation.[10] Considering the potential risks of such effects associated with exposure to radiation during SPEs, the availability during a mission of such radioprotective compounds would be highly desirable. Unfortunately, WR-2721 requires the administration of an oral dose that produces side effects not desirable during spaceflight. These include vomiting and vasodilatation, which results in hypotension. Other compounds need to be examined to determine their efficacy as radioprotective agents at doses that have fewer toxic side effects.

More recently, a series of studies by Grdina and his colleagues have suggested that low doses of WR-2721 (which are substantially below toxic levels) and its active metabolite, WR-1065, given up to 3 hours after exposure can reduce the mutagenic and carcinogenic effects of radiation by means of a mechanism independent of its protective effects against cytotoxicity.[11-13] It is not known whether this compound would be effective in preventing effects produced by protons and heavy ions; its proposed mechanism of action suggests that its effects might be applicable for both high- and low-LET radiation. Therefore, it is quite

possible that this drug would be useful following exposure to radiation encountered in space as well. Unfortunately, daily use of this compound is not possible since multiple low doses eventually result in toxic effects similar to those seen with higher single doses. This makes the use of such a compound inappropriate for modifying the effects of daily doses of radiation encountered during spaceflight. On the other hand, the use of this drug or similar drugs on a short-term basis following exposure to radiation associated with SPEs might be reasonably considered. Clearly, more research is required before this strategy could be incorporated into an overall radiation protection program.

Diet is known to be an important influence on cancer development. A full discussion of dietary factors and cancer is beyond the scope of this report and the expertise of this task group. However, it is recommended, in planning a mission to Mars, that careful consideration be given to the inclusion of dietary supplements, including vitamins and antioxidants that have been shown to have the potential for modifying oxidative damage and for reducing the lifetime risk of contracting cancer.

CREW SELECTION

The Chapter 2 sections titled "Variation in Susceptibility to Radiation Across Subject Types" and "DNA Repair" provide examples of genotypes that could predispose individuals to adverse health effects from exposure to ionizing radiation. In general, the genotypes that produce large increases in sensitivity and/or susceptibility are rare in the population and frequently are phenotypically obvious. The probability of an individual with such a genotype being enrolled in a crewed spaceflight program is very low. Thus, the normal process for crew selection should generally be adequate for screening unusually susceptible individuals. However, as noted above, there is the potential for some genotypes (particularly heterozygous ones, such as that for AT) to confer a small increase in sensitivity to radiation for cell killing, induction of mutations, and even cancer. At this time it is either not possible or not feasible to type individuals genetically for the purpose of identifying the status of a range of "sensitivity genes." Many of the genes have not been identified or have not been characterized; if they have been cloned, they are generally too large for routine individual characterization. If the G_2 radiosensitivity assay of Jones et al.[14] turns out to be able to identify a range of sensitive individuals who are cancer prone, it might be feasible to use this method as a screening assay to at least allow the range of sensitivities to be incorporated into a risk estimate or to guide investigators to estimate dose limits for individuals with different sensitivities.

OPTIMAL TIME FOR FLIGHT

Because of the long period of the solar cycle (typically 11 years), it may be possible with a judicious choice of starting date to significantly reduce the radiation dose equivalent received by space crew members. During the solar maximum, there are increased numbers of SPEs with a concurrent reduction in fluence rate for the GCR, in comparison with the rate during solar minimum. During the solar minimum, there is a significant decrease in the probability of solar events and a corresponding increase in GCR fluence rates of particles in some energy ranges by as much as a factor of 10. Based on previous studies, it is the general consensus of the task group that the optimal time for a planetary mission is probably during solar minimum, despite the increased total fluence and dose equivalent associated with the increased galactic fluence.[15] This consensus is in part based on the total estimated dose equivalents for each flight scenario, but also is based on the variability of the doses expected from solar events. Moreover, the potential for acute effects arising from exposure at high levels is greater from solar events, although such large exposures are unlikely even during solar maximum except for specific cases such as a large SPE exposing personnel engaged in extravehicular activities.

The optimal launch date would still appear to be one that takes full advantage of the solar minimum, but this conclusion is partially dependent on RBE values for the primary galactic HZE particles relative to those for primary photons, the materials chosen for spacecraft construction and shielding, and the distribution of secondary particles arising from the HZE particles and protons traversing these materials. The task group concluded that the choice of a launch date should be reexamined periodically as better information is acquired.

SOLAR PARTICLE EVENT WARNING SYSTEM

Flares

Clearly the most prominent signal we have of a flare occurrence is the bursts of electromagnetic radiation that originate in the flare event and travel in a straight-line path to Earth, thus reaching Earth in about 8 minutes, compared with flare-generated solar energetic particles (SPEs), which can arrive as soon as 18 minutes after the flare.

Our ability to predict the occurrence of SPEs due to flares is imprecise at best, and the accuracy of the prediction varies inversely with the length of the advance warning desired. In addition, the probability of flare SPEs reaching Earth depends on the location of the flare on the sun's surface. The magnetic field line that connects Earth to the sun has its origin on the sun at location W55. Thus the closer the flare event is to this location, the shorter the time it takes the solar flare particles to reach Earth. With increasing distances from location W55 on the sun, the protons take longer to reach Earth or may not be connected by magnetic field lines to Earth; thus such SPEs would not be observed on Earth.

Coronal Mass Ejections/Interplanetary Shocks

Coronal mass ejections are large eruptions of coronal material that produce interplanetary shocks when they move at high speeds from the sun through the solar wind. These shocks produce SPEs by accelerating a small fraction of the solar wind particles during their passage through interplanetary space. It is now appreciated that not all coronal ejections that produce SPEs have related flares, and the contribution of nonflare events to the SPE population has only recently been appreciated. Such events are detectable in soft x-ray images obtainable above Earth's absorbing atmosphere. However, it is not yet possible to predict from such images whether the disturbance launched toward Earth is fast enough to produce a shock and thus SPEs.

Conclusions

Assuming the goal of allowing time for crew members, in space or on another planetary body, to reach shielded locations, current monitoring systems using visual observations for predicting SPEs are not acceptable. The fact that a space vehicle during its travel may be connected to a flare on the sun by magnetic field lines that originate on the far side creates a blind spot for Earth-based monitoring stations. A series of satellite platforms for monitoring the sun's activity could keep the sun's surface and corona under continual surveillance, but such a system is complex and costly. Thus there is a need for new and innovative ideas in this area. The spacecraft itself may be equipped with the necessary instrumentation to allow crew members to participate in the monitoring process. However, this system would, like Earth-based stations, have blind spots and should be viewed as a complement to any series of space platform monitoring stations.

The required advance warning time will be dictated by the mission program. Under the assumption that crew members will return to a base camp on Mars for rest at the end of each day, an advance warning of 8 hours would be desirable. Shorter warning periods may curtail the scope of a mission if the level of safety is to be maintained.

The current state of the science is that Earth-based monitoring stations can only partially support a space vehicle in predicting the occurrence of SPEs at the vehicle. A system that monitors the global surface of the sun and corona should be developed and knowledge improved on how to interpret information acquired by monitoring the sun. Research is necessary to provide an understanding of the basic mechanisms that trigger solar events, the precursor signals that can be detected from terrestrial or satellite observation, and the ability to determine the location of flare occurrence.

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4

Priority Research Questions and Strategies

As is pointed out often in preceding chapters, values for the risk of late effects occurring in humans exposed to external radiation are based almost entirely on epidemiological studies of acute exposure of humans, primarily Japanese atomic bomb survivors, to low-LET radiation. Analysis of these data shows, for example, that there is a lifetime risk per Sievert of 8.0×10^{-2} for excess cancer mortality to an individual in the general population.[1] Assessing the risk of effects from low-LET radiation thus consists simply of determining the physical dose associated with a specific scenario and then multiplying the dose by the above factor to obtain the lifetime risk of excess cancer mortality. For types of radiation with differing LET, the dose is converted to a dose equivalent in sieverts and the risk calculated as above. However, the proper conversion factors for HZE particles and the products they generate in passing through shielding are poorly known at present, as chapters above emphasize.

An estimate of the risk of adverse biological effects due to irradiation during a space mission corresponds to a determination of the relevant deterministic and stochastic biological consequences of exposure to radiation as a function of (1) dose, (2) dose rate, and (3) radiation quality as a function of radiation type and of the shielding thickness for each type of spacecraft material, and the uncertainty should be included in that risk estimate.

Below are outlined what the task group believes to be the most important of the research questions and issues that must be addressed in any endeavor to significantly reduce the risk and uncertainty of radiation hazards to the crews of interplanetary missions. The research strategy recommended for addressing each question is narrowly focused on that question and describes the minimum research model likely to provide the necessary data. The development of such a narrow set of strategies should not necessarily be taken as a recommendation to limit the scope of studies to those outlined below. If funds should become available, many of these studies could be usefully expanded to provide additional relevant information.

In accordance with current understanding of the risks and uncertainties, the research questions are separated into higher- and lower-priority groups. As more data become available some questions may shift in priority. Some strategies may be carried out independently, while others will be influenced by the outcome of the other programs and should be scheduled accordingly. The reasoning that forms the basis of these recommendations is discussed in detail in Chapters 2 and 3.

HIGHER-PRIORITY RESEARCH QUESTIONS

The higher-priority research questions and issues listed below are followed by the suggested strategy for addressing each question. Research questions that were deemed important but of a lower priority are given in the next section.

1. What are the carcinogenic risks following irradiation by protons and HZE particles?
2. How do cell killing and induction of chromosomal aberrations vary as a function of the thickness and composition of shielding?
3. Are there studies that can be conducted to increase the confidence of extrapolation from rodents to humans of radiation-induced genetic alterations that in turn could enhance similar extrapolations for cancer?
4. Does exposure to heavy ions at the level that would occur during deep-space missions of long duration pose a risk to the integrity and function of the central nervous system?
5. How can better error analyses be performed of all factors contributing to estimation of risk by a particular method, and what are the types and magnitude of uncertainty associated with each method? What alternate methods for calculation of risk can be used to compare with conventional predictions in order to assess absolute uncertainties? How can these analyses and calculations be used to better determine how the uncertainties in the methods affect estimates of human risks and mission costs?
6. How do the selection and design of the space vehicle affect the radiation environment in which the crew has to exist?
7. Can solar particle events be predicted with sufficient advance warning to allow crew members to return to the safety of a shielded storm shelter?

Question 1: What are the carcinogenic risks following irradiation by protons and HZE particles?

Answering this key question requires that two related research questions be addressed. First, can the risk due to irradiation by protons in the energy range of the space environment be predicted on the basis of the risk posed by exposure to low-LET radiation; i.e., is it appropriate to assume that the quality factor is 1, and is there evidence for repair of damage in cells following fractionated exposure to protons and HZE particles? Second, what are the appropriate quality factors for making risk calculations with respect to HZE particles?

The answers to these questions are fundamental to understanding the risk of contracting cancer as a result of travel in deep space. Without these answers, it will not be possible to improve the understanding of risk beyond the current state. These important questions can be addressed using solely ground-based studies if appropriate funding and additional radiation resources such as accelerator time are made available.

Initial studies of the effects of exposure to protons should focus on cellular effects that are relevant to cancer. Research with cells would provide a more rapid resolution than would tumor induction studies with animals of whether effects of exposure to high-energy protons are similar to those arising from low-LET radiation. Theoretical models of radiation effects as well as currently available data for cellular and tumorigenic effects of exposure to protons (mostly at energies lower than those encountered in space) would argue that risks due to proton irradiation are similar to those from low-LET irradiation. To determine whether such a prediction is appropriate for higher-energy protons, the task group recommends that a series of studies be conducted in several cellular systems, including human fibroblasts and lymphocytes, to examine the effects of protons in the 1-GeV energy range on cell killing, induction of chromosomal aberrations, and induction of gene mutations. To bridge the gap between in vitro and in vivo results, chromosomal aberrations could also be studied in lymphocytes from animals irradiated in vivo. By conducting such studies with both acute and fractionated exposure regimens, it would be possible to determine whether fractionation effects (sparing of radiation response by allowing for DNA repair between fractions) similar to those for low-LET radiation exist. Animal carcinogenesis experiments with protons should be conducted only if the results of cellular studies indicate discrepancies from the predictions. If, on this basis, tumorigenesis studies are warranted, the same animal models recommended for the study of tumorigenesis following exposure to HZE particles (described below) should be employed. Facilities to conduct proton experiments are available at Brookhaven and Los Alamos national laboratories in the United States (see Appendix C). Lower-energy protons such as those at Loma Linda University Medical Center Proton Therapy Facility are somewhat useful for studies related to solar events. Although considerable data are already available for protons in this energy range, these data are not satisfactory to answer questions related to high-energy protons in the 1-GeV energy range. If animal studies are required, irradiation of sufficient numbers of animals would generally require at least 1 to 1.5 years, while conduct of the animal studies subsequent to completion of the irradiation would require 3 to 4 additional years.

To obtain reliable quality factors (and ultimately better risk coefficients) for HZE particles, a systematic series of studies of RBE-LET relationships for a select number of heavy ions with emphasis on iron particles should be conducted using well-defined animal models for tumorigenesis. Adequately defining these relationships requires that the dose-response relationship be determined for these particles in the dose range below 20 to 30 cGy, because at higher doses of high-LET radiation, the response appears to reach a maximum followed by a decrease. The model systems chosen should be those for which substantial dose-response data for other high- and low-LET radiation are already available. The task group recommends that model systems that are particularly amenable to concomitant cellular and molecular studies be given priority. Given these constraints and the fact that mice have been used more extensively than other mammalian species in studies of carcinogenesis,[2] the task group recommends the murine models for radiation-induced myelogenous leukemia and mammary gland cancer. The conduct of these studies would require considerable commitment of beam time at an appropriate facility. Under the assumption that 3 months of beam time would be available per year, the task group estimated that these studies would take approximately 6 years to complete. This time estimate assumes that irradiation of sufficient numbers of animals would require 2 years. Following irradiation, completion of the animal studies can be expected to require approximately 4 years. Under current conditions, which provide only 2 weeks of beam time each year, it would be almost impossible to complete a meaningful series of animal studies, because the period of time between the first set of animal irradiations and the last would probably be on the order of 6 years (assuming that half of the beam time could be devoted to animal irradiation). This long temporal separation of experimental groups makes comparisons more difficult even with well-defined systems. Under these conditions, completion of the carcinogenesis studies would require a minimum of 10 years after the first irradiation.

Improvements in risk estimates beyond those attained with these data would require a more complete understanding of mechanisms and of principles that will aid in the direct extrapolation of results from experimental systems to astronauts. These kinds of studies will likely require the development and exploration of new model systems and the application of developing technologies in cell and molecular biology.

Question 2: How do cell killing and induction of chromosomal aberration vary as a function of the thickness and composition of shielding?

The data obtained from the answers to question 1 are necessary background for determining the biological effects of the specific radiation qualities and fluences in a spacecraft. The quality and dosimetry of radiation produced from HZE particles traversing shielding of different thicknesses and composition would be assessed from studies that address question 6. The cellular studies should not be initiated for any particular energy (of HZE particle) and shielding until the physical characterization of that radiation is completed.

The task group recommends that at a minimum, studies using cell killing and chromosomal aberrations as end points be conducted using radiation qualities defined in dosimetry studies (question 6). For the sake of relative ease of experimentation, only the effects from acute exposures should be measured. Ground-based HZE particle sources, used with appropriate shielding to simulate in-flight conditions, should be quite suitable for such experiments. In-flight studies would be prohibitively difficult to conduct, and little gain in information would be realized.

It would be appropriate to conduct the initial studies in vitro using the same cell lines used to address question 1, i.e., both rodent and human cell lines. Subsequent cytogenetic studies would need to be conducted in vivo to develop a more appropriate database for use in risk assessment calculations. The task group recommends that bone marrow cells and peripheral lymphocytes, which are easily analyzed cytogenetically, be analyzed for chromosomal aberrations. Based on the information obtained in these cytogenetic studies, it would then be feasible to design a study to assess induction of leukemia and breast cancer in mice exposed, behind shielding, to acute doses of HZE particle radiation incident on the shielding if it appears necessary from the cellular studies. Irradiation for the in vitro studies could be accomplished in a relatively short period of time, i.e., about 2 days for each radiation type and energy. Typically, about 6 months would be required for the analysis. If six radiation types were examined in consecutive order, as might be expected for a single research team, then such a study would require on the order of 3 years. Similarly, the in vivo cytogenetic studies also require about 2 days of irradiation time for each radiation quality. Assuming that the

in vivo studies were performed in parallel with the in vitro studies, then both might reasonably be completed during the 3-year period.

The in vitro studies would allow comparison of animal and human sensitivities to changes in shielding parameters. The in vivo experiments would provide data for in vitro and in vivo comparisons of cytogenic responses for the mouse. This parallelogram approach would provide the chromosomal aberration frequencies induced in humans in vivo (for bone marrow cells and lymphocytes). The mouse cancer studies (leukemia and breast cancer) can then be extrapolated in terms of human tumors assuming the chromosomal aberration sensitivity factors apply. This approach would seem to be particularly reasonable for leukemias, as chromosomal alterations are involved in the etiology of the cancer (see "Experimental Techniques and New Data Required" in Chapter 5).

Question 3: Are there studies that can be conducted to increase the confidence of extrapolation from rodents to humans of radiation-induced genetic alterations that in turn could enhance similar extrapolations for cancer?

The studies recommended for addressing question 2 would give relative sensitivity factors for mutations, chromosomal aberrations, and cell killing in rodent and human cells in vitro, and the in vivo cytogenetic studies would allow comparison of in vitro and in vivo responses in a single species, most likely the mouse. The sensitivity factors and other comparative data could then be used to provide an estimate of responses mentioned above in humans using the cancer induction data obtained in rodents. However, the reliability of the use of a relative sensitivity factor must first be established. Chromosomal aberration and mutation frequencies induced by exposure to radiation are influenced to a great extent by the kinetics and fidelity of DNA repair processes. Therefore, a secondary measure of relative sensitivity pertinent to cancer risk assessment would be a comparison of the features of DNA repair in human and rodent cells in vitro following acute exposure to protons and HZE particles. Techniques based on pulsed field gel electrophoresis have been developed that can measure DNA strand breaks at very low exposure levels (<10 cGy). These experiments would require a minimum of 1 day of irradiation time for each radiation quality studied. A typical analysis of chromosomes would consume about 2 months for each particle type: therefore a 12-month study could be reasonably estimated for an examination of six particles, if beam time were readily available. If these experiments had to compete with other high-priority items for beam time within the total of ~100 hr/yr currently available, they would probably extend over 3 years.

Question 4: Does exposure to heavy ions at the level that would occur during deep-space missions of long duration pose a risk to the integrity and function of the central nervous system?

A multifaceted research approach is required to answer this question so as to relate molecular changes to alterations in functions. Considering that some of the experiments could take a long time and that a few definitive answers must be obtained before final decisions about shielding and mission planning can be made, it is essential to ensure coordination of the strategy for this field of research. The studies range from induction of DNA damage, repair, and maintenance of the fidelity of DNA into old age to studies of the heavy-ion induced morphological and functional changes outlined in the Chapter 2 section titled "Central Nervous System." The time taken would vary from about 2 years for the DNA studies to perhaps 10 or more years for studies of functional changes, depending on the species required for a definitive assessment.

The scope of the research should be agreed upon by representatives of the disciplines that should be involved, including both experimental and clinical neurologists. One essential study that could be started now is confirmation of the findings of Lett et al. on retinal cells, that late breakdown of DNA exposed to heavy ions occurs and that age at exposure is important.[3] New sensitive techniques for assessing DNA damage can be applied to the problem and also to the determination of the dose-response relationships and the influence of LET.

The studies described for this question could not be performed at all with only 2 wk/yr of beam time. If 3 mo/yr were available, then experience with similar studies[4] suggests a rough time estimate for the performance of all the required studies of 5 to 7 years because of the long time interval required to observe late

effects. This estimate is based on the assumption that sufficient animal facilities and staff will be available at the beam site and that rodents will be used as the animal model. For rodents, a post-irradiation period of around 3 years could be needed to observe the onset of possible late effects. If rodents are not used, then another way to complete these studies in the time frame proposed might be to repeat, confirm, and extend the work of Lett et al. A minimum of three ions with a spread of LET values would need to be examined in order to answer question 4. Iron should be one of the ions selected.

Question 5: How can better error analyses be performed of all factors contributing to estimation of risk by a particular method, and what are the types and magnitude of uncertainty associated with each method? What alternate methods for calculation of risk can be used to compare with conventional predictions in order to assess absolute uncertainties? How can these methods be used to better determine how the uncertainties in the methods affect estimates of risk to humans and mission costs?

The relative significance of uncertainties in risk assessments must be adequately established and the impact of reductions in the level of these various uncertainties must be determined.

The conventional approach for the assessment of risks is initially to calculate a dose, defined as the equivalent dose for the radiation field of interest corresponding to the dose of low-LET radiation that produces the same level of risk. The simplest method for obtaining the equivalent dose is to multiply the physical dose by a quality factor for the radiation field, but there are several other approaches, including models for normal-tissue responses, microdosimetric methods, and fluence-based techniques. In any of these cases, there is uncertainty associated with the method itself and additional uncertainty associated with each of the input quantities used to calculate that risk. In the former case, each of the quantities, such as the physical dose or quality factors, needed as input to establish the risk has a level of uncertainty associated with it. Reductions in the uncertainties in the values of the specific input quantities have differing effects on the magnitude of the uncertainty of the total risk, depending on the method chosen. For example, in the conventional approach, the squares of the fractional uncertainties in the absolute physical doses and in the quality factors will contribute additively to the total uncertainty irrespective of the absolute values of the two quantities if they are two independent quantities. In such a situation, the larger fractional contribution will dominate the total uncertainty. In contrast, for an extrapolation of effects at low doses or low dose rates with a linear-quadratic model, the squares of the absolute uncertainties, rather than the fractional uncertainties in dose and quality factor, contribute additively. Currently, the lack of knowledge concerning the uncertainties in the values of the quantities needed to assess risks is a major limitation in establishing realistic design requirements for a planetary mission.

In addition to the uncertainties in the values of the input quantities, there is an intrinsic uncertainty associated with the method used. Recognizing that use of only one method with a possible large uncertainty is at best questionable, the task group recommends that risk estimates be determined by different independent methods as a means of determining the overall uncertainty from input quantities and methods. The results of an error analysis (i.e., an analysis of the relative and absolute uncertainties) should be used to evaluate which methods will most effectively reduce the uncertainties in risk estimates and, therefore, uncertainties in cost of shielding. It would be useful if this analysis were preceded by a review of the improvements that have occurred in the physical data and theoretical methods now available compared to those available approximately 1 decade ago.

An analysis of the uncertainties in risk based on present data and methods could be achieved within about 1 year with proper support. Such analyses, however, should be updated routinely as part of a continuing effort throughout the entire project, and all investigators should be required to provide error analyses of their results.

Care should be exercised to distinguish between uncertainties in the input data owing to lack of knowledge and variability in the input data owing to fluctuations in the data themselves. For example, a lack of knowledge of cross sections for producing secondary nuclear particles in the materials used to construct a spacecraft represents a source of uncertainty that might be reduced, with a consequent potential for cost savings. However, the variability in the types and energies of the incident particles resulting from variation in the number and quality of solar events is not representative of an error in the input data used to calculate

risk. In this latter case, there is little, if anything, that can be done to reduce the variability; the best that should be anticipated is a reduction of the uncertainty in the prediction of the variability.

Question 6: How do the selection and design of the space vehicle affect the radiation environment in which the crew has to exist?

The answer to this question is based in part on an accurate knowledge of the incident radiation field, the reaction cross sections for the incident particles reacting with the vehicle materials, and the fragmentation/recoil products that such reactions produce. Current knowledge of the fragmentation products produced by HZE particles is limited to only a few particles in a few materials. For knowledgeable shielding design, the initial radiation fields, the reaction probabilities, and the secondary particles produced as a function of angle must be determined through physical measurements, at a HZE particle accelerator, of the particle types and energies resulting behind different compositions and thicknesses of shielding.

Based on the predictions of current transport codes, hydrogenous materials are preferred for shielding because they offer better shielding than other materials on a per unit mass basis (see Figure 2.5). To properly assess the accuracy of these predictions, the transport codes used to calculate the shielding efficiency have to be benchmarked against measured data for elemental (Al, Fe, etc.) and composite shields.

Complementary measurements should be made with a microdosimetric detector of the type currently being flown in space. The absorbed dose as a function of depth should likewise be measured along the axis of the beam at selected positions along the axial plane. The measured data should be compared with predictions by the Langley Research Center transport code and/or a Monte Carlo transport code. Similar measurements as a function of depth should be made for the simplest possible geometry in space and these results compared with calculations of the dose, the radiation quality, and the particle spectra.

Engineering of the storage for a spacecraft's supplies so as to form an enhanced "storm shelter" against transient high levels of radiation would be subject to the same verification of the accuracy of data and calculations. At the current level of availability of heavy ion particle accelerator time, the task group estimates (see "Knowledge Base Development" in Chapter 3) that more than 10 years will be required to collect the necessary data. With increased availability of accelerator time and other resources, data collection and analysis could be compressed into a time frame of about 4 years.

Question 7: Can solar particle events be predicted with sufficient advance warning to allow crew members to return to the safety of a shielded storm shelter?

The ability to predict the time of occurrence and/or magnitude of solar particle events (SPEs) is currently an inexact science at best. Protecting a mission crew from SPE radiation requires improving the capability to accurately predict solar events. This effort requires that information on the status of the total solar surface be continually available. One mechanism for accomplishing this would be a series of space platform monitoring stations. Given the necessary information on the status of the sun's surface, the science and models that interpret these data must be enhanced with the goal of achieving accurate forecasts 8 hours in advance of a spacecraft encountering a SPE. Prediction of the resources and time required to reach this state of capability is beyond the expertise of the authors of this report. However, the capability to predict solar events 8 hours in advance of their occurrence is thought to be an operational requirement for a safe interplanetary mission.

LOWER-PRIORITY RESEARCH QUESTIONS

1. What are the risks of reduced fertility and sterility as a result of exposure to radiation on missions of long duration in deep space?
2. What are the risks of clinically significant cataracts being induced by exposure to radiation at the levels that will occur on extended spaceflights?
3. Can drugs be used to protect against the acute or carcinogenic effects of exposure to radiation in space?

4. Is there an assay that can provide information on an individual's sensitivity to radiation-induced mutagenicity and that can be predictive of a predisposition for susceptibility to cancer?

5. Are there differences in biological response arising from exposure to particles with similar LET, but with different atomic numbers and energies?

Question 1: What are the risks of reduced fertility and sterility as a result of exposure to radiation on missions of long duration in deep space?

- *Female:* Studies of women receiving pelvic and abdominal radiotherapy in which there is good dosimetry could provide useful information on the effects of radiation on ovarian function. It is probable that prospective studies of women treated with cytotoxic drugs at young enough ages in whom ovarian function is compromised could provide valuable information when combined with modeling. Complementary studies of both normal and radiation-induced loss of ovarian follicles, preferably in a nonhuman primate, will be required.
- *Male:* An assessment of the effect of dose rate and protraction of radiation on spermatogenesis is essential. The study should be carried out on a primate, but studies previously done on other mammals could also be extended to include low dose rate or fractionated proton exposures. Sperm counts are an easy and economical assay of the effect of exposure. However, histological studies of the testes are required, especially in cases of azoospermia (total loss of sperm). The stem cells may not be the most sensitive target, because loss of the ability of the supporting tissue to enable differentiation in the spermatogenic process may determine the probability of sterility. Paracrine mechanisms, which release locally acting substances from cells directly into intracellular space, are involved in the differentiation process, but little is known about either their role or the effects of radiation on them. Studies of men receiving cyclophosphamide could provide some help in the comparison of the relative effects of acute and chronic administration of radiation doses on sperm production.

To improve understanding of the effects of radiation on fertility, pragmatic studies of the loss of ova or sperm and studies of the basic aspects of ovarian function or spermatogenesis should be carried out hand in hand. As much clinical data as can be obtained and are relevant should be collected, and priority should be given to animal experiments designed to answer the questions that cannot be answered by research on humans. Ideally, the studies should include the effects of repeated exposure to protons and heavy ions at low fluences. However, protracted exposure to gamma rays may be the most practical approach, and gamma rays should be an adequate surrogate for protons. Since there are several sources available for both gamma rays and protons, beam time is probably not a limiting factor for conducting this study. If the group conducting the study were co-located with the source, and the appropriate support staff and animal care facilities were available, then such a study might be completed in as little as 4 years. Currently, however, such a resource does not exist.

Question 2: What are the risks of clinically significant cataracts being induced by exposure to radiation at the levels that will occur on extended spaceflights?

A considerable body of data provides information about the induction of cataracts in different species by different types of radiation. There is, however, no consensus on how to collate the data and use it to estimate risk to humans. This objective, however, appears to be within reach and should be pursued. Another approach is to determine experimentally the relationship of RBE for cataractogenesis to LET, and to apply the RBE value to the data for induction of cataracts in humans by low-LET radiation. A better understanding is needed of the effects of protracted exposure at low-dose-rates for both low- and high-LET radiation, because the data currently available for humans are for high-dose-rate low-LET radiation.

As research efforts are already under way on atomic bomb survivors (who were exposed to low-LET radiation), the results of which could readily be applied to question 2, the most cost- and time-effective approach to this issue would be to ensure that current work on the survivors receives continued support.[5] The cataractogenic effects of protons, the most prevalent particles in galactic cosmic rays, can be estimated

directly with reasonable confidence from data on the effects of low-LET radiation. Moreover, estimating the risk from exposure to HZE particles by any of the methods suggested so far in this report depends on the use of data obtained from humans exposed to low-LET radiation, and the major source of that data is the atomic bomb survivors. Under these circumstances a sufficient answer to the question of the magnitude of the risk for cataractogenesis owing to long-duration spaceflight might be obtained in a time frame of 4 or 5 years.

Question 3: Can drugs be used to protect against the acute or carcinogenic effects of exposure to radiation in space?

A program to develop drugs capable of protecting humans against the acute toxic effects of radiation has been conducted for many years under the auspices of the Department of Defense. These efforts have yielded a number of drugs that are moderately protective against the effects of low-LET radiation because they are free-radical scavengers. Such scavengers are relatively less effective against high-LET radiation because ionizations are produced more frequently as a result of direct effects rather than indirectly through the products of water radiolysis. At the present time, the effectiveness of such agents against acute high-dose exposure to protons, such as might be experienced during an SPE, is not known. Studies should be conducted in animal models to determine the efficacy of single doses of such drugs in protecting against the damaging effects of protons, similar to those associated with an SPE, on blood-forming cells.

More recently, studies have suggested that agents related to the compound WR-2721 may be efficacious at relatively low doses in protecting against the mutagenic and carcinogenic effects of radiation through a mechanism independent of the drug's activity as a free-radical scavenger. The task group recommends that studies be pursued to determine whether such protective effects can be obtained after exposure to HZE particles. Such studies could concentrate on radiation-induced somatic cell mutagenesis, since these effects are likely to be reasonably predictive of protective effects observed for carcinogenesis in animals. Additional mechanistic studies would allow the possibility of the development of more effective and less toxic agents that might be useful for protection against late effects associated with doses resulting from SPEs. It is unlikely that a strategy of daily doses of such agents is warranted as a means of modifying the risks from daily exposure to cosmic radiation, given the relatively low risks associated with exposure at these levels.

These studies would require access to appropriate facilities for irradiation with HZE particles. Under current conditions (2 weeks' available beam time per year), it is estimated that such studies would require approximately 4 years to complete, assuming that cells for these studies could be "piggybacked" with other cellular studies. Under more ideal conditions, with 3 months of beam time available each year, these studies would require approximately 2 years to complete.

Question 4: Is there an assay that can provide information on an individual's sensitivity to radiation-induced mutagenicity and that can be predictive of a predisposition for susceptibility to cancer?

For at least 10 years, Sanford and colleagues have reported on the use of a G_2 chromatid aberration assay for detecting individuals with a predisposition for cancer.[6-8] In this assay, human lymphocytes or cultured skin fibroblasts are irradiated with x rays and metaphase cells arrested with colcemid between 0.5 and 1.5 hours after exposure. The analysis of chromatid aberrations gives a measure of chromosomal damage that was induced in G_2; a comparison of this aberration frequency with that for metaphase cells collected in the first 0.5 hours after exposure provides an estimate of DNA repair capacity. It has been reported that individuals designated as cancer prone, irrespective of the tumor type, show an enhanced frequency of aberrations and a reduced repair capacity. Attempts to duplicate the assay in other laboratories have proven to be unsuccessful.[9] Scott et al., for example, found no difference in sensitivity between controls and lymphocytes from individuals who were homozygous or heterozygous for xeroderma pigmentosum (which is a DNA repair deficiency disease), who had familial adenomatous polyposis, or who had the syndromes Li-Fraumeni, basal cell nevus, Down, or Fanconi.[10] They were able to show an enhancement with ataxia telangiectasia homozygotes, a very predictable result. They report that preliminary studies using their own G_2 sensitivity assay are giving promising results.[11] In this assay, the x-ray dose is 0.5 Gy (vs. 1.4 Gy, used by Sanford et al.), cells are not centrifuged prior to irradiation, and cells are harvested at ice temperature. It

remains to be determined if this modified assay can detect all individuals with a cancer predisposition, or at least a predisposition in specific cases. To validate the assay, it is also of considerable importance that it be conducted in several different laboratories, and that an extensive sample from the general population be assessed in order to obtain an estimate of the range of sensitivities. Since the assay can be validated with low-LET x or gamma rays, no beam time is required. The analysis of at least 100 individuals in the general population and at least 10 cancer-prone families (in several laboratories simultaneously) would take approximately 2 years to complete.

Question 5: Are there differences in biological response arising from exposure to particles with similar LET, but with different atomic numbers and energies?

There is experimental evidence to suggest that differences in both the energy and track structure of particles may lead to differing biological effects of exposure to radiation that are independent of LET.[12-14] The differences in observed RBE generally have been in the range of 2 to 3. However, the available data are derived from various sources that utilize different models and experimental conditions, thus making comparison among them difficult. Carefully designed experiments should be carried out under controlled dosimetric conditions such that the effect of factors such as atomic number, track structure, and energy can be specifically compared in the same system. It would seem reasonable to employ well-defined experimental systems such as those proposed to address higher-priority questions 1 and 2, for which substantial data for various types of radiation are already available. These would include cellular systems to examine effects on cell killing, mutagenesis, and chromosomal aberrations. If the differences observed are restricted to a factor of 2 to 3 or less, as predicted from the currently available data, conducting additional experiments in animal models for tumorigenesis would not be warranted.

Based on the assumptions that the appropriate heavy ions are available, that a dedicated facility is used to minimize tuning time, and that 2 wk/yr of beam time are set aside for this strategy, the in vitro experiments could be completed in 2 years, particularly if they were carried out in parallel with those intended to address higher-priority question 2. This estimate is based on the use of three biological end points and three different LET ranges, with three particles in each LET range. Since it is doubtful, however, that the necessary level of resources would be reserved for lower-priority projects such as this, an estimate of 3 years is probably more realistic at current levels of availability for HZE particle accelerator time.

If the annual available beam time were increased to 3 months, then it should still be possible to carry out this strategy in 2 years.

TIME SCALE OF RESEARCH

In order to carry out the research necessary to reduce the physical and biological uncertainties inherent in estimating risk and to design shielding to protect against a credible maximum risk, approximately 3,000 hours of beam time are required for experiments with HZE particles and energetic protons. At the present utilization rate of approximately 100 hr/yr at the Brookhaven Alternating Gradient Synchrotron, the research could take over 20 years—an unacceptably long time.

Figures 4.1 and 4.2 show potential research time lines based on the assumption that the currently available beam time at a heavy ion accelerator of about 2 wk/yr (Figure 4.1) remains unchanged or that 3 mo/yr becomes available (Figure 4.2).

The task group recommends that, if the goal of safe interplanetary missions with human crews is sought, NASA explore various possibilities, including the construction of new facilities, to increase the research time available for experiments with HZE particles.

FIGURES 4.1 and 4.2 (pp. 52-53) HP indicates strategies to address higher-priority research questions 1 through 7 and LP indicates strategies to address lower-priority research questions 1 through 5, given 2 weeks of beam time per year (Figure 4.1) and 3 months of beam time per year (Figure 4.2), respectively. In both figures, the bottom axis indicates the estimated amount of time required to carry out the various strategies; the top axis indicates the general dependence of the mission time line on the research. Strategies that can be carried out independently are separated by dotted lines. The length of the time bar associated with each strategy is based on the approximate amount of time estimated for the required research except in the case of HP 5 and HP 7. HP 5 (the shaded box) is not a laboratory research strategy, but rather a computational methodology, and the amount of time reserved for it may be flexible. It is therefore set to end when the construction of shielding begins. The amount of time devoted to HP 7 will depend on the time available between the initiation of research and flight. Since HP 1(b) utilizes protons and therefore does not require a heavy ion accelerator, it is not affected by the given restrictions on beam time.
KEY: 1(a), cell studies; 1(b), animal carcinogenesis studies with protons; and 1(c), RBE-LET relationship studies.

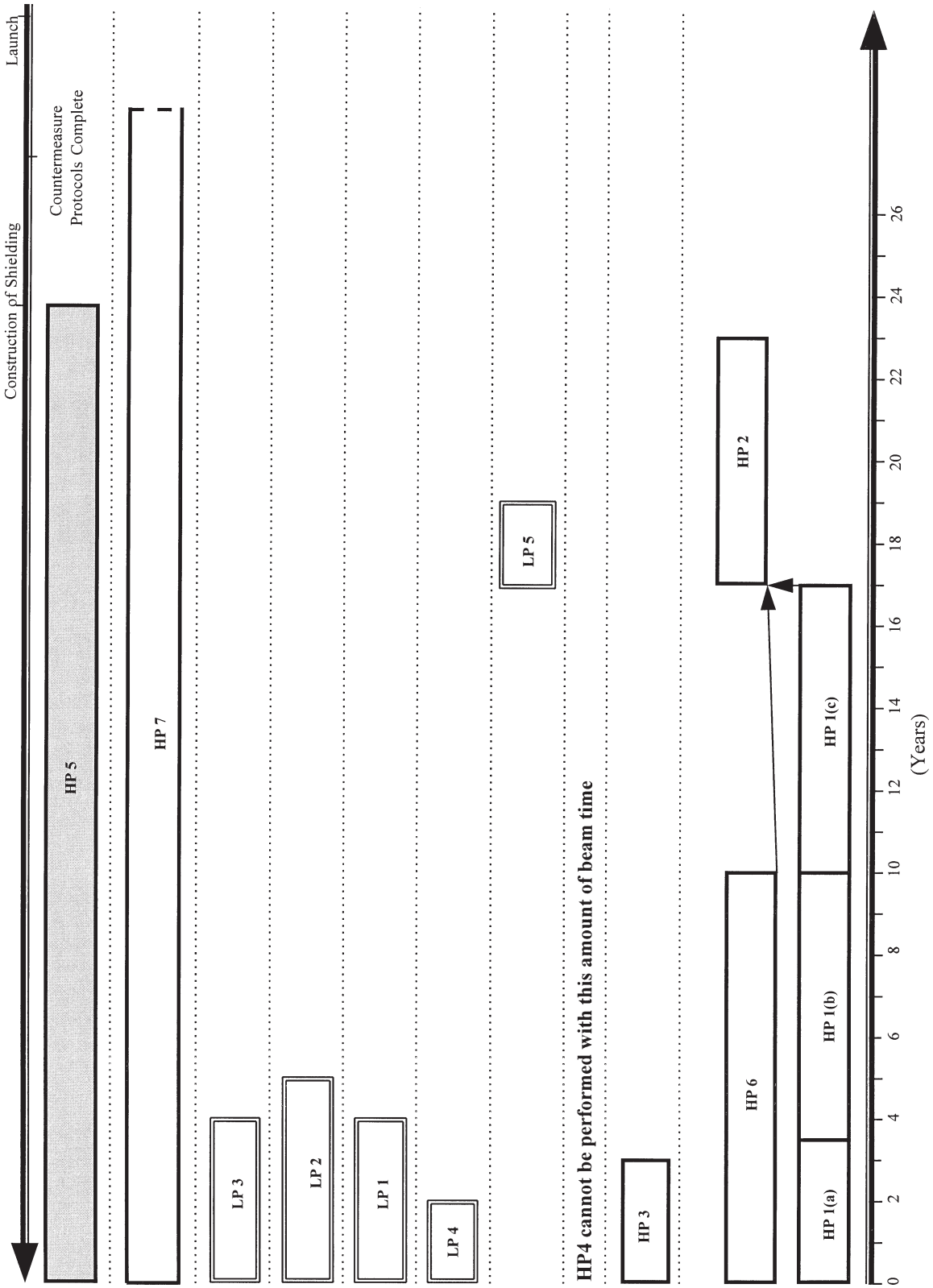

FIGURE 4.1 Potential research time line, given beam time of about 2 wk/yr.

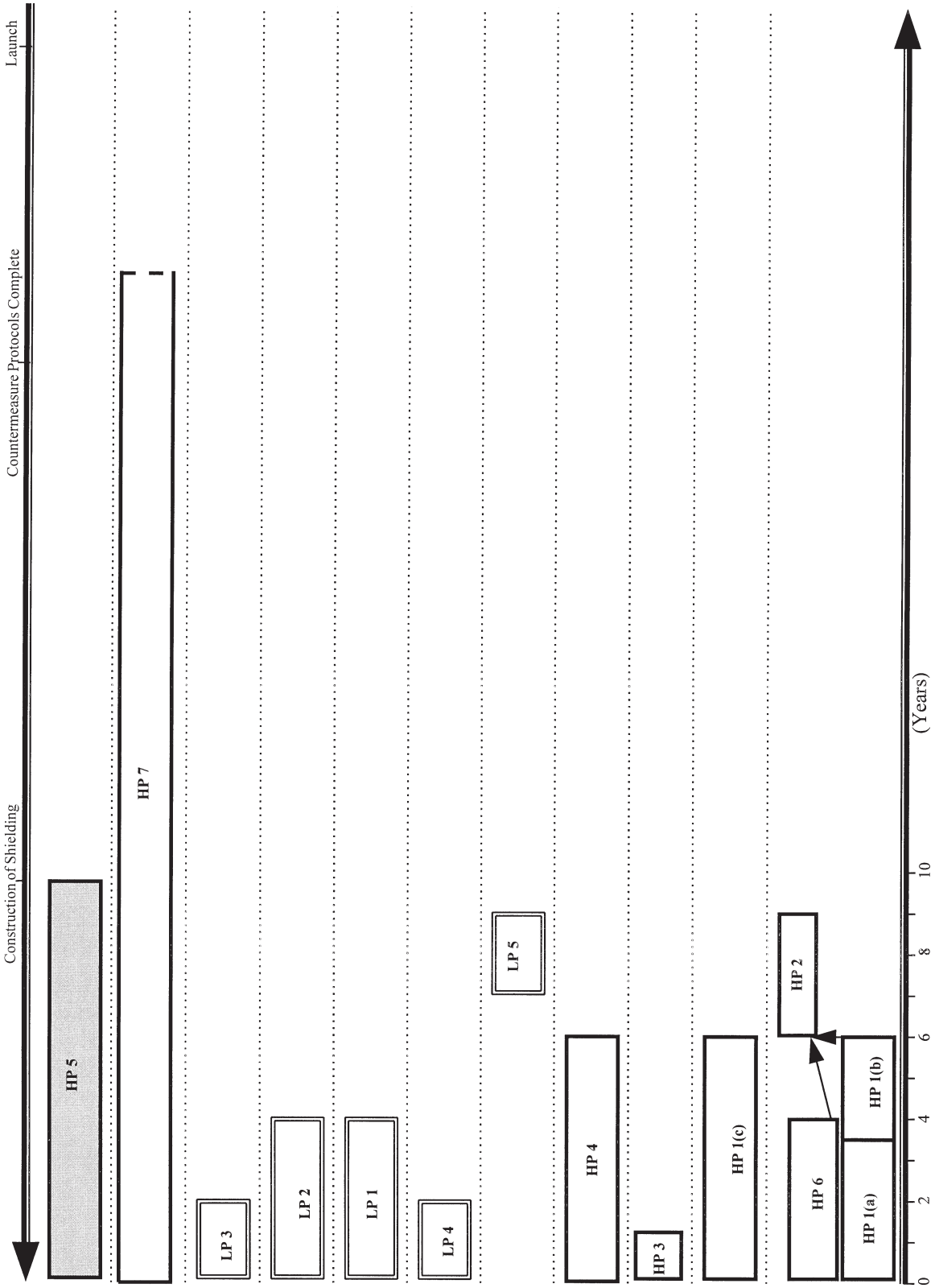

FIGURE 4.2 Potential research time line if beam time of 3 mo/yr becomes available.

WHAT WILL STILL REMAIN UNKNOWN, AND WHAT RISK DOES THIS REPRESENT?

The benefits gained from pursuing these strategies will be not only a reduction by a factor of 2 or more in the uncertainty in estimates of the risk of late effects for crew members exposed to radiation in space, but also greater understanding of CNS and other effects about which little is currently known. These benefits will result in a narrowing of the scope of the types and designs of shielding that need to be considered for crew protection, and thus should result in a significant cost savings. The liability of following these strategies is that the time required to complete them may delay a decision on shielding design and consideration of any near-term (within 25 years) launch dates if suitable resources are not made available to complete the research expeditiously.

Since these research strategies are narrowly focused and based entirely on current understanding of space radiation issues, there is also no guarantee that this approach will necessarily address all of the significant radiation hazards for crews of deep-space missions. Utilizing a wider range of radiation and biological models could lead to recognition of previously unappreciated hazards for those crews and reveal useful new avenues of research.

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5

Other Issues

The research questions and strategies discussed in Chapter 4 describe the higher- and lower-priority research that is necessary to improve the risk estimate for adverse biological effects of exposure to radiation in a space environment. The scientific requirements of the experiments proposed include the need to use animal models as surrogates for humans in assessing cancer risk and effects in the central nervous system. It is also important to consider how new techniques, already developed or currently being developed, might affect the collection of data to be used in risk assessment. In particular, the use of molecular biology techniques will enhance the ability to characterize mutations and chromosomal aberrations in cellular systems and tumors. Both as a practical and fiscal issue, it is necessary to consider the relative benefits of conducting research in space versus on the ground. In addition, the effects of radiation on plants, which would constitute a major part of the food supply in extended spaceflight, should be noted. These issues are briefly discussed below.

NEED FOR ANIMAL USE

There are no estimates for the risk of cancer induction in humans exposed to protons, the major component of galactic cosmic radiation and solar radiation, or to heavy ions such as iron. Therefore, risk estimates currently must be based either on (1) information on the risks incurred by exposure to low-LET radiation modified by radiation weighting factors (W_R) or quality factors (Q) to allow for the different relative biological effectiveness (RBE) values for the different types of radiation involved or (2) data from animal experiments used in conjunction with some method of extrapolating the risk estimates to humans. The first approach relies on experimental data because the W_R and Q factors are based on RBE values obtained from animal experiments and, to some extent, studies of chromosomal aberrations. The values for W_R (Table 2.1) are based on the judgment of a National Council on Radiation Protection and Measurements task group that examined the available relevant data.[1] Quality factors are based on the relationship of RBE to the linear energy transfer (LET) of the dose.

Both approaches to estimating the risk of adverse biological effects for humans exposed to various types of radiation suffer because of insufficient experimental data. For example, it is essential to have adequate data on the induction of cancer by radiation at a sufficient range of LET values to obtain the RBE values or Q factors needed to estimate the risk from exposure to GCR in deep space. Obtaining such data involves use of animals and to a lesser extent in vitro studies on human chromosomes and cells. As indicated in Chapter 2, specific deterministic effects such as reduction in fertility, cataractogenesis, and damage to the central nervous system are important in assessing the total risk posed by prolonged sojourns in the radiation environments in space. The effects of heavy ions on the central nervous system are of particular importance. While

no information about such effects on humans is available that is suitable for setting radiation limits, it is essential that the possibility of effects on the central nervous system be adequately assessed. Because the ideal of obtaining data from primates exposed to heavy ions is unlikely to be realized, critical animal experiments must be carefully crafted and executed.

EXPERIMENTAL TECHNIQUES AND NEW DATA REQUIRED

This section touches on new techniques being used for the qualitative assessment of mutations and chromosomal aberrations, and the characterization of molecular events involved in tumor development. It is assumed that significant progress in the next few years will be made in the above broad areas.

As pointed out in previous chapters, estimates of cancer risk posed by low-LET radiation are quite well founded and are based on fairly extensive animal but limited human studies (those of atomic bomb survivors). Testing the reliability of the extrapolation of results from rodent studies to humans would require a better understanding of the mechanism of formation of specific tumor types, both background and x ray induced, for both human and animal models (with the same tumor type). Although rather little information is available on the genetic alterations associated with radiation-induced tumors, the methods exist and candidate genes such as p53 have been proposed.[2] What remains to be developed are sufficiently sensitive assays for detecting mutations in nonselectable genes that could be markers of early stages in tumor development. While specific polymerase chain reaction (PCR) methods are becoming more sensitive, they are still 1 or 2 orders of magnitude away from being able to detect induced mutations at the needed frequencies of occurrence, typically at mutation frequencies of 1 in 10^7 cells.

Limited data are available on cancer induction in rodents exposed to high-LET radiation; information on other biological effects is also sparse. It will be necessary to conduct additional cancer studies in rodents exposed to different types of high-LET radiation and to characterize the resulting tumors at the molecular level. In fact, for high-LET radiation, the conversion of DNA lesions into mutations is not well understood. In order to better simulate conditions of exposure during spaceflight, it is necessary to consider the effectiveness of induction of mutations by low-dose-rate exposure to both high- and low-LET radiation. The use of fluorescence in situ hybridization allows reciprocal translocations to be assessed following protracted exposure. A translocation is a significant chromosomal end point when considering genomic alterations that are associated with adverse health effects. Assays are also under development for detecting low-frequency aberrations in genes above background. Although currently available only for selectable genes such as that for HPRT (hypoxanthine phosphoribosyl transferase), for which mutants have a growth advantage (i.e, they are selected for their ability to grow faster than non-mutants), it is anticipated that new assays will be available for nonselectable tumor genes and genes such as p53 and other tumor suppressor genes in the future.

The identification of populations that are genetically susceptible to cancer development is also of considerable importance. Uncovering the mechanisms involved in tumor formation is critical for this purpose but despite considerable progress is still a distant goal. A more attainable goal may be development of surrogate assays for predicting increased sensitivity for tumor induction. The G_2 chromosomal aberration assay described by Jones et al.[3] is promising. It appears to be able to identify individuals who have at least increased radiosensitivity of lymphocytes, and in one case, this increase was quite marked in about 40% of breast cancer patients.[4] More work and probably a number of modifications to the technique are in order before it can be used as a predictor of radiation sensitivity.

GROUND- VS. SPACE-BASED RESEARCH

The influence of microgravity on the effects of low-LET radiation have been reviewed by Horneck and by Nelson.[5,6] Most experiments showed negligible or small effects of microgravity on radiation-induced changes. Typical changes observed had to do with increased chromosomal alterations in fruit flies and in *Tradescantia* (the spiderwort plant) following irradiation before lift-off. Horneck suggests that changes in chromosomal structure or position in microgravity could have prevented effective rejoining of chromosomes. On the other hand, there was no control in such experiments for vibration or acceleration during lift-off or return of the satellites. In another example cited in these reviews, an experiment measuring viability in yeast,

survival was lower for microorganisms irradiated before lift-off compared to survival for ground-based controls treated in the same way. It was noted that the difference in survival did not seem to be dose dependent. These results were interpreted as indicating that DNA repair was less efficient in microgravity. No experiments were carried out in space using a 1-g centrifuge for controls.

Recent ground-based experiments, summarized by Kronenberg, on radiation-induced DNA fragmentation, neoplastic transformation of cells plated 24 hours after irradiation, and the effects of a chemical radioprotector on mutation induction showed that DNA repair and cell recovery take place readily after low-LET radiation, but not following exposure to HZE particles.[7] Since the only reported significant effect of microgravity may be on DNA repair and cell recovery following low-LET exposure and there seems to be no DNA repair/cell recovery following high-LET exposure, microgravity should not be important for HZE particle effects.

The above considerations indicate that HZE particles are a very important factor in the damage resulting from long space missions and that the effects of microgravity probably will not alter the cellular response to HZE particles but might actually increase the effect of low-LET radiation.

Hence, the task group concluded that the majority of the useful information on radiation effects and risks will come from ground-based experiments described in Chapter 4 and that radiation experiments in space, with all their logistical difficulties, will not be rewarding and may not be worth the effort.

PLANTS AND FOOD SUPPLY

Since any interplanetary spaceflight will be of long duration (up to 3 years), it will be necessary not only to have packaged food available, but also to grow additional plant food. The very high doses of radiation used to sterilize food do not significantly affect food quality. Hence, no significant effects of irradiation are plausible for packaged food, and given the predicted magnitude of exposure during spaceflight, no effect is likely on growing plants. In general, plants are relatively radiation resistant when growing and extremely resistant as dormant seeds. The most sensitive response of plants to irradiation would be overall growth, and this occurs at doses above those predicted during spaceflight.

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Appendixes

Appendix A

Acronyms and Abbreviations

AFRRI:	Armed Forces Radiobiology Research Institute
AGS:	Alternating gradient synchrotron
AP:	Apurinic or apyrimidinic
AT:	Ataxia telangiectasia
ATM:	AT mutated gene
BEIR:	Biological Effects of Ionizing Radiations, Committee on (National Research Council)
CNS:	Central nervous system
DNA:	Deoxyribonucleic acid
DNA-PK:	DNA-dependent protein kinase
DOD:	Department of Defense
DOE:	Department of Energy
DREF:	Dose rate effectiveness factor
EVA:	Extravehicular activity
GCR:	Galactic cosmic radiation
HPRT:	Hypoxanthine phosphoribosyl transferase
HZE:	High atomic number (Z) high energy
ICRP:	International Commission on Radiological Protection
LANL:	Los Alamos National Laboratory
LEO:	Low Earth orbit
LET:	Linear energy transfer
LQ:	Linear-quadratic
MIM:	Multiplicative interaction model
NASA:	National Aeronautics and Space Administration
NCRP:	National Council on Radiation Protection and Measurements
NER:	Nucleotide excision repair
NRC:	National Research Council
PCR:	Polymerase chain reaction
PK:	Protein kinase
Q:	Quality factor
RBE:	Relative biological effectiveness
RMS:	Root mean square

SPE:	Solar particle event
TGBESR:	Task Group on the Biological Effects of Space Radiation
UNSCEAR:	United Nations Scientific Committee on the Effects of Atomic Radiation
USAF:	United States Air Force
W_R:	Radiation weighing factor
XP:	Xeroderma pigmentosum

Appendix B

Glossary

Absolute risk: An expression of excess risk based on the assumption that the excess risk from exposure to radiation adds to the underlying (baseline) risk by an increment dependent on dose but independent of the underlying natural risk.

Absorbed dose: The mean energy imparted by ionizing radiation to an irradiated object per unit mass. Units: Gray, rad.

Acute effects of radiation: Effects that occur shortly after exposure to radiation, usually within a week. They result from exposure to radiation at relatively high doses, usually greater than 1 Gy. They are usually due to the killing of cells in critical tissues in the body.

Alpha radiation: A type of particulate radiation released from a radioactive atom. Alpha particles are helium nuclei. Alpha particle radiation is densely ionizing (high-LET) radiation and can be very damaging, but it is very limited in its ability to penetrate tissue. For example, alpha radiation will not penetrate the outer layers of the skin.

Ataxia telangiectasia: A disorder inherited as a recessive trait that is characterized by neurological changes, such as cerebellar ataxia, immunological deficiency, an increased susceptibility to cancer, especially lymphomas, and an increased cellular radiosensitivity.

Background radiation: Radiation received by the entire human population due to naturally occurring radiation and radioactive materials in the environment. The three major sources of natural background radiation are (1) cosmic radiation, (2) radiation from naturally occurring radioactive elements in Earth's surface, and (3) internal radiation arising from radioactive atoms normally present in foodstuffs or in the air.

Becquerel: International System (SI) unit of activity of a radionuclide, equal to 1 radioactive decay per second (equals 2.7×10^{-11} Ci).

Cancer: A malignant tumor of potentially unlimited growth, capable of invading surrounding tissue or spreading to other parts of the body by metastasis.

Carcinogen: A physical agent such as ionizing radiation or ultraviolet radiation or chemical agents, such as vinyl chloride, that may cause cancer.

Cell-killing effect: The cessation of cell division and/or metabolism. Sufficient doses of radiation may kill cells in the body. Cell death is responsible for most of the acute effects of radiation.

Cell sensitivity to radiation: The relative sensitivity (radiosensitivity) of individual cell types to the cell-killing or mutagenic effects of radiation.

Cell transformation: A process by which cells in vitro, which have a limited ability to divide, are altered by radiation or chemicals so as to have an unlimited division potential. (See *Neoplastically transformed cells*.)

Curie: A unit of radioactivity equal to 3.7×10^{10} disintegrations per second.

Deterministic effects: Effects formerly known as nonstochastic effects that may appear early or late after irradiation. There is a threshold dose above which both the probability of occurrence and the severity of the effect increase. Most deterministic effects involve cell killing.

Dose: See *Absorbed dose*.

Dose effect (dose response) model: A mathematical formulation used to predict the magnitude of an effect that would be produced by a given dose of radiation.

Dose equivalent: See *Equivalent Dose.*

Dose rate: The quantity of absorbed dose delivered per unit of time.

Doubling dose: Amount of radiation needed to double the natural incidence of a genetic or somatic abnormality.

DREF: A factor by which the effect caused by a specific dose of radiation changes at low dose rates as compared with high dose rates.

Electron volt: A unit of energy (1.6×10^{-19} J). 1 eV is equivalent to the amount of energy gained by an electron passing through a potential difference of 1 volt.

Epidemiologic study: The study of human populations designed to establish the relationships among various factors that determine the frequency and distribution of a disease. For example, a number of such studies have examined the role of radiation (the factor) in the induction of cancer (the disease). The science of epidemiology is derived from the word "epidemic."

Epilation: Loss of hair.

Equivalent dose: Absorbed dose averaged over an organ or tissue and weighted for the radiation quality for the type of radiation of concern.

Erythema: Redness of the skin. A transient erythema can occur a few hours after irradiation due to increased permeability of the capillaries. The main erythematous reaction occurs some weeks after exposure to radiation and is due to loss of cells in the basal layer. A late phase 8 to 20 weeks after irradiation is associated with damage to the dermis.

Excess cancers: The number of individuals in a population who develop cancer over and above the number that would be expected to do so normally. Normally, about one out of every four people will develop cancer during his or her lifetime, and cancer will strike two out of every three families.

Fractionation: The delivery of a given total dose of a radiation as several smaller doses, separated by intervals of time.

Gamma rays: Short-wavelength electromagnetic radiation of nuclear origin with an energy range of about 10 keV to 9 MeV.

Gene: The biological unit of heredity in a cell. Each gene determines and controls a specific characteristic or function of the cell. Genes are composed of DNA and are arranged linearly at definite positions on the chromosomes in the nucleus of each cell. Because genes are duplicated at the time of cell division, the characteristics for which they encode are heritable and are transmitted to future generations of cells.

Genetic effects of radiation: Effects arising from damage to genes in the germ cells of the mother or father, which are thus passed on to their children. The genetic effects of radiation will therefore not be seen in an irradiated individual but may occur in his or her offspring or in future generations.

Gray: SI unit of absorbed dose, equal to the energy transferred by ionizing radiation to a mass of matter corresponding to 1 J/kg (equals 100 rad).

HZE particles: Heavy (high-atomic-number) high-energy particles, such as carbon or iron nuclei, with an energy range in cosmic rays between approximately 10^2 to 10^3 MeV per nucleon.

In vitro study: Study carried out in individual cells grown in a flask or test tube in the laboratory.

In vivo study: Study carried out in a living organism.

Ionizing radiation: Radiation that is able to penetrate and deposit its energy at random within cells and tissues by ejecting electrons from atoms, thus "ionizing" them. Alpha and beta radiation and protons are examples of charged particles that can ionize. X rays, gamma rays, and neutrons are not charged, but they too may ionize.

Kinase: An enzyme that transfers a phosphate group to a substrate, such as the side chain of a protein (and in doing so changes the reactivity of the protein).

Latent period: The period of time between exposure and expression of a disease. After exposure to radiation, there may be a delay of several years (the minimum latent period) before any cancers are seen.

Linear dose response model: A dose response model that predicts a direct (linear) straight-line relationship between cause and effect over a wide range of doses. That is, for each increase in dose there would be a corresponding increase in the effect. For example, if 1 Gy caused cancer to develop in 5% of a group of animals in an experiment, then 2 Gy would lead to 10%, 3 Gy to 15%, and so on.

Linear energy transfer: Average amount of energy lost per unit of particle track length. *Low linear energy transfer (LET)* radiation is characterized by light charged particles such as electrons produced by x rays and gamma rays where the distance between ionizing events is large on the scale of a cellular nucleus. *High linear energy transfer (LET)* radiation is characterized by heavy charged particles such as alpha particles and heavy nuclei, where the distance between ionizing events is small on the scale of a cellular nucleus.

Linear-quadratic model: Also, linear-quadratic dose-effect relationship; expresses the effect (e.g., mutation or cancer) as partly proportional to the dose (linear term) and partly proportional to the square of the dose (quadratic term). The linear term predominates at lower doses, the quadratic term at higher doses.

Minisatellite regions: Regions of small repetitive DNA sequences. A hypervariable locus, also known as minisatellite DNA, consists of a block of tandem repeats of short "core" sequences. Core sequences range in size from 11 to 60 base pairs. The number of repeats varies among individuals and this variation is a basis for DNA fingerprinting.

Modal energy:	Energy of the maximum number of particles.
Monte Carlo calculation:	A statistical method that evaluates a probability distribution by means of random sampling.
Multiplicative interaction model:	A model in which the relative risk (the relative excess risk plus one) resulting from exposure to two risk factors is taken to be the product of the relative risks from the two factors taken separately.
Neoplasm:	Any new and abnormal growth, such as a tumor; neoplastic disease refers to any disease that forms tumors, whether malignant or benign.
Neoplastically transformed cells:	Tissue culture cells changed in vitro from growing in an orderly pattern and exhibiting contact inhibition to growing in a pattern more like that of cancer cells, due to the loss of contact inhibition.
Neutron:	Uncharged subatomic particle capable of producing ionization in matter by collision with charged particles.
Nonstochastic effect:	See *Deterministic effects*.
Nuclide:	A species of atom characterized by the constitution of its nucleus, which is specified by the atomic mass (M) and atomic number (Z).
Photon:	A unit of electromagnetic radiation. One gamma ray is a photon of electromagnetic radiation.
Polymerase chain reaction:	An enzymatic method used to amplify minute amounts of specific DNA sequences in order to analyze the sequences precisely.
Promoter:	An agent that is not by itself carcinogenic but that can amplify the effect of a true carcinogen by increasing the probability of late-stage cellular changes needed to complete the carcinogenic process.
Protraction:	The spreading out of a radiation dose over time by continuous or periodic delivery at a lower dose rate.
Quadratic dose response model:	A model that predicts that a biological effect continually increases out of proportion to an increase in dose. Effects at low doses would thus be relatively small.
Quality factor:	A LET-dependent factor, established by consensus, by which absorbed doses are multiplied to obtain for radiation-protection purposes the equivalent dose, a quantity that expresses the effectiveness of an absorbed dose on a common scale for types of ionizing radiation.
Rad:	Unit of absorbed dose of ionizing radiation, based on the amount of energy absorbed in a given mass of tissue; replaced by the Gray, an SI unit (equals 0.01 Gy or 100 erg/g).
Radiation weighting factor (W_R):	A factor, established by consensus and used in radiation protection, to weight the absorbed dose averaged over an organ to obtain the equivalent dose for the radiation quality of interest.
Radiation quality:	The radiation environment described in terms of the distribution of rays and particles and their energies or the distribution of LET.
Radiogenic:	Caused by radiation.
Radioisotope:	Radioactive species of an element with the same atomic number and identical chemical properties.

Radionuclide: Radioactive species of an atom characterized by the constituents of its nucleus (atomic number).

Radiosensitivity: Relative susceptibility of cells, tissues, organs, and organisms to the injurious action of radiation; radiosensitivity and its antonym, radioresistance, are used in a comparative sense rather than an absolute one.

Recessive gene disorder: Requires that a pair of mutant genes, one from each parent, be present in order for a disease to be manifested. Examples are cystic fibrosis and ataxia telangiectasia.

Relative biological effectiveness: Biological potency of one type of radiation compared with another that produces the same biological end point. It is numerically equal to the dose of gamma rays needed to produce a specific effect divided by the dose of particle radiation that produces the same effect. The reference radiation is often 200-keV x rays.

Relative risk: An expression of risk relative to the underlying (baseline) risk. If the relative risk is 2, the excess risk equals the baseline risk.

Rem: Unit of equivalent dose of ionizing radiation. The equivalent dose in rems is numerically equal to the absorbed dose in rads multiplied by the quality factor, the distribution factor, and any other necessary modifying factor. Replaced by Sievert in the SI system.

Repair processes: Metabolic processes within a cell that can repair radiation damage before it is expressed as a biological effect such as cell killing.

Risk coefficient: The increase in the incidence of disease or mortality per person exposed per unit equivalent dose: the relative-risk coefficient is the fractional increase in the baseline incidence or mortality rate for a unit dose.

Risk estimate: The number of cases (or deaths) that are projected to occur in a specified exposed population per unit of collective dose, for a specified exposure regime and expression period, e.g., number of cases per person-Gray.

SI units: The International System of Units as defined by the General Conference of Weights and Measures in 1960. These units are generally derived from the meter, kilogram, second, and SI-based units with special quantities for radiation including the Becquerel, Gray, and Sievert.

Sievert: SI unit of radiation equivalent dose, equal to dose in Grays times a quality factor times other modifying factors, for example, a distribution factor; 1 Sievert equals 100 rem.

Solar flare: A result of the explosive release of magnetic energy. Although solar flares were once thought to be the cause of solar particle events, coronal mass ejections are gaining favor as a key cause of solar particle events and certainly as a means of intensifying them.

Solar maximum: Period of maximum probability of emission of solar event radiation, including protons, alpha radiation, and electromagnetic energy.

Solar minimum: Period of minimum probability of emission of solar event radiation.

Solar particle event: A flux of energetic ions and/or electrons of solar origin. Solar particle events substantially increase radiation above the background level set by galactic cosmic rays. The protons in such events are usually of greatest concern, although electrons sometimes dominate and a smaller component of heavier ions (especially alpha particles—doubly ionized helium) is also present. Solar particle events are associated

with very energetic solar flares or fast coronal mass ejections. Such events, which accelerate particles, tend to cluster in the more active phases of the approximately 11-year solar cycle.

Somatic effects of radiation: Effects that occur in an irradiated individual due to damage produced in various tissues of the body, as opposed to genetic effects, which occur in the offspring of an irradiated individual owing to damage in germ cells. Potentially important somatic effects of radiation include induction of cancer and damage to the central nervous system. Cataract formation is also possible.

Specific energy: The actual energy per unit mass deposited per unit volume in a given event. This is a stochastic quantity as opposed to the average value over a large number of instances (i.e., the absorbed dose).

Stochastic: Random events leading to effects whose probability of occurrence in an exposed population of cells or individuals (rather than severity in an affected cell or individual) is a direct function of dose; these effects are commonly regarded as having no threshold. Hereditary effects are regarded as being stochastic; some somatic effects, especially carcinogenesis, are regarded as being stochastic.

Target theory (hit theory): A theory explaining some biological effects of radiation on the basis that ionization, which occurs in a discrete volume (the target) within a cell, directly causes a lesion that later results in a physiological response to the damage at that location; one, two, or more hits (ionizing events within the target) may be necessary to elicit the response.

Threshold hypothesis: The assumption that no radiation injury occurs below a specified dose.

Transport calculation: Calculation of particle distributions and energy behind a specific shield, derived from the basic nuclear cross sections for interactions and fragmentation in shielding.

Whole-body external dose: The dose of radiation from sources outside the body that irradiate the entire body. The dose from cosmic radiation is an example of a whole-body external dose.

x radiation: Also x rays; penetrating electromagnetic radiation, usually produced by bombarding a metallic target with fast electrons in a high vacuum.

Xeroderma pigmentosum: An inherited disease in which individuals are highly susceptible to cancer induced by exposure to solar radiation. Xeroderma pigmentosum cells have a defect in the ability to repair ultraviolet damage to their DNA, a defect that apparently accounts for the susceptibility.

C

Beam Sources

U.S. FACILITIES

Alternating Gradient Synchrotron, Brookhaven National Laboratory, Upton, New York

The Alternating Gradient Synchrotron (AGS) is a high-energy machine used for physics research: ^{1}H up to 30 GeV, heavy ions up to 10 GeV per nucleon. One beam line is available for NASA-sponsored research, when high-energy physics is not in progress. In 1995, 1 GeV/nucleon was available. The AGS delivers ^{56}Fe at 1-10 Gy/min, 100 hr of irradiation time (cost: ~ $350,000).

Booster Facility

This is a relatively small circular accelerator that injects pulses of heavy ions into the AGS. It is capable of sequentially delivering independent alternate pulses of different ions for two applications such as high-energy nuclear physics and radiation biology. Brookhaven proposed the construction of a separate beam line—the Brookhaven Applications Facility (BAF)—off the Booster, to be used for radiobiology and physical dosimetry of HZE particles. The proposal was reviewed and approved in 1991 by a panel with representatives from NASA and DOE. The proposed BAF would include a switching magnet and focusing magnets that could abstract ion pulses from their circular orbit into a to-be-constructed straight beam line and irradiation room suitable for biological applications and physical studies of energy loss and spallation products from HZE particles traversing shielding material. The BAF would supply reliable beam delivery, guaranteed by the need to maintain all the systems in good operating condition for the main mission of the facility (injection of AGS), and eventually of the Relativistic Heavy Ion Collider. A large variety of HZE particles can be produced ranging from maximum energies of 1.5 GeV/nucleon for ions lighter than iron, to ~ 1.25 GeV/nucleon for iron at ~ 70 Gy/min on 10 cm^2, and to ~ 350 MeV/nucleon for gold.

The construction cost is estimated to be $18.7 million, and the annual operating costs would be about $4 million for 2,000 hr/yr, in FY 96 dollars.

Other Facilities

Extensive animal and cell culture facilities exist in the Medical and Biology departments. Housing is available on the site.

National Superconducting Cyclotron Laboratory, Michigan State University, East Lansing, Michigan

The National Superconducting Cyclotron Laboratory is primarily a user facility for experimental physics research using protons and heavy nuclei at energies from ~ 0.2 GeV/nucleon for protons through O and decreasing to 0.07 GeV/nucleon for Fe. The facility is not set up for radiobiology and the energies are too low to be useful for many of the research strategies suggested in the main text of this report, but the facility could be used for some physics that would be of interest to NASA.

88-inch Cyclotron, Lawrence Berkeley National Laboratory, Berkeley, California

The 88-inch cyclotron is used primarily for physics research using protons and heavy ions up to Ne, at energies up to 0.3 GeV/nucleon. For heavier ions, the energy per nucleon decreases with increasing mass. Fundamental radiobiology experiments can be carried out at this site, but the energies are too low to be useful for many of the research strategies suggested in this report.

Proton Therapy Facility, Loma Linda University Medical Center, Loma Linda, California

The primary mission of the Loma Linda facility is cancer therapy, using protons with energies up to 250 MeV. Eight beam lines enter five shielded rooms. Three of the lines enter one room, where they are used for biological, physical, and engineering studies. The facilities are excellent and are currently used by NASA for up to 400 hr/yr, during the times that therapies are not in progress. This facility would be useful for experiments studying solar events, but not for those studying the effects of protons in the 1-GeV range.

LAMPF, Los Alamos National Laboratory, Los Alamos, New Mexico

Protons at 850-MeV are available in a parasitic mode from the LAMPF facility, which is used for physics research and radioisotope production. Although the energy range is useful, the radiobiology and animal facilities are not as extensive as those at Brookhaven National Laboratory, and LAMPF's long-term future as a research facility is not assured.

Northeast Proton Therapy Center, Massachusetts General Hospital, Boston, Massachusetts

The Northeast Proton Therapy Center facility is now under construction, with operation expected in 1998. A cyclotron will deliver 235-MeV protons to three treatment rooms (total budgeted cost, $46 million). There are no provisions, at present, for radiation biology.

Cyclotron, University of California at Davis, Davis, California

At the cyclotron at the University of California at Davis, 4- to 70-MeV protons may be used for radiobiology, but the research facilities and energies do not compare to those at Loma Linda.

Other Proton Facilities

Other U.S. facilities for physics research run at energies that overlap those described above but have not been adapted for radiation biology.

FACILITIES IN OTHER COUNTRIES

Heavy Ion Medical Accelerator, National Institute of Radiological Sciences, Chiba, Japan

The Heavy Ion Medical Accelerator (HIMAC) consists of a high-energy synchrotron that accelerates nuclei of He, C, Ne, Si, and Ar from 100 to 800 MeV/nucleon in three treatment rooms at dose rates up to 5 Gy/ min, and four experimental rooms, one of which is for radiation biology. The treatment rooms are used during the day, while the experimental rooms are used during the night.

Fe beams are not available at present but may be available in a few years.

Conventional radiation (x ray, gamma ray) sources and extensive animal and tissue culture facilities are readily available at HIMAC.

If Fe beams became available at this facility and appropriate agreements were developed, the HIMAC could present a viable option for NASA to acquire more of the beam time needed to perform the research recommended in the main text of this report. Such an approach would also require the establishment of appropriate animal colonies in Japan, collaborative efforts with a number of Japanese investigators, and numerous sojourns by U.S. investigators to help coordinate efforts.

SIS Accelerator, Institute for Heavy Ion Research (GSI), Darmstadt, Germany

The SIS accelerator provides many heavy ions, from Ne to Pb, with energies up to 1 GeV/nucleon. The major emphasis of the facility is physics research. GSI is heavily utilized by national and international research groups, and about 300 scientists and engineers are employed on site.

Biology investigators generally can utilize only parasitic beams, and the beam parameters are not usually under the control of biologists. As a result, in vitro experiments can be carried out, but it is very difficult to repeat any of the experiments. There are also significant political problems involved in carrying out animal experiments at this location. In the absence of significant policy changes at this institute, it is unlikely that NASA would be able to utilize it for any of the long-term, repetitious in vitro or animal experiments recommended in the main text of this report.

Other Proton Facilities

Proton accelerators in Canada and in Switzerland run at ~ 500 MeV for cancer therapy or isotope production. They are not seriously used for radiobiology and have no significant advantages over Loma Linda.

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Previous Advice of the National Research Council Regarding the BEVALAC Facility

The Space Studies Board and its Committee on Space Biology and Medicine addressed the following letter to Secretary of Energy James D. Watkins and NASA Administrator Daniel J. Goldin on August 20, 1992.

On May 14, 1992, the Committee on Space Biology and Medicine (CSBM) of the Space Studies Board (SSB) was briefed by the acting director of NASA's Life Sciences Division, Mr. Joseph K. Alexander, concerning various issues and activities in which the division is engaged. Among the issues raised was the impending decommissioning of the BEVALAC at the Lawrence Berkeley Laboratory as outlined in correspondence from Dr. David Hendrie, director of the Department of Energy's Division of Nuclear Physics. Subsequently, the CSBM discussed this issue with the Board at its meeting in Huntsville, Alabama, in June.

The Board and the CSBM are in agreement with a host of advisory committees' recommendations concerning the importance of gaining a better understanding of the biological effects of high Z element (HZE high-energy) particles.[1] Critical to planning for extended human sojourns in deep space is quantitative knowledge about the dose rates and types of radiation that will be encountered and the related biological effects.

The SSB and CSBM are concerned about the closing of the BEVALAC given that there is no alternative facility at which to continue the radiobiological research conducted as part of this country's goal of expanding the human presence in space. This facility is the only accelerator in the United States capable of producing the spectrum of energies required for research concerning the physical and biological effects of the heavy ions that will be encountered during deep-space missions. Providing adequate shielding against radiation and taking other measures to protect astronauts during deep-space travel are directly dependent on information derived from research concerning the biological effects of protons and HZE particles.

It is our understanding that even if funding for an alternative facility were provided today, there would be at least a five-year hiatus before suitable beams could become available. An interruption of the radiobiological research currently under way at the BEVALAC would have a number of deleterious effects on this well-established program that is a critical component of the national goal of human space exploration. Research teams that have been assembled to conduct this work would disperse and transfer to other areas of research. The flow of valuable long-term data derived from the BEVALAC studies would cease. Thus it would be necessary to start all over with new research animals, when another accelerator became available, in order to

[1]Attachments citing 14 supporting statements drawn from internal NASA and advisory documents and National Research Council reports accompanied the original correspondence; they are here appended to the letter.

obtain data from repeated, increasingly longer periods of exposure—a condition absolutely crucial to this type of research. Finally, losing this capability would seriously damage the research program of the recently established NASA Specialized Center for Research and Training (NSCORT) in Space Radiation Health at Lawrence Berkeley Laboratory and contribute to the loss of expertise in basic radiobiological research—an outcome that would be contrary to the conclusion reached in NASA's Space Radiation Health Program Plan.[2]

> There is an acute need for additional well-trained and well-qualified researchers in space radiation physics and biology. A continuous supply of trained space researchers needs to be developed and adequate numbers of trained personnel need to be available to enable program expansion. (p. 30)

Various heavy-ion facilities exist worldwide that could, theoretically, support the type of space-related research under way at Berkeley. However, the SSB and CSBM have no evidence that any of these facilities could be made available to support NASA's HZE radiation research program. The BNL Booster at Brookhaven National Laboratory has limited capability, and no beam time will be available until a new irradiation facility is built. The Darmstadt accelerator has provisions for cell research but not for animal research, and beam time at the facility is currently oversubscribed by a factor of two. The JINR at Dubna has obsolete equipment, low beam intensity, and beam contamination—significant limiting factors. The Synchrophasotron at Saclay has no provisions for conducting animal or cell research, and at least a year would be required to prepare the facility to provide iron beams. Beams generated at the facility at Geneva are beyond the energy range required by NASA researchers. Finally, the accelerator at Chiba is not yet in operation and will not produce iron ion particles.

Understanding that the NASA-sponsored research at the BEVALAC may be relatively minor in the context of the Department of Energy's (DOE) overall mission, the SSB and CSBM believe that the decision to decommission this facility should be considered in the context of the importance of the BEVALAC to the U.S. space program—one in which DOE plays an increasing role.[3] Until a suitable alternative can be provided that supports research related to long-term plans for human space exploration, the SSB and CSBM urge that the BEVALAC remain available to NASA researchers. Given the importance of the radiobiological research conducted at the BEVALAC and its fundamental role in realizing the national goal of human space exploration, the SSB and CSBM strongly recommend that DOE and NASA agree on a means for continuing without interruption the capability now provided by the BEVALAC.

Signed by
Louis J. Lanzerotti
Chair, Space Studies Board
and
Fred W. Turek
Chair, Committee on Space Biology and Medicine

Excerpts and Recommendations Concerning Biological Effects of Radiation Exposure

It is critical for NASA to formalize agreements to utilize one or more of the federal accelerator facilities, and to assure that those facilities remain in operation until necessary ground-based research is completed.

> —Aerospace Medicine Advisory Committee/NASA Advisory Council, *Strategic Considerations for Support of Humans in Space and Moon-Mars Exploration Missions, Life Sciences Research and Technology Programs.* 1992

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[2]Space Radiation Health Program Plan, Life Support Branch, Life Sciences Division, NASA, Washington, D.C., November 1991.
[3]National Space Policy Directive for Space Exploration Initiative Strategy, Section III, paragraphs *c* and *d*, March 13, 1992.

In order to protect crews, to the extent possible, from the various harmful effects of radiation, it is necessary to thoroughly characterize the radiation environment, understand the biological effects of HZE radiation and protons (leading to the establishment of appropriate risk levels and limits for radiation exposure), and accurately predict and provide warning of any increased levels of radiation.

—Discipline Working Group on Radiation Health and Environmental Health, NASA, *Space Radiation Health Program Plan.* 1991

Determining the long-term medical consequences of exposure to high Z element (HZE) particles present as a component of galactic cosmic radiation (GCR) is critical. The biological hazards associated with HZE particles, i.e., the "late effects," are not adequately known and may pose unacceptable long-term cancer risks. Exposure can result in life-threatening and life-shortening effects, such as cancer, and other detrimental consequences including cataract formation, mutagenesis, and other tissue damage.

—Aerospace Medicine Advisory Committee/NASA Advisory Council, *Strategic Considerations for Support of Humans in Space and Moon-Mars Exploration Missions, Life Sciences Research and Technology Programs.* 1992

NASA should make a commitment to support fundamental research on the biological effects of radiation. This support and commitment should take the form of expanding NASA's role in and funding for basic research and of contributing to the necessary facilities, such as the BEVALAC accelerator.

—Life Sciences Strategic Planning Committee, NASA, *Exploring the Living Universe—A Strategy for Space Life Sciences.* 1988

In summary, the highest priorities are for improved dosimetry and for studies of the effects of HZE particles so that the risks of both stochastic effects, such as carcinogenesis, and nonstochastic effects such as CNS damage, can be estimated with confidence.

—National Council on Radiation Protection and Measurements, *Guidance on Radiation Received in Space Activities.* 1989

One concern requiring further study in this area is the high-energy high-charge component of the cosmic ray flux, which can damage non-dividing cells, including those of the central nervous system.

—National Commission on Space, *Pioneering the Space Frontier.* 1986

The Space Exploration Initiative requires understanding and management of space radiation hazards. Uncertainties in these radiation effects on cells, tissue and small organisms could be reduced by simulations using the BEVALAC at the Berkeley Radiation Laboratory.

—Synthesis Group, NASA, *America at the Threshold.* 1991

Reports from the National Research Council

The availability of HZE particles for experimental radiation biology is extremely limited. The only feasible approach to obtaining the required information is to carry out controlled studies in adequate ground-based facilities.

—Radiobiological Advisory Panel/Space Science Board, *Radiobiological Factors in Manned Space Flight.* 1967

The availability of a ground-based accelerator capable of producing HZE particles now permits the design of precisely ordered experiments. Such experiments should be supported.

—Committee on Space Biology and Medicine/Space Science Board, *A Strategy for Space Biology and Medical Science for the 1980's and 1990's*. 1979

It is important to learn more about the relative biological effects of radiation influences, particularly high-Z galactic cosmic rays and solar flare electrons and their relationship to cancer and cataract induction in order to set meaningful guidelines for radiation protection. The question of appropriate shielding in flight is complex and requires further study.

—Committee on Human Exploration of Space/National Research Council, *Human Exploration of Space—A Review of NASA's 90-Day Study and Alternatives.* 1990

Terrestrial studies of the biological effects of low-level, high-LET irradiation on cell cultures and animals (using particle accelerators) should be expanded, with particular attention paid to the space radiation problem.

—Life Sciences Task Group, Space Studies Board, *Space Science in the Twenty-First Century—Imperatives for the Decades 1995 to 2015—Overview and Life Sciences.* 1988

Planning for extended human sojourns in space mandates that we have quantitative knowledge about the dose rates and the types of radiation that will be encountered. Similarly, the effects of the different types of radiation encountered in space, especially deep space, must be defined quantitatively. Much of the necessary radiobiology research can be carried out on Earth with defined radiation sources.

—Committee on Space Biology and Medicine/Space Studies Board, *Assessment of Programs in Space Biology and Medicine*. 1991

One way to maximize the return on investment in research is through various modes of cooperative research, with foreign partners, private concerns, and between federal agencies . . . . [An] example for collaboration between federal agencies [is] facilities supported by the Department of Energy such as the BEVALAC, which has the capability of providing for study of very high-Z particles and their biological effects.

—Space Studies Board, *Priorities in Space Life Sciences Research,* testimony by Space Studies Board Member Robert A. Moser to the House Budget Committee Task Force on Defense, Foreign Policy and Space, April 28, 1992

Improved measurements of cross sections and better modeling of heavy-ion interactions, particularly for the yield and spectra of neutrons and other secondary particles generated in the shielding material, are also required. NASA currently helps support the BEVALAC heavy-ion accelerator and some cross-section studies. However, the BEVALAC has been threatened with closure, thus endangering some of the enabling research on both cross-section measurements and the long-term biological effects of ionizing radiation.

—Committee on Human Exploration/Space Studies Board, *Scientific Prerequisites for the Human Exploration of Space*. 1993