Technical Evaluation of the NASA Model for Cancer Risk to Astronauts Due to Space Radiation

ISBN
978-0-309-25305-5

86 pages
8 1/2 x 11
PAPERBACK (2012)

Committee for Evaluation of Space Radiation Cancer Risk Model; National Research Council of the National Academies

Technical Evaluation of the NASA Model for Cancer Risk to Astronauts Due to Space Radiation

Committee for Evaluation of Space Radiation Cancer Risk Model

Space Studies Board

Division on Engineering and Physical Sciences

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS **500 Fifth Street, NW** **Washington, DC 20001**

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

Support for this project was provided by Contract NNH10CC48B between the National Academy of Sciences and the National Aeronautics and Space Administration. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the agency that provided support for the project.

International Standard Book Number-13: 978-0-309-25305-5
International Standard Book Number-10: 0-309-25305-5

Copies of this report are available free of charge from:

Space Studies Board
National Research Council
The Keck Center of the National Academies
500 Fifth Street, NW
Washington, DC 20001

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

Printed in the United States of America

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Charles M. Vest is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

OTHER RECENT REPORTS OF THE SPACE STUDIES BOARD

Assessment of Impediments to Interagency Collaboration on Space and Earth Science Missions (Space Studies Board [SSB], 2011)
Panel Reports—New Worlds, New Horizons in Astronomy and Astrophysics (Board on Physics and Astronomy [BPA] and SSB, 2011)
Recapturing a Future for Space Exploration: Life and Physical Sciences Research for a New Era (SSB, 2011)
Report of the Panel on Implementing Recommendations from the New Worlds, New Horizons Decadal Survey (BPA and SSB, 2011)
Sharing the Adventure with the Public—The Value and Excitement of "Grand Questions" of Space Science and Exploration: Summary of a Workshop (SSB, 2011)
Vision and Voyages for Planetary Science in the Decade 2013-2022 (SSB, 2011)

Capabilities for the Future: An Assessment of NASA Laboratories for Basic Research (Laboratory Assessments Board with SSB and the Aeronautics and Space Engineering Board [ASEB], 2010)
Controlling Cost Growth of NASA Earth and Space Science Missions (SSB, 2010)
Defending Planet Earth: Near-Earth-Object Surveys and Hazard Mitigation Strategies: Final Report (SSB with ASEB, 2010)
An Enabling Foundation for NASA's Space and Earth Science Missions (SSB, 2010)
Forging the Future of Space Science: The Next 50 Years (SSB, 2010)
Life and Physical Sciences Research for a New Era of Space Exploration: An Interim Report (SSB with ASEB, 2010)
New Worlds, New Horizons in Astronomy and Astrophysics (BPA and SSB, 2010)
Revitalizing NASA's Suborbital Program: Advancing Science, Driving Innovation, and Developing a Workforce (SSB, 2010)

America's Future in Space: Aligning the Civil Space Program with National Needs (SSB with ASEB, 2009)
Approaches to Future Space Cooperation and Competition in a Globalizing World: Summary of a Workshop (SSB with ASEB, 2009)
Assessment of Planetary Protection Requirements for Mars Sample Return Missions (SSB, 2009)
Near-Earth Object Surveys and Hazard Mitigation Strategies: Interim Report (SSB with ASEB, 2009)
A Performance Assessment of NASA's Heliophysics Program (SSB, 2009)
Radioisotope Power Systems: An Imperative for Maintaining U.S. Leadership in Space Exploration (SSB with ASEB, 2009)

Ensuring the Climate Record from the NPOESS and GOES-R Spacecraft: Elements of a Strategy to Recover Measurement Capabilities Lost in Program Restructuring (SSB, 2008)
Launching Science: Science Opportunities Provided by NASA's Constellation System (SSB with ASEB, 2008)
Opening New Frontiers in Space: Choices for the Next New Frontiers Announcement of Opportunity (SSB, 2008)
Science Opportunities Enabled by NASA's Constellation System: Interim Report (SSB with ASEB, 2008)
Severe Space Weather Events—Understanding Societal and Economic Impacts: A Workshop Report (SSB, 2008)
Space Science and the International Traffic in Arms Regulations: Summary of a Workshop (SSB, 2008)

Assessment of the NASA Astrobiology Institute (SSB, 2007)
An Astrobiology Strategy for the Exploration of Mars (SSB with the Board on Life Sciences [BLS], 2007)
Building a Better NASA Workforce: Meeting the Workforce Needs for the National Vision for Space Exploration (SSB with ASEB, 2007)
Decadal Science Strategy Surveys: Report of a Workshop (SSB, 2007)
Earth Science and Applications from Space: National Imperatives for the Next Decade and Beyond (SSB, 2007)
Exploring Organic Environments in the Solar System (SSB with the Board on Chemical Sciences and Technology, 2007)
Grading NASA's Solar System Exploration Program: A Midterm Review (SSB, 2007)
The Limits of Organic Life in Planetary Systems (SSB with BLS, 2007)
NASA's Beyond Einstein Program: An Architecture for Implementation (SSB with BPA, 2007)
Options to Ensure the Climate Record from the NPOESS and GOES-R Spacecraft: A Workshop Report (SSB, 2007)
A Performance Assessment of NASA's Astrophysics Program (SSB with BPA, 2007)
Portals to the Universe: The NASA Astronomy Science Centers (SSB, 2007)
The Scientific Context for Exploration of the Moon (SSB, 2007)

Limited copies of SSB reports are available free of charge from

Space Studies Board
National Research Council
The Keck Center of the National Academies
500 Fifth Street, N.W., Washington, DC 20001
(202) 334-3477/ssb@nas.edu
www.nationalacademies.org/ssb/ssb.html

COMMITTEE FOR EVALUATION OF SPACE RADIATION CANCER RISK MODEL

R. JULIAN PRESTON, U.S. Environmental Protection Agency, *Chair*
JOEL S. BEDFORD, Colorado State University
AMY BERRINGTON de GONZALEZ, National Cancer Institute
B. JOHN GARRICK, Garrick Consulting
DUDLEY T. GOODHEAD, Medical Research Council, United Kingdom (Emeritus)
BERNARD A. HARRIS, JR., Vesalius Ventures, Inc.
KATHRYN D. HELD, Massachusetts General Hospital
DAVID G. HOEL, Medical University of South Carolina
JACK R. JOKIPII, University of Arizona, Lunar and Planetary Laboratory
INSOO JUN, Jet Propulsion Laboratory, California Institute of Technology
CHARLES E. LAND, National Cancer Institute (retired)
HANS-GEORG MENZEL, CERN (retired)
PETER O'NEILL, University of Oxford

Staff

SANDRA J. GRAHAM, Senior Program Officer, *Study Director*
CATHERINE A. GRUBER, Editor
AMANDA R. THIBAULT, Research Associate
RODNEY HOWARD, Senior Program Assistant

MICHAEL H. MOLONEY, Director, Space Studies Board

Acknowledgment of Reviewers

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

Sally A. Amundson, Columbia University Medical Center,
John D. Boice, Jr., International Epidemiology Institute Ltd.,
Leslie A. Braby, Texas A&M University,
James E. Cleaver, University of California, San Francisco,
Howard D. Ozer, University of Illinois Cancer Center,
Jonathan M. Samet, University of Southern California, and
Ronald E. Turner, Analytic Services, Inc. (ANSER).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by John R. Ball, American Society for Clinical Pathology (retired). Appointed by the NRC, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Contents

Summary

At the request of NASA, the National Research Council's (NRC's) Committee for Evaluation of Space Radiation Cancer Risk Model[1] reviewed a number of changes that NASA proposes to make to its model for estimating the risk of radiation-induced cancer in astronauts. The NASA model in current use was last updated in 2005, and the proposed model would incorporate recent research directed at improving the quantification and understanding of the health risks posed by the space radiation environment. NASA's proposed model is defined by the 2011 NASA report *Space Radiation Cancer Risk Projections and Uncertainties—2010* (Cucinotta et al., 2011). The committee's evaluation is based primarily on this source, which is referred to hereafter as the 2011 NASA report, with mention of specific sections or tables cited more formally as Cucinotta et al. (2011).

The overall process for estimating cancer risks due to low linear energy transfer (LET)[2] radiation exposure has been fully described in reports by a number of organizations. They include, more recently:

- The "BEIR VII Phase 2" report from the NRC's Committee on Biological Effects of Ionizing Radiation (BEIR) (NRC, 2006);[3]
- *Studies of Radiation and Cancer* from the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2006),
- *The 2007 Recommendations of the International Commission on Radiological Protection (ICRP),* ICRP Publication 103 (ICRP, 2007); and
- The Environmental Protection Agency's (EPA's) report *EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population* (EPA, 2011).

The approaches described in the reports from all of these expert groups are quite similar. NASA's proposed space radiation cancer risk assessment model calculates, as its main output, age- and gender-specific risk of exposure-induced death (REID) for use in the estimation of mission and astronaut-specific cancer risk. The model also calculates the associated uncertainties in REID.

[1]Biographical information about the members of the committee is presented in Appendix B.

[2]See Appendix C, "Glossary and Acronyms," for definitions of terms and acronyms.

[3]The BEIR VII Phase 2 report is the most recent in a series of reports by NRC committees dealing with ionizing radiation; these are widely known as the BEIR reports.

The general approach for estimating risk and uncertainty in the proposed model is broadly similar to that used for the current (2005) NASA model and is based on recommendations by the National Council on Radiation Protection and Measurements (NCRP, 2000, 2006). However, NASA's proposed model has significant changes with respect to the following: the integration of new findings and methods into its components by taking into account newer epidemiological data and analyses, new radiobiological data indicating that quality factors differ for leukemia and solid cancers, an improved method for specifying quality factors in terms of radiation track structure concepts as opposed to the previous approach based on linear energy transfer, the development of a new solar particle event (SPE) model, and the updates to galactic cosmic ray (GCR) and shielding transport models. The newer epidemiological information includes updates to the cancer incidence rates from the life span study (LSS) of the Japanese atomic bomb survivors (Preston et al., 2007), transferred to the U.S. population and converted to cancer mortality rates from U.S. population statistics. In addition, the proposed model provides an alternative analysis applicable to lifetime never-smokers (NSs). Details of the uncertainty analysis in the model have also been updated and revised.

NASA's proposed model and associated uncertainties are complex in their formulation and as such require a very clear and precise set of descriptions. The committee found the 2011 NASA report challenging to review largely because of the lack of clarity in the model descriptions and derivation of the various parameters used. The committee requested some clarifications from NASA throughout its review and was able to resolve many, but not all, of the ambiguities in the written description.

PROPOSED MODEL—OVERALL CONCLUSION

In considering NASA's proposed model as a whole, the committee noted that the general approach to estimating cancer risks from exposure to low-LET radiation follows that utilized by ICRP, NCRP, EPA, and BEIR VII, and as such is state of the art. The specific data incorporated into NASA's proposed model are generally appropriate, with some exceptions, noted below, relating to new data that have become available since the development of the model or additional data sets that were already available and not selected for use by NASA. There remains a need for development of additional data to enhance the current approach and to reduce uncertainty in the model; specific needs have been identified by the committee. The committee has some concerns about specific model components, particularly related to the change to an "incidence-mortality" approach for calculating mortality and to the risk-transfer approach used by NASA. The question of the effectiveness of the combination of the several modules into the proposed integrated model was most appropriately answered by the committee's observing of a live demonstration by NASA of the application of the model for assessing risk to astronauts under some selected specific mission conditions. This demonstration showed that the model was indeed an integrated one—something that was not immediately apparent from the rather complex descriptions provided in the 2011 NASA report. The committee's overall evaluation is that NASA's proposed model represents a definite improvement over the current one. However, the committee urges that the necessary improvements identified in the specific recommendations provided below be incorporated before the proposed integrated model is implemented.

NASA's proposed model is composed of a number of components or modules that separately address highly distinct aspects of radiation risk and uncertainty. The committee assessed each of the individual components of the model as well as the integrated model as a whole. The key results of its evaluations are summarized below. Possible improvements to components of the model and to the integrated model are provided, together with recommendations for addressing gaps in the model. In some cases, specific research is identified that could help NASA address gaps and/or uncertainties in its proposed model for cancer risk projections. The specific research identified is not necessarily a comprehensive list but is intended to include efforts that would have a significant impact and at the same time would be feasible to undertake within the short to medium term (less than 5 years). The recommendations provided in this Summary address those areas for which the committee perceived more substantial gaps or issues. The model components are discussed in more detail in the main body of the report (see Chapter 2), which contains advice in addition to the major recommendations and conclusions. It is the integrated model that will actually be implemented by NASA, and so it is also assessed in detail in Chapter 2 of this report, particularly with regard to the integration methodology.

PROPOSED MODEL—ASSESSMENT OF COMPONENTS

Tissue-Specific Particle Spectra

The committee considers that the radiation environment and shielding transport models used in NASA's proposed model are a major step forward compared to previous models used. This is especially the case for the statistical solar particle event model. The current models have been developed by making extensive use of available data and rigorous mathematical analyses. The uncertainties conservatively allocated to the space physics parameters (i.e., environment and shielding transport models) are deemed to be adequate at this time, considering that the space physics uncertainty is only a minor contributor to the overall cancer risk assessment. Although further research in this area could reduce the uncertainty, the law of diminishing returns may prevail.

Given the above considerations, the committee does not recommend any specific research to improve the proposed model for tissue-specific particle spectra at this time. However, in this report the committee has identified several specific research areas that could improve the proposed environment models for tissue-specific particle spectra, including additional statistical analysis of the radial dependence of SPE intensity and solar-cycle dependence of SPE frequency and extreme events. The estimates could be further improved by adding physics-based studies of particle transport using the current picture of the heliosphere and its magnetic fields. Particle transport in the interplanetary medium is determined by its electric and magnetic fields. Theoretical and numerical studies of particle trajectories would certainly result in improved transport models and smaller uncertainties in the environmental estimates, but would involve a major effort and a change in modeling approach. NASA would need to weigh the added value of such an approach to its model outputs.

Cancer Risk Projection Model for Low-LET Exposures

Epidemiology Data

A major change proposed in NASA's model is to use the "incidence-mortality" approach used by BEIR VII (NRC, 2006) for the development of a REID. For this approach, risk coefficients from LSS cancer incidence models are converted into cancer mortality risks. A major reason for the use of the LSS cancer incidence data is that these are likely to be more accurate with respect to diagnosis than are mortality data, which suffer from misclassification of causes on death certificates. The approach results in considerable changes in the REID estimates, particularly in the pattern with age at exposure, and the committee considers this to be an improvement for site-specific cancer mortality estimation.

> **Recommendation:** Before NASA implements its proposed major change to the "incidence-mortality" approach, the committee recommends that NASA conduct more research into the specific patterns of the underlying epidemiological biases that drive these changes. The committee also highlights a specific problem with the method of estimating the mortality probability from the ratio of cancer mortality to incidence as developed by the BEIR VII report published by the National Research Council in 2006 and proposed for use by NASA. In response, the committee recommends that NASA consider alternative methods for improved estimation of mortality probabilities for each cancer site. For example, as presented in its 2011 report *EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population,* the Environmental Protection Agency has developed an alternative approach for breast cancer mortality estimation, and this could serve as a suitable approach to be applied by NASA.

Transfer of Cancer Risk Estimates from the Japanese to the U.S. Population

Because underlying cancer incidence rates for some cancer sites differ greatly between the Japanese and the U.S. populations, risk estimates based on an excess relative risk (ERR) model can give REID values very different from those based on an excess absolute risk (EAR) model. A number of organizations and committees (ICRP, the

National Council on Radiation Protection and Measurements [NCRP], BEIR VII) have recommended that a site-specific weighted average of the ERR and EAR models be used. The proposed NASA approach follows BEIR VII (NRC, 2006) in calculating a weighted average with uncertain weights and generally follows the recommended BEIR VII weights.

Recommendation: Because there are some deviations in NASA's proposed model from the weights recommended by BEIR VII for the excess relative risk and excess absolute risk models, the committee recommends that NASA provide additional justification for these alternative weights.

Dose and Dose Rate Effectiveness Factor

A dose and dose rate effectiveness factor (DDREF) value is applied, when appropriate, to reduce the LSS-based cancer risk coefficients for protracted exposures. A median value of 1.75 was selected by NASA for its proposed model, based on an assessment made by the National Institutes of Health (NIH) for a previous estimate and its uncertainty (NIH, 2003). For its proposed model, NASA assumed that the DDREF applies only to low-LET radiations and consequently that there is no dependence of space radiation risks on dose rate. Differences in risks between space radiation charged particles and gamma rays at low dose rate are encompassed entirely within the quality factor, QF, discussed below. A number of publications issued since the NIH report are relevant to this issue, and although these were discussed in the 2011 NASA report, they were not used by NASA in its choice of DDREF or in the associated uncertainty analysis. These studies include the Mayak workers study (Shilnikova et al., 2003), the third analysis of the United Kingdom's National Registry for Radiation Workers (Muirhead et al., 2009), and the 15-country nuclear workers study (Cardis et al., 2007), together with the review of these studies and comparison with the life span study by Jacob et al. (2009).

Conclusion: Although the proposed NASA approach for estimating a DDREF describes a number of limitations in these newer epidemiological studies and in the BEIR VII DDREF methodology, the justification given for preferring the older approach taken by the National Institutes of Health in 2003 is that it is close to the average of various recommended values of slightly less than 2. The use of this average value is somewhat problematic, given that the recommended values used to derive this average are not independent and thus applying equal weights to these is not justifiable.

Recommendation: The committee agrees with the use of an uncertainty approach for estimating DDREF, but it recommends that NASA use a central value and distribution that better accounts for the recent epidemiological and laboratory animal data.

Risk Models for Never-Smokers

The issue of the smoking status of astronauts and the potential implications for risk projections for smoking-related cancers are important, and it is appropriate that this should be investigated. Most astronauts are non-smokers, which would likely lower the risk projections for astronauts compared to estimates for the general population (a mix of never- and ever-smokers).

Recommendation: The proposed NASA approach for estimating lung cancer risks for astronauts who are never-smokers is limited and does not consider competing risks. Thus, the committee recommends that the NASA approach be developed further, given the important impact that it has on reducing estimated risk. The revised approach should use survival probabilities for competing risks that are specific to never-smokers. Further, the committee recommends that NASA make no changes at this time in the proposed model to include other smoking-related cancers. The data are not sufficiently robust for use in the modification of the REID estimate.

Uncertainties in Low-LET Cancer Risk Model and Overall Uncertainties in Cancer Risk Projections for High-LET Exposures

The 2011 NASA report addresses risk estimates and their uncertainties associated with exposure to low-LET radiation. Uncertainties are important because risk protection involves the use of safety factors, and NASA sets radiation permissible exposure limits (PELs) based on the 95 percent confidence limit that takes into account the uncertainties in risk projection models (NASA, 2005).

Uncertainty Limits and Methodology

Conclusion: Uncertainty limits on radiation-related risk reflect information about anticipated environmental radiation dose levels and accumulated knowledge about the relationship between radiation dose and cancer risk. For the approach used by NASA, more information, if available, might reduce statistical uncertainty and, assuming that the new information did not increase the central risk estimate, lower the upper 95 percent uncertainty bound criterion used by NASA to evaluate the acceptability of activity-related mortality risk.

Maximum Likelihood and Empirical Bayes Estimates

In the 2011 NASA report's description of the proposed model, the discussion of the use of a maximum likelihood estimate (MLE) and/or empirical Bayes (EB) estimate of site-specific ERR per sievert is ambiguous with respect to the specific approach that was used in specific instances. For example, the site-specific EB estimate of ERR per sievert for kidney cancer (0.40) would be similar to the MLE (also 0.40 for this particular organ site), with a lower estimated standard error (0.19) compared to the MLE standard error of 0.32.

Recommendation: On the assumption that the empirical Bayes approach has been used in NASA's proposed model, the committee recommends that the authors ensure that the off-diagonal covariance information has been taken into account. If the EB approach has not been used, either this fact should be stated in the text of the 2011 NASA report (Cucinotta et al., 2011) or the references to the EB approach should be removed from the text.

Uncertainty in the Value of the Quality Factor

The uncertainty analysis in NASA's proposed model reveals that the value of the quality factor (QF, as defined in NASA's proposed model) is the largest contributor to the uncertainty of REID, introducing about a 3.4-fold uncertainty in risk. Additional analysis by NASA (Cucinotta et al., 2011) using its proposed model finds that this component could be reduced to a 2.8-fold uncertainty if two of the track structure parameters were constrained to a fixed algebraic relationship to one another (such that the Z^{*2}/β^2 position of the maximum value of QF is held fixed). In this context, the committee notes that different values of QF are used for leukemia and solid cancers based on recent studies using animal tumor models.

Conclusion: According to NASA's proposed model, the observation that the use of a fixed relationship between two track structure parameters reduces the uncertainty is a potentially valuable finding that may provide a method to reduce uncertainty in estimations of the risk of exposure-induced death. However, little indication is given in the 2011 NASA report as to why such a fixed position might be justified or expected. The committee suggests that further investigations into the validity and usefulness of this approach would be worthwhile.

Radiation Quality and Track Structure Risk Cross Section

The main parameter used to specify radiation quality is Z^{*2}/β^2, where Z^* is the effective charge number of the particle and β its speed relative to the speed of light. Z^{*2}/β^2 replaces LET used in the conventional quality factor definition, and also by NASA in its current model. However, three additional empirical parameters (κ, Σ_0/α_γ, and m) are introduced to define the quality factor-risk relationships as a function of Z^{*2}/β^2. For NASA's proposed model, values for these parameters have been selected by comparison with experimentally observed variations in relative biological effectiveness (RBE) for different types of radiation for various cellular biological effects and for selected cancer types. While this approach is broadly appropriate for the proposed model parameters, the committee was unable to determine from the 2011 NASA report or from inquiries how the particular parameter values were selected.

Recommendation: The committee recommends that NASA make a detailed comparison of the relative biological effectiveness versus Z^{*2}/β^2 dependence of the experimental data with the proposed form and parameters of the quality factor, QF, equation in order to improve the transparency of the basis for the selection of the proposed parameter values for the model and to provide guidance for future research to test, validate, modify, and/or extend the parameterization. This analysis needs to include the defined selection of different values for parameters κ and Σ_0/α_γ for ions of $Z \leq 4$ compared to all ions of higher charge.

Conclusion: In the proposed model, different maximum values of quality factor, QF, are assumed for leukemia (maximum 10) and for solid tumors (maximum 40). This is a change from the current NASA risk model. The committee agrees that it is reasonable to make such a distinction on the basis of the limited animal and human data available.

Effective Dose

NASA's proposed model defines a quantity that is analogous to "effective dose" as defined by ICRP, but it uses different gender-specific sets of normalized tissue weighting factors (w_T) to match the estimated risks to the various tissues in representative space radiation environments. NASA proposes to use this as a summary quantity for mission operational purposes and, in NASA's proposed model, it is simply termed "effective dose." Effective dose is, strictly speaking, a quantity defined by ICRP that includes the ICRP-defined specification of numerical values for weighting factors and sex-averaging. If considerably different tissue weighting factors and radiation quality specifications are used and "effective dose" is evaluated without sex-averaging, it is problematic for the resulting quantity still to be termed "effective dose," and the unit sievert given to its numerical values.

The committee believes that the NASA description of the proposed model would be improved by the use of terminology and notation that distinguish NASA-defined quantities (especially the quantity termed "effective dose") from quantities defined by ICRP.

Other Issues

Non-Cancer Effects (Tissue Reactions)

In its proposed approach to estimating the safe days in deep space, NASA has used a 3 percent REID for fatal cancer as the limit. In its current model, NASA also considers dose limits for non-cancer effects—lens, skin, blood-forming organs, heart, and central nervous system. For example, "career limits for the heart are intended to limit the REID for heart disease to be below approximately 3 to 5 percent, and are expected to be largely age and sex independent" (NASA, 2005, p. 65). It was further assumed by NASA that the limits established would restrict mortality values for these non-cancer effects to less than the risk level for cancer mortality. The cancer and non-cancer risks were not combined into a single REID. More recent data have led ICRP to reconsider the threshold dose values particularly for the cardiovascular system (and cataracts) (see ICRP, 2011). It is concluded by ICRP

(2011) that a threshold absorbed dose of 0.5 Gy should be considered for cardiovascular disease (and cataracts) for acute and for fractionated/protracted exposures. It is appreciated by ICRP that these values have a degree of uncertainty associated with them.

Conclusion: The revised value for the threshold dose value proposed by ICRP suggests that NASA may need to consider how it might account for cardiovascular disease in its calculations of dose limits. However, it is noted that to date there exists very little of the information on relative biological effectiveness for non-cancer effects that is needed for estimates of risks posed by exposure to space radiation.

Delayed Effects

Delayed effects pertinent to the assessment of risk principally relate to observations whereby ongoing radiation-induced genomic instability is expressed, even at long times after radiation exposure. Such effects could have important implications for radiation protection in view of current notions of the multistep mutational processes involved in carcinogenesis. An early induced change in subsequent and ongoing mutation rates in irradiated somatic cells could accelerate this process.

Conclusion: There are conflicting reports on the generality of the phenomenon of radiation-induced delayed genomic instability and some question about variation in the susceptibilities of cells from different individuals with regard to this effect. Thus, the committee concludes that it is appropriate that genomic instability not be incorporated into NASA's proposed model, in agreement with the proposed NASA approach. However, the committee considers that further investigation of the phenomenon is certainly warranted.

Non-Targeted Effects

Non-targeted effects (NTEs) largely refer to the so-called bystander effects, by which responses can be produced in an unirradiated cell as a result of the transfer of a signal from an irradiated cell. For high atomic number and energy (HZE) radiations, doses that may be received by astronauts are very non-uniform in the sense that some cells will be traversed by the primary particle itself, whereas other cells will not be traversed; thus, an NTE is also a phenomenon that is of considerable interest.

Conclusion: Although the 2011 NASA report (Cucinotta et al., 2011) contains an extended discussion on non-targeted effects and their potential impact on risk estimates, NASA appropriately chose not to include these NTEs in its proposed model at this time. Little is known in qualitative or quantitative terms of the contribution of these NTEs directly related to radiation-induced carcinogenesis, but the committee believes that studies to elucidate any such relevance should be encouraged.

Qualitative Differences

It is recognized that there are qualitative differences in the nature of the initial energy depositions and hence in initial chemical, biochemical, and biological damages from different types of ionizing radiation. Differences are particularly great between low-LET gamma rays and the wide variety of high-LET heavy ions in space radiation. This may lead to observed differences in responses of cells, tissues, and organisms such as differences in spectra of mutations and chromosome aberrations, altered gene-expression patterns, and different spectra and latencies for carcinogenesis. There is some experimental evidence for qualitative differences at each of the above levels of biological effect. As a result, it may not be entirely appropriate to apply universal values for quality factors as quantitative scaling factors, based on empirical data such as RBE that assume similar underlying biological processes.

The committee notes that this is an area in which experiments quantifying types, frequencies, and latencies of various cancers—for example, lung, colon, and breast cancer, with further study of liver cancer and leukemia—are sorely needed for radiations of varying LET, especially for high-LET particles at low particle fluences such as

occur in space. Furthermore, the committee suggests that the tumor studies should be coupled with appropriate mechanistic investigations to provide an understanding of the underlying carcinogenic processes.

Probabilistic Risk Assessment

The committee notes that the risk projections discussed in NASA's proposed space radiation cancer risk assessment model and uncertainties are not presented or intended as being based on a probabilistic risk assessment (PRA) approach. NASA's proposed model is a health-effects model intended to provide estimates of cancer risk and uncertainties for defined space radiation exposure scenarios. More generally, however, the cancer risk to astronauts is dependent on much more than a defined scenario model of health effects, with engineered barriers, in the space radiation environment. Experience with full-scope PRAs of complex systems indicates the importance of accounting for the "what can go wrong during actual operations" scenarios, as such scenarios generally drive the overall risk. Thus, the committee suggests that comprehensive, mission-specific PRAs also be considered so as to enable accountability for the "what can go wrong" scenarios in the overall risk projections.

REFERENCES

Cardis, E., Vrijheid, M., Blettner, M., Gilbert, E., Hakama, M., Hill, C., Howe, G., Kaldor, J., Muirhead, C.R., Schubauer-Berigan, M., and Yoshimura, T., et al. 2007. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Estimates of Radiation-Related Cancer Risks. *Radiation Research* 167(4):396-416.

Cucinotta, F.A., Kim, M.-H.Y., and Chappell, L.J. 2011. *Space Radiation Cancer Risk Projections and Uncertainties—2010.* NASA/TP-2011-216155. NASA Johnson Space Center, Houston, Tex. July.

EPA (Environmental Protection Agency). 2011. *EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population.* U.S. Environmental Protection Agency, Washington, D.C.

ICRP (International Commission on Radiological Protection). 2007. *The 2007 Recommendations of the International Commission on Radiological Protection*. ICRP Publication 103. Ann ICRP 37 (2-4). International Commission on Radiological Protection, Ottawa, Ontario, Canada.

ICRP. 2011. Early and Late Effects of Radiation in Normal Tissues and Organs: Threshold Doses for Tissue Reactions in a Radiation Protection Context. Draft Report for Consultation. ICRP Ref 4844-6029-7736. International Commission on Radiological Protection, Ottawa, Ontario, Canada. January 20.

Jacob, P., Ruhm, W., Walsh, L., Blettner, M., Hammer, G., and Zeeb, H. 2009. Is cancer risk of radiation workers larger than expected? *Occupational and Environmental Medicine* 66:789-796.

Muirhead, C.R., O'Hagan, J.A., Haylock, R.G.E., Phillipson, M.A., Willcock, T., Berridge, G.L.C., and Zhang, W. 2009. Mortality and cancer incidence following occupational radiation exposure: Third analysis of the National Registry for Radiation Workers. *British Journal of Cancer* 100:206-212.

NASA (National Aeronautics and Space Administration). 2005. *NASA Space Flight Human System Standard, Volume 1: Crew Health.* NASA-STD-3001. (Approved 03-05-2007) NASA, Washington, D.C.

NCRP (National Council on Radiation Protection and Measurements). 2000. *Radiation Protection Guidance for Activities in Low-Earth Orbit.* NCRP Report No. 132. NCRP, Bethesda, Md.

NCRP. 2006. *Information Needed to Make Radiation Protection Recommendations for Space Missions Beyond Low-Earth Orbit*. NCRP Report No. 153. NCRP, Bethesda, Md.

NIH (National Institutes of Health). 2003. Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables. NIH Publication No. 03-5387. Bethesda, Md.

NRC (National Research Council). 2006. *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2.* The National Academies Press, Washington, D.C.

Preston, D.L., Ron, E., Tokuoka, S., Funamoto, S., Nishi N., Soda, M., Mabuchi, K., and Kodama, K. 2007. Solid cancer incidence in atomic bomb survivors: 1958-1998. *Radiation Research* 168:1-64.

Shilnikova, N.S., Preston, D.L., Ron, E., Gilbert, E.S., Vassilenko, E.K., Romanov, S.A., Kuznetsova, I.S., Sokolnikov, M.E., Okatenko, P.V., Kreslov, V.V., and Koshurnikova, N.A. 2003. Cancer mortality risk among workers at the Mayak Nuclear Complex. *Radiation Research* 159(6):787-798.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). 2006. *Studies of Radiation and Cancer.* Report to the General Assembly, with Scientific Annexes A and B. United Nations. New York.

1

Introduction

NASA's current missions to the International Space Station (ISS) and potential future exploration missions involving extended stays by astronauts on the lunar surface, as well as the possibility of near-Earth object (NEO) or Mars missions, present challenges in protecting astronauts from radiation risks. These risks arise from a number of sources, including solar particle events (SPEs), galactic cosmic rays (GCRs), secondary radiation from surface impacts, and even the nuclear isotope power sources transported with the astronauts. The serious early and late radiation health effects potentially posed by these exposures are equally varied, ranging from early signs of radiation sickness to cancer induction. Other possible effects include central nervous system damage, cataracts, cardiovascular damage, heritable effects, impaired wound healing, and infertility. Recent research, much of which has been sponsored by NASA, has focused on understanding and quantifying the radiation health risks posed by space radiation environments. Although many aspects of the space radiation environments are now relatively well characterized, important uncertainties still exist regarding biological effects and thus regarding the level and types of risks faced by astronauts. The career dose limits for radiation exposure to astronauts are based on cancer mortality risks, and so NASA's current (2005) model and the proposed model reviewed in this report have both been developed for estimating such risks. This report presents an evaluation of NASA's proposed space radiation cancer risk assessment model, which is described in a 2011 NASA report (Cucinotta et al., 2011). The evaluation in the present report considers the model components, input data (for the radiation types, estimated doses, and epidemiology), and the associated uncertainties.

GENERAL CANCER RISK ESTIMATION APPROACH

The overall process for estimating cancer risks due to low linear energy transfer (LET) radiation exposure has been fully described in reports by a number of organizations. They include, more recently:

- The "BEIR VII Phase 2" report from the NRC's Committee on Biological Effects of Ionizing Radiation (BEIR) (NRC, 2006);[1]
- *Studies of Radiation and Cancer* from the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2006),

[1]The BEIR VII Phase 2 report is the most recent in a series of reports by NRC committees dealing with ionizing radiation; these are widely known as the BEIR reports.

- *The 2007 Recommendations of the International Commission on Radiological Protection (ICRP),* ICRP Publication 103 (ICRP, 2007); and
- The Environmental Protection Agency's (EPA's) report *EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population* (EPA, 2011).

The processes described in all of these reports are similar. The estimation of human cancer and non-cancer effects at low doses (less than 100 millisievert [mSv]) is based on the epidemiological data from atomic bomb survivors together with selected data for occupational and medical exposures. There is a continued reliance on the assumption that, at these low doses, a given increment in dose produces a directly proportionate increase in the probability of the development of cancer or heritable effects that are attributable to the radiation. This relationship is described as the linear no-threshold (LNT) model. The ICRP, for example "considers that the adoption of the LNT model combined with a judged value of a dose and dose rate effectiveness factor (DDREF) provides a prudent basis for the practical purposes of radiological protection, i.e., the management of risks from low-dose radiation exposure" (ICRP, 2007, p. 51). This is an important position because the LNT hypothesis and some of the other assumptions behind the estimation of risks are based on models and projections and not on direct scientific observation.

The ICRP, UNSCEAR, and EPA have developed cancer risk estimates that include the risks for cancer incidence (as opposed to mortality) now that the cancer incidence data described above have become quite extensively available (UNSCEAR, 2006; Preston et al., 2007). Because incidence data allow for a more accurate diagnosis than do mortality data, the use of incidence data is preferred. For the purposes of radiation protection, the general approach used by the radiation protection community is to calculate sex-specific or sex-averaged detriment-adjusted nominal risk coefficients. The calculation of these nominal risk coefficients for cancer requires the estimation of nominal risks for different organs and tissues, and the adjustment of these for dose and dose rate effectiveness factor (DDREF), lethality, and quality of life to derive a set of site-specific values of relative detriment. The relative detriment values are used to calculate tissue weighting factors to allow for differences in the sensitivity of different tissues to tumor induction (ICRP, 2007). In addition, account needs to be taken of the relative biological effectiveness (RBE) of radiations of different LET values in the derivation of risk estimates. This is of particular importance in the case of exposures to astronauts when high-LET radiations are the major source of exposure. The topic is discussed comprehensively in ICRP Publication 92 (ICRP, 2003). The ICRP, again for example, uses the calculations of detriment-adjusted risk estimates to develop nominal probability coefficients for detriment-adjusted cancer risks of 5.5×10^{-2} Sv^{-1} for the whole population and 4.1×10^{-2} Sv^{-1} for adult workers (ICRP, 2007, pp. 53, 177-194). Of importance to the present discussion, these values are intended to be applied to the whole population and not to individuals (ICRP, 2007). Considerably more detail can be found in the reports themselves (NRC, 2006; UNSCEAR, 2006; ICRP, 2007; EPA, 2011). Thus, the intent is that this introductory chapter describe a generalized approach to risk estimation and to the development of nominal risk coefficients as a starting point for the specific discussions of NASA's proposed model, which is applicable to a specific subgroup of the population.

EVALUATING THE NASA MODEL

Updating of the Current Model

The basis for NASA's *current* model was NCRP (2000) Report No. 132. The risk estimation model applied in NCRP Report No. 132 was developed several years ago, and the approaches to uncertainty assessment and the underlying epidemiological and biological data incorporated into the model have advanced over the intervening period. NASA has therefore proposed updates to its space radiation cancer risk assessment model. The recent developments important for the NASA update include the following:

- The publication of BEIR VII (NRC, 2006), the UNSCEAR (2006) studies, ICRP (2007) Publication 103, and other reports in the scientific literature have introduced new assessments of human radioepidemiology data and DDREFs;

- New research results from the NASA Space Radiation Laboratory have begun to modify the understanding of radiation quality and dose-rate effects in animal and cellular systems; and
- NASA has a revised evaluation of uncertainty factors (Cucinotta and Durante, 2009)—Chapter 4 found at the NASA site for NASA Human Research Program (HRP) Evidence at http://humanresearchroadmap.nasa.gov/evidence/).

Further, NASA determined that, because its proposed model, described in the 2011 NASA report (Cucinotta et al., 2011), is used to project the cancer risk for current ISS crews and future explorations missions, it requires independent review and validation. Thus, the NRC's Committee for Evaluation of Space Radiation Cancer Risk Model (see Appendix B for biographical information) was established to review NASA's proposed space radiation cancer risk assessment model. Based on this recognized need, the statement of task for the committee is broadly as follows (see Appendix A for the full statement of task):

1. The committee will evaluate proposed updates to the NASA cancer projection model taking into consideration the following:

- Current knowledge of low-LET radiation cancer epidemiology,
- Effects of tissue weighting factors, radiation weighting factors, and DDREFs used in projecting risks, and
- Current uncertainties in quality factors, DDREFs, and organ dose assessment.

This will be done taking into consideration possible qualitative differences between low LET and heavy ion biological effects to determine if the use of quality factors are appropriate or inappropriate for GCR risk assessments.

2. The committee will identify gaps in NASA's current research strategy for reducing the uncertainties in cancer induction risks.

NASA's Proposed Model

In NASA's current (2005) model for projecting cancer risk for ISS crews and to support the assessments of risks and uncertainties associated with potential lunar, NEO, and Mars missions, NASA uses the overall approach recommended by the National Council on Radiation Protection and Measurements (NCRP) Report No. 132 (NCRP, 2000). Of note is the fact that the NCRP (2000) approach used cancer mortality data from life span study Report 12 (Pierce et al., 1996). The major cancer epidemiology input data for both the current and proposed NASA models are from the life span study, Report 13, on the effects of atomic bomb radiation, particularly cancer mortality (Preston et al., 2003). For its proposed model, NASA also developed an assessment of the uncertainty in the NCRP model risk coefficients that took into account errors in low-LET human radioepidemiology data, dose and dose rate effectiveness factors, radiation quality factors, and space physics. For astronaut occupational exposures, the 95 percent confidence level is used as a supplementary requirement as part of the permissible exposure limit (PEL) of a no greater than 3 percent increase in the risk of exposure-induced death (REID). REID is defined by ICRP (ICRP, 2007, p. 26) as "the difference in a cause-specific death rate for exposed and unexposed populations of a given sex and a given age at exposure, as an additional cause of death introduced into a population." However, for the NASA REID calculations, death is considered to be cancer death. The PEL standards are approved by the NASA Chief Health and Medical Officer. A detailed description of the NCRP model, developed in response to a request from NASA, can be found in NCRP (2000) Report No. 132, *Radiation Protection Guidance for Activities in Low-Earth Orbit,* and so only a brief summary is presented here.

NCRP (2000) Report No. 132 continues the earlier practice of taking into account both age at first exposure to radiation in space, and gender, for estimating risks and setting limits. This is necessary because of age and gender differences in cancer risks. New data for age and gender effects were taken into account compared to the earlier NCRP (1989) Report No. 98. The authors noted that because it was considered that risks to female and male astronauts should be equivalent, the exposure limits were adjusted appropriately, resulting in lower limits for females than males. NCRP (2000, p. 11) Report No. 132 concluded: "The new recommended career dose limits

for males and females of ages 25, 35, 45 and 55 at first exposure, based on a three percent career fatal cancer risk derived from the risks in Pierce et al. (1996) are reproduced in Table 1.3 [see Table 1.1 in the present report]. As noted earlier, the revised risk estimates on which these career dose limits are based have remained essentially the same for a decade now and further revisions, hopefully, should not be necessary." The values provided in Table 1.1 can be used to estimate the number of safe days in space, provided that information for specific mission conditions is included (e.g., space environment, shielding, age of astronaut). The proposed model has been used by NASA, for specific conditions, to estimate the number of safe days in space; these estimates are provided by NASA: see Table 6.9 in the 2011 NASA report (Cucinotta et al. 2011).

The basis for the career dose limits in NASA's current (2005) model and in NASA's proposed model requires some explanation because it is rather different from that used for estimating occupational dose limits for occupational exposures on Earth, although the outcome is, perhaps coincidentally, quite similar. On the one hand, using the NCRP recommendations in place in 2000 (NCRP, 1993), to limit a worker's occupational exposure to no more than 50 mSv y^{-1} in any one year, with a cumulative limit (age × 10 mSv) after age 18, results in an estimated average maximum lifetime risk of fatal cancer of approximately 3 percent (NCRP, 2000). On the other hand, for NASA's career dose limit estimate, the average lifetime risk of accidental death in occupations such as construction and agriculture is taken to be about 1.5 to 3 percent, and for significantly more dangerous occupations (e.g., test pilot) it is assessed at 10 percent or more. There are clearly some problems with using comparative risks as the basis for dose limits, particularly because there has been a very significant drop in death rates for many occupations in the United States in recent years (starting during the 1990s) (see the Bureau of Labor statistics website, http://www.bls.gov/iif/oshcfoi1.htm). NCRP (2000) Report No. 132 concluded that this was still a reasonable approach to take at the time. That report further concluded that "the choice of a three percent career excess risk of cancer mortality [made in NCRP (1989) Report No. 98] remains reasonable and justified" (NRCP, 2000, p. 13). It was also recognized that a number of uncertainties are associated with the estimates of cancer risk, and that to obtain the range on these estimates, it is necessary to establish the quantitative value of these uncertainties—an approach taken in NCRP (2000) Report No. 132. These same model uncertainties carry over to NASA's proposed model, reviewed in the present report.

The committee's review of NASA's proposed model considers each component of the revised approach and the model as a whole in the context of how it addresses its task of developing dose limits for astronauts conducting space explorations and thereby providing adequate protection against radiation-induced cancer. The model is composed of the following components: Space Radiation Environmental and Transport Models, Cancer Risk Projections for Low-LET Radiation, Uncertainties in Low-LET Risk Model Factors, Cancer Risks and Radiation Quality, and Revised NASA Risk Projections for Cancer Risks and Uncertainties. In addition, as requested by NASA in the statement of task presented above in this chapter, the committee has considered what it views as gaps in the NASA approach and has recommended research that could address these gaps.

TABLE 1.1 Ten-Year Career Limits Based on Three Percent Excess Lifetime Risk of Fatal Cancer

	E (Sv)	
Age at Exposure (y)	Female	Male
25	0.4	0.7
35	0.6	1.0
45	0.9	1.5
55	1.7	3.0

NOTE: Limits are expressed in effective dose (E). A 3 percent excess lifetime risk of cancer mortality has additional components associated with it: namely, the risk of heritable effects (0.6 percent) and of nonfatal cancer (also 0.6 percent) for a total detriment of 4.2 percent. These nominal risks are given in ICRP (1991) and NCRP (1993).

SOURCE: Table 1.3 in National Council on Radiation Protection and Measurements (NCRP), *Radiation Protection Guidance for Activities in Low-Earth Orbit,* NCRP Report No. 132, NCRP, Bethesda, Md., December 31, 2001, reprinted with permission of the National Council on Radiation Protection and Measurements, http://NCRPpublications.org. Based on data from D.A. Pierce, Y. Shimizu, D.L. Preston, M. Vaeth, and K. Mabuchi, Studies of the mortality of atomic bomb survivors, Report 12, Part I. Cancer: 1950-1990, *Radiation Research* 146(1):1-27, 1996.

APPROACH TO THE COMMITTEE'S EVALUATION

The committee held three closely spaced meetings during the course of the study and communicated continuously between meetings by way of telephone conferences and e-mail exchanges. In briefings to the committee, representatives of NASA's operations support and research staff provided details of the space operations for which NASA's proposed space radiation cancer risk assessment model, under review, was developed, together with an extended description of the model itself. From research scientists currently funded by NASA, the committee heard summaries of research pertinent to cancer risks in the space environment. This research was based on cellular and laboratory animal studies. The committee used the 2011 NASA report *Space Radiation Cancer Risk Projections and Uncertainties—2010* (Cucinotta et al., 2011) as its primary source in understanding the content of NASA's proposed model. That report was originally provided to the committee by NASA in draft form and then, at the request of the committee, in a published form that could be referenced following the second committee meeting. In order to gain a better understanding of the content of the 2011 NASA report and the details of NASA's proposed model, the committee posed numerous clarification questions to NASA during and between meetings. The questions were intended to help the committee understand both the content of NASA's proposed model and the supporting scientific data behind the model. Although the expedited schedule of the study precluded the committee from indefinitely continuing an iterative process of questioning, answers were provided by NASA that in most cases offered sufficient clarification for purposes of the committee's review. However, the 2011 NASA report (Cucinotta et al. 2011) will continue to serve in the future as the principal source of explanation of and justification for the proposed model. Therefore, in addition to a discussion of possible improvements to NASA's proposed model itself, the committee has included numerous suggestions in this report for additions and improvements to the 2011 NASA report that describes the proposed model.

As noted throughout this report, the committee also relied heavily on an extensive list of pertinent reference resources in the form of journal publications and past reports produced by groups such as the National Council on Radiation Protection and Measurements and the National Research Council. Of these, the committee paid particular attention to those reports that provided the basis for approaches utilized in NASA's proposed model, and which were incorporated by reference into the 2011 NASA report describing the proposed model.

REFERENCES

Cucinotta, F.S., and Durante, M. 2009. Risk of radiation carcinogenesis. Chapter 4 in *NASA Human Health and Performance Risks of Space Exploration Missions* (J.C. McPhee and J.B. Charles, eds.). NASA Johnson Space Center, Houston, Tex.

Cucinotta, F.A., Kim, M.-H.Y., and Chappell, L.J. 2011. *Space Radiation Cancer Risk Projections and Uncertainties—2010.* NASA/TP-2011-216155. NASA Johnson Space Center, Houston, Tex. July.

EPA (Environmental Protection Agency). 2011. Radiogenic Cancer Risk Models and Projections for the U.S. Population. EPA, Washington, D.C.

ICRP (International Commission on Radiological Protection). 1991. *1990 Recommendations of the ICRP.* ICRP Publication 60. Pergamon Press, Elsevier Science, Oxford, U.K.

ICRP. 2003. *Relative Biological Effectiveness, Quality Factor, and Radiation Weighting Factor.* ICRP Publication 92. Pergamon Press, Elsevier Science, Oxford, U.K.

ICRP. 2007. *The 2007 Recommendations of the International Commission on Radiological Protection.* ICRP Publication 103. Pergamon Press, Elsevier Science, Oxford, U.K.

NASA (National Aeronautics and Space Administration). 2005. *NASA Space Flight Human System Standard. Volume 1: Crew Health.* NASA Technical Standard NASA-STD-3001 (Approved 03-05-2007). NASA, Washington, D.C.

NCRP (National Council on Radiation Protection and Measurements). 1989. *Guidance on Radiation Received in Space Activities.* Report No. 98. Bethesda, Md.

NCRP. 1993. *Risk Estimates for Radiation Protection.* Report No. 115. Bethesda, Md.

NCRP. 2000. *Radiation Protection Guidance for Activities in Low-Earth Orbit.* Report No. 132. Bethesda, Md.

NRC (National Research Council). 2006. *Health Risks from Exposure to Low Levels of Ionizing Radiation, BEIR VII Phase 2.* The National Academies Press, Washington, D.C.

Pierce, D.A., Shimizu, Y., Preston, D.L., Vaeth, M., and Mabuchi, K. 1996. Studies of the mortality of atomic bomb survivors, Report 12, Part I. Cancer: 1950-1990. *Radiation Research* 146(1):1-27.

Preston, D.L., Shimizu, Y., Pierce, D.A., Suyama, A., and Mabuchi, K. 2003. Studies of the mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiation Research* 160(4):381-407.

Preston, D.L., Ron, E., Tokuoka, S., Funamoto, S., Nishi N., Soda, M., Mabuchi, K., and Kodama, K. 2007. Solid cancer incidence in atomic bomb survivors: 1958-1998. *Radiation Research,* 168:1-64.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). 2006. *Studies of Radiation and Cancer.* Report to the General Assembly, with Scientific Annexes A and B. United Nations, New York.

2

Review of NASA Model

INTRODUCTION

NASA's proposed space radiation cancer risk assessment model for radiation-induced cancer in astronauts is described in the 2011 NASA report *Space Radiation Cancer Risk Projections and Uncertainties—2010* (Cucinotta et al., 2011). That 2011 NASA report, as it is called hereafter, is divided into discussions of the various components of the proposed model, including the discussion of the key data sets that either were used to develop the component or are intended as inputs to calculations made by the model. It should be noted that the components of the proposed model are not, in every case, described in the 2011 NASA report. Instead they are incorporated by reference to earlier reports, such as the "BEIR VII Phase 2" report from the National Research Council's (NRC's) Committee on Biological Effects of Ionizing Radiation (BEIR) (NRC, 2006) and NCRP Report No. 132, *Radiation Protection Guidance for Activities in Low-Earth Orbit* (NCRP, 2000).

This chapter closely follows the organization of the 2011 NASA report (Cucinotta et al., 2011), with each of the individual model components first reviewed separately below, followed by a review of the integrated model in the chapter's final text section entitled "Integration and Completeness of the Model." This review of the integrated model summarizes the present report's major conclusions and recommendations regarding the model, including those pertaining to the individual components discussed in the chapter. When recommending research that could help improve future versions of the model, the committee primarily considered research that could feasibly be carried out in the next 5 years, since the NASA model is generally updated every 5 years. While suggestions appear throughout the discussions in the report, the most important recommendations and conclusions are highlighted in bold in the text, and the majority of these appear in the final section of this chapter. This report does not attempt to duplicate the extensive background and descriptive material contained in the 2011 NASA report, but rather it refers the reader, as appropriate, either to specific sections of the NASA report or to the prior reports incorporated by NASA's proposed model.

SPACE RADIATION ENVIRONMENTS AND TRANSPORT MODELS

The assessment of cancer risk due to space radiation begins with defining the external (or ambient) radiation environments. Data describing these environments are inputs to transport calculations to obtain the local radiation environment, modified by spacecraft and body shielding, at tissues of concern. Galactic cosmic rays (GCRs)

and particles from solar particle events (SPEs) are two major components[1] of the space radiation environment that pose radiation risk to astronauts during space missions away from the protective zone of Earth's magnetic field. The GCR and SPE environments in the solar system have a strong correlation with the approximately 11-year solar cycle.

Galactic Cosmic Rays

Overview

Note that much of the material in this Overview section is contained in *Heliophysics—Evolving Solar Activity and the Climates of Space and Earth,* in the chapter by J.R. Jokipii (2010).[2]

Galactic cosmic rays constitute a major part of the space radiation environment near Earth. GCRs are very energetic charged particles (electrons and atomic nuclei) that are believed to be accelerated by vast, spheroidal blast waves from supernova explosions that propagate in the interstellar gas. The accelerated cosmic rays enter the heliosphere on their way to the inner solar system and Earth. In the process they are changed, and so understanding their transport is essential to understanding the space radiation environment.

The heliosphere is a vast spheroidal cavity in the local interstellar plasma, some 150 to 200 astronomical units (AU) in size, created by a supersonic, radial flow of plasma, called the solar wind, that flows outward from the Sun. The spatial scale of the heliosphere is determined by both the Sun and the back pressure of the surrounding interstellar plasma and magnetic field. Far from the Sun, the outward-flowing solar wind is spread over such a large volume that it can no longer continue out into the surrounding interstellar plasma. Because the wind is flowing supersonically (faster than waves can propagate), the supersonic flow ends at a spheroidal shock wave, which is called the heliospheric termination shock, where the flow changes suddenly to a subsonic (slower than the wave speed) outward flow.

The interstellar plasma is moving at about 26 km/sec relative to the heliosphere, pushing it in on one side. Beyond the termination shock, the solar plasma continues to flow outward, but it is deflected and eventually turns to flow in the same direction as the interstellar plasma, forming a large, trailing, heliospheric tail. The interstellar medium also contains neutral atoms, and these also play a role in the interaction of the heliosphere with the interstellar medium, although the effects are small and may be neglected.

Energetic particles including cosmic rays pervade the heliosphere, as they do all regions of low-enough density in the universe. The energetic particles are in four basic types: galactic cosmic rays, anomalous cosmic rays, interplanetary energetic particles, and solar energetic particles. This discussion concentrates primarily on galactic cosmic rays. They come from the galaxy, where they are thought to be accelerated by supernova blast waves. They envelop the heliosphere with a very nearly constant, isotropic bath. The particles are then partially excluded from the inner parts of the heliosphere. Therefore, their intensity reflects the varying properties of the heliosphere. GCRs have a typical energy of 1 GeV and are present continuously, but fluctuate on a variety of timescales. Solar cosmic rays are produced sporadically by the Sun, at considerably lower energies than those of the galactic particles (see Figure 2.1). Their spectrum is also a much more rapidly decreasing function of energy. The time-averaged intensity of these two types of cosmic rays, as a function of energy, is illustrated in Figure 2.1, where the solar particles are a solar-cycle average. The average spectrum over time is therefore dominated by the GCRs, although for short periods (hours to days) the solar particles can be quite intense.

The intensity of GCRs in the inner solar system is observed to vary with time over a wide variety of timescales. The time variations of galactic particles are due to variations in the solar wind and its entrained magnetic field, which are accessible to direct measurement. There exists a generally accepted physical model that can account quantitatively for these modulations.

---

[1]Trapped-particle models are not covered here because they contribute very little to the organ dose for missions aboard the International Space Station or missions to the Moon or to Mars.

[2]J.R. Jokipii, The heliosphere and cosmic rays, Chapter 9 in *Heliophysics—Evolving Solar Activity and the Climates of Space and Earth* (C.J. Schrijver and G.L. Siscoe, eds.), Cambridge University Press, New York, 2010. Copyright © 2010 Cambridge University Press. Used with permission.

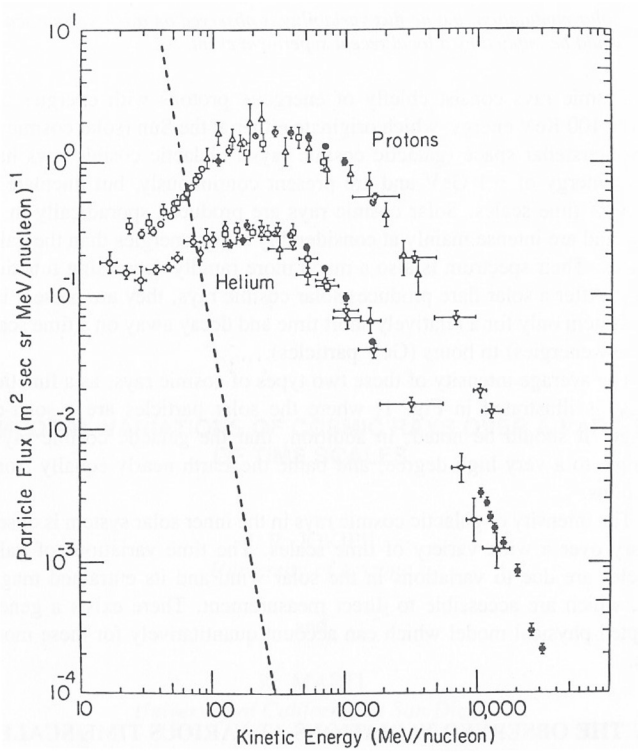

FIGURE 2.1 The observed intensity of cosmic rays at Earth orbit at quiet times. Shown are galactic cosmic-ray protons and helium. The dashed line is a time average of solar energetic particles. SOURCE: J.R. Jokipii, The heliosphere and cosmic rays, Chapter 9 in *Heliophysics—Evolving Solar Activity and the Climates of Space and Earth* (C.J. Schrijver and G.L. Siscoe, eds.), Cambridge University Press, New York, 2010. Copyright © 2010 Cambridge University Press. Reprinted with permission.

It is reasonably certain that cosmic-ray variations on timescales of less than about 50,000 years must be caused by changes in the heliosphere resulting from changes in the Sun. Interstellar variations over longer time periods can be caused either by the motion of the solar system through the interstellar medium or by transient changes in the interstellar cosmic-ray intensity caused by changes in local interstellar conditions such as by a supernova blast wave. In addition, the heliospheric structure, and hence its effects on cosmic rays, can be affected by changes in the interstellar medium caused by, for example, interstellar clouds.

The largest observed periodic variation is the variation of GCRs in anti-phase with the 11-year sunspot cycle. The variation of the GCR intensity over the past five sunspot cycles is illustrated in Figure 2.2. Note the very obvious 11-year cyclic variation and the alternating shapes of successive cosmic-ray maxima. At this time it is not completely understood how solar activity changes the interplanetary medium to produce the observed temporal variations. There are four principal elements:

1. Co-rotating, high-speed streams produce nearly periodic variations at the solar rotation period of approximately 27 days.
2. Coronal mass ejections (CMEs) and high-speed solar wind streams combine to produce large-scale, long-lived structures (known as global merged interaction regions, or GMIRs) of enhanced magnetic field that propagate out to the termination shock and into the heliosheath. There is a strong correlation between the rate of CMEs and sunspot numbers that have been observed over periods of high and low solar activity. From this one may conclude that the almost 400 years of sunspot observations provide a useful tool for studying the levels of solar activity over that time.

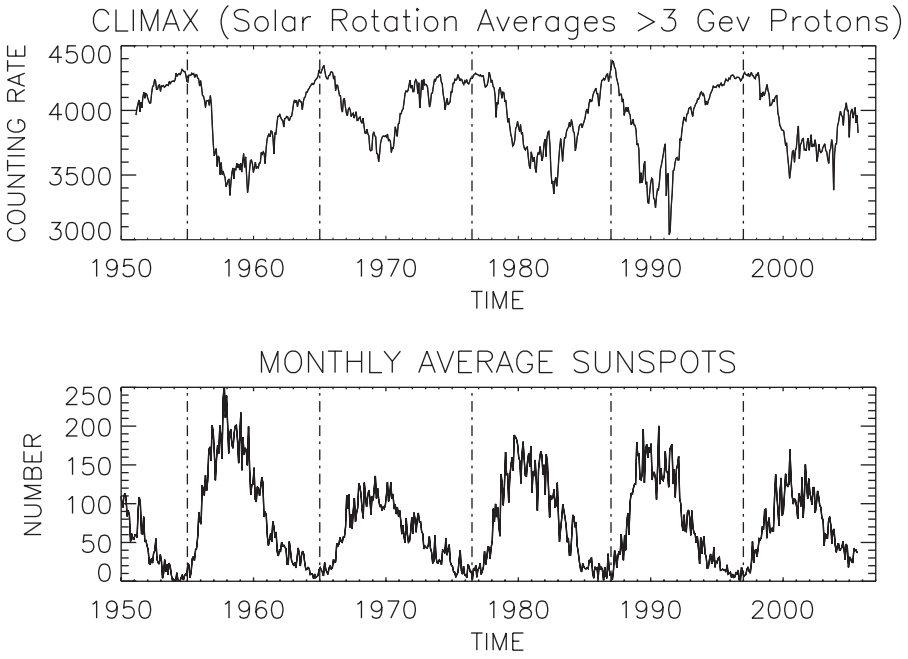

FIGURE 2.2 The modulation of galactic cosmic rays during five sunspot cycles. Top: The intensity of cosmic rays as measured by the Climax neutron monitor as a function of time since 1951. Bottom: The sunspot index as a function of time since 1950. Note the alternation of the cosmic-ray maxima between sharply peaked and more-rounded shapes. This corresponds to the change in the direction of the solar magnetic field. SOURCE: J.R. Jokipii, The heliosphere and cosmic rays, Chapter 9 in *Heliophysics—Evolving Solar Activity and the Climates of Space and Earth* (C.J. Schrijver and G.L. Siscoe, eds.), Cambridge University Press, New York, 2010. Copyright © 2010 Cambridge University Press. Reprinted with permission.

3. Changes in magnitude of the heliospheric magnetic field (HMF) occur over many scales (see Section 9.2 of Jokipii, 2010). The gyroradii of cosmic rays are inversely dependent on the strength of the HMF, and this, together with the observed turbulence of interplanetary plasma, produces changes in the cosmic-ray diffusion coefficients that are approximately inversely proportional to the magnetic field magnitude B (see Section 9.4 of Jokipii, 2010).

4. The changing inclination of the heliospheric current sheet that changes from a nearly flat configuration in the equatorial plane at solar minimum to a 90° inclination at solar maximum and then with decreasing solar activity returns to its near equatorial position at the next solar minimum (see Figure 14 of Jokipii, 2010). This is associated with a change in magnetic polarity, leading to a 22-year solar magnetic cycle.

Review of the NASA GCR Model

The GCR model used in NASA's proposed model (see Cucinotta et al., 2011) is based on Badhwar-O'Neill (O'Neill, 2006). The model uses a simplified version of the currently well established paradigm of the effects of the heliosphere GCRs. Since the GCRs come from the interstellar medium, this complete model is quite complicated and detailed, involving the spatial and temporal variations of the solar wind, its entrained magnetic field, and the boundary conditions at the interface, which is at a distance from the Sun of some 130 AU. The outer parts of this model are still being debated. However, the basic picture for the inner heliosphere (out to several astronomical units) seems to be well grounded.

The simplified GCR model being used in NASA's proposed model is often used by scientists in the field to categorize the observations of GCRs. The modulation at Earth as a function of time is represented by one parameter, Φ, called the modulation parameter. For convenience, it is expressed as an energy. This parameter, of course, is a

quite crude representation of the complicated physical situation, but it can be shown to account reasonably well for observations.

The observational data seem to be consistent and generally accepted. Research on how to incorporate more of the physics, such as the 22-year magnetic cycle, into the cancer risk assessment model would make the estimates of risk more accurate. It is not clear at this point, however, whether the extra effort, which would indeed make the uncertainties less, would make enough difference to reduce the overall risks significantly. It would, however, make the sources of uncertainty more certain. Also, incorporating the new understanding resulting from the recent (2009-2011) historically deep solar minimum will certainly decrease the uncertainties, but, again, it is not clear that the improvement is enough to warrant the effort. The primary uncertainty in the GCR environment calculation comes from a lack of understanding of the physical conditions of transport and the use of statistically based models. The committee also points out that the differences in the GCR intensity at Mars relative to Earth are less than other uncertainties, and so using Earth-based models to address doses at Mars introduces very little uncertainty. Having just passed through an unexpected historically deep solar minimum, it is clear that environmental uncertainties increase with time over years to decades.

The recent incorporation of the CREME96 (Tylka et al., 1997) and Nymmick (Nymmick et al., 1996) models adds more complication, but basically tweaks the Badhwar-O'Neill model to try to make more physical the variation of the modulation parameter Φ. However, there is no simple parameterization of the current models that yields the 22-year effects except in an ad hoc manner. The NASA GCR model could be improved by incorporating the 22-year-cycle variation.

Solar Particle Events

Overview

"Solar energetic particle" (SEP) and "solar particle event" (SPE) are names for a very energetic process and for the potentially damaging situation that occurs when very strong magnetic fields in the solar photosphere reach a critical instability. These are also called solar proton events as protons are the most abundant (>90 percent) species in SPEs. There are also substantial radio bursts, X-ray and gamma-ray emissions accompanying SPEs. A schematic illustrating the timescales for the different emissions from solar events is presented in Figure 2.3 (the 27-day period is the approximate rotation rate of the Sun as seen from Earth). SPEs are typically divided into two classes: (1) gradual events, which are typically the largest events and are associated with coronal mass ejection shocks and typically last for several days; and (2) impulsive events (often called solar flares), which are short, longitudinally localized events on the solar surface. There are usually fewer than 10 gradual events a year. The particle abundances in these events are similar to the composition of the solar corona. They have sharp rise times and decay slowly over hours to days and cover a large longitudinal extent. The impulsive events, associated with instabilities in the solar atmosphere, are rich in heavy ions and show a sharp peak in X rays and gamma rays. These two types of events are illustrated in Figure 2.4. SPEs are stochastic in nature. Their characteristics—composition, intensity, energy spectra, and temporal profile—are highly variable. Typical SPEs are known to pose a small health risk to astronauts and can be effectively attenuated by using relatively thin shield materials, although they can influence mission planning or interfere with mission activities such as extravehicular activities (EVAs). However, large SPEs can be lethal, although they are rare.

The intensity and number of very large solar events (CMEs) vary dramatically from solar cycle to solar cycle. The lack of correlation between sunspots and SPEs illustrates the difficulty in reliably predicting the level or frequency of activity for the future. One fact is clear, however: SPEs occur far more frequently during solar maximum (Figure 2.5). The energy spectra vary significantly from event to event, as illustrated in Figure 2.6. The energy spectrum of an SPE is an important consideration for accurate radiation risk assessment, but it is also not predictable at the present time. Feynman and Gabriel (1988) assume a radial dependence of r^{-3} for the flux inside 1 AU and a radial dependence of r^{-2} outside 1 AU. This implies that the fluence and dose will be trajectory-dependent for interplanetary missions such as exploration missions to near-Earth objects or to Mars. However, the validity of this scaling law is in question, because there are very few simultaneous measurements of SPEs at Earth and at

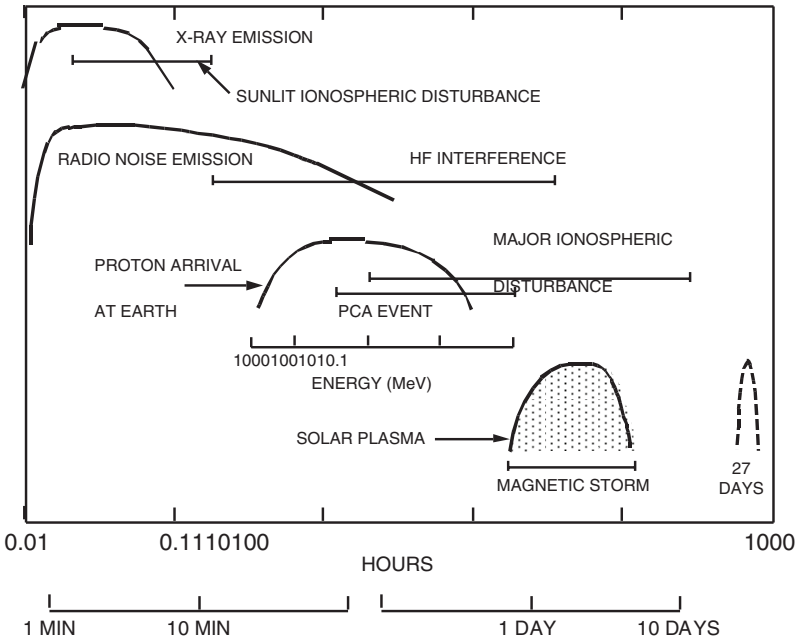

FIGURE 2.3 Schematic plot of the relative variations in time of the amplitudes of the X-ray, radio noise, high-energy particle, and solar plasma fluxes for a "typical" large solar flare. NOTE: HF, high frequency; PCA, polar cap absorption. SOURCE: Reprinted from M.A. Shea and D.F. Smart, History of solar proton event observations, *Nuclear Physics B* (Proc. Suppl.) 39A: 16-25, 1995. Copyright 1996, with permission from Elsevier.

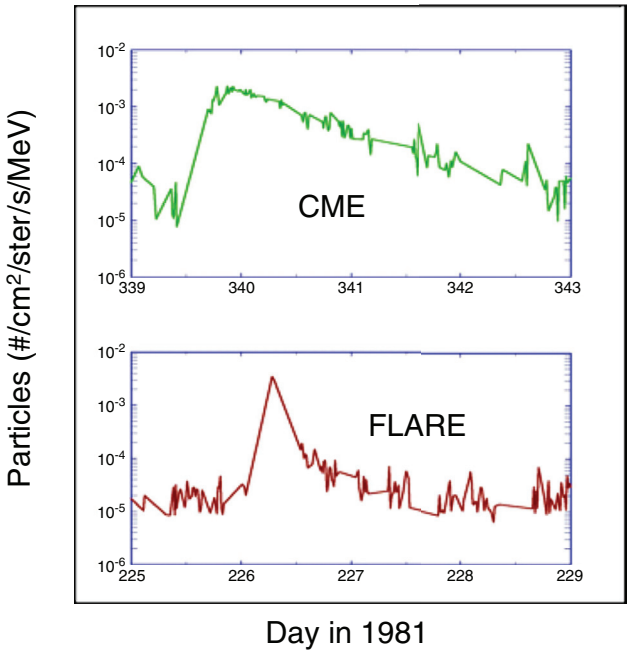

FIGURE 2.4 Two types of solar proton events: (1) gradual events, which are typically the largest events and are associated with coronal mass ejection (CME) shocks and typically last for several days; and (2) impulsive events (often called solar flares), which are short, longitudinally localized events on the solar surface. SOURCE: J. Barth, NASA Goddard Space Flight Center, "Modeling Space Radiation Environments," presentation at the IEEE Nuclear and Space Radiation Effects Conference Short Course: Applying Computer Simulation Tools to Radiation Effects Problems, July 21, 1997.

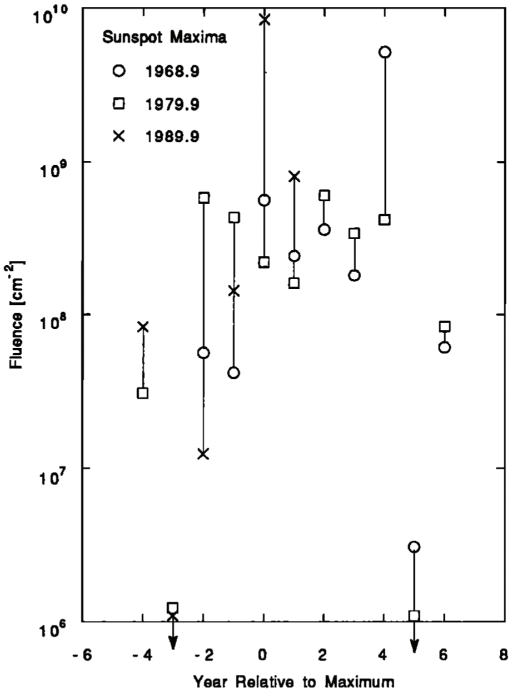

FIGURE 2.5 Yearly event fluences for protons of energy >30 MeV versus year relative to sunspot maximum. SOURCE: J. Feynman, G. Spitale, and J. Wang, Interplanetary proton fluence model, *Journal of Geophysical Research* 98:13281-13294, 1993. Copyright 1993 American Geophysical Union. Reproduced by permission of American Geophysical Union.

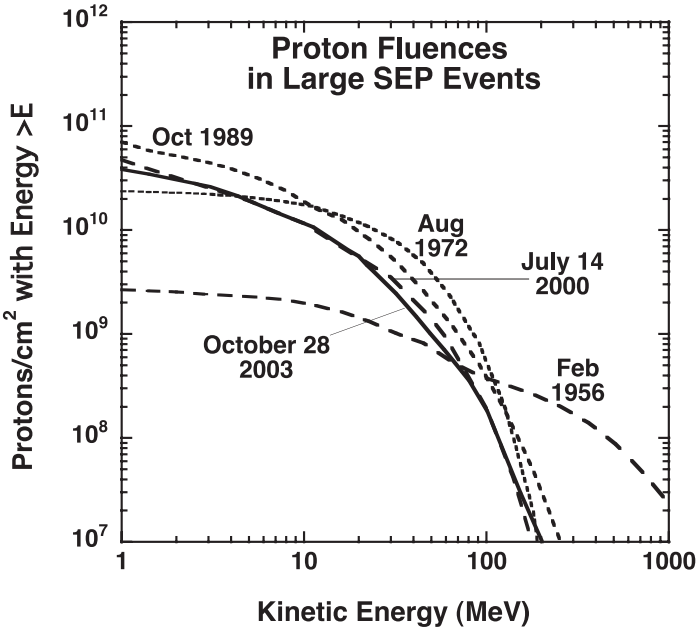

FIGURE 2.6 Energy spectra of several large solar energetic particle (SEP) events. SOURCE: R.A. Mewaldt, C.M.S. Cohen, A.W. Labrador, R.A. Leske, G.M. Mason, M.I. Desai, M.D. Looper, J.E. Mazur, R.S. Selesnick, and D.K. Haggerty, Proton, helium, and electron spectra during the large solar particle events of October-November 2003, *Journal of Geophysical Research* 110:A09S18, 2005. Copyright 2005 American Geophysical Union. Reproduced by permission of American Geophysical Union.

other locations in the heliosphere. Simply stated, there is no clear understanding of the radial scaling law of SPE flux at the present time.

In addition to a high flux of protons, solar flare events also typically are accompanied by small but variable amounts of heavy ions. However, previous estimates (Kim et al., 1999; NCRP, 1989) indicate that solar heavy ions do not contribute much to the SPE radiation hazard to astronauts.

Review of the NASA SPE Model

The SPE model used in NASA's proposed space radiation cancer risk assessment model (Cucinotta et al., 2011) is described in Kim et al. (2009, 2011). This SPE model was developed using an extensive events list compiled from King (1974), Feynman et al. (1990), and Shea and Smart (1990) for Solar Cycles 19 to 21, and geostationary operational environmental satellite (GOES) data from 1986 to the present (Solar Cycles 22 and 23). Also, the database includes the SPE events estimated using impulsive nitrate enhancements in polar ice cores (McCracken et al., 2001). From this events list, NASA used non-homogeneous Poisson statistics (Parzen, 1967) for describing SPE frequency distribution and a hazard function from survival analysis to estimate the expected number of events in a given mission duration. Then, from the prediction of the mean number of SPEs with integral fluence (i.e., Φ_{30}) exceeding given thresholds, a (e.g., $a = 10^7$, 10^8, and 2×10^9 cm^{-2}), the cumulative probabilities of SPE frequencies and total proton fluences are defined at various percentiles during a given mission duration. As for the energy spectrum of the expected SPEs, the event-integrated fluence above an arbitrary energy level of E MeV from the 34 historically largest SPEs is fit with the Weibull function up to 1 GeV.

As described above, the new NASA SPE model uses a comprehensive collection of historical SPEs from an extensive database using rigorous mathematical analysis and formulation to determine the total proton fluence and energy spectrum for a given mission length. The new NASA SPE model is an advance over the past model, in which NASA used the fixed event fluence and spectrum from the 1972 August SPE. However, it should be noted that the new model is a statistical SPE model from a data set constructed from past measurements, although the new NASA SPE model is called a probabilistic risk assessment (PRA) model in the NASA report (Cucinotta et al., 2011). The model is not a predictive model for the future, and one must be cautious in extrapolating from the past and present conditions to the future. For both GCR and SPE, the radiation environment at the present time appears to be relatively mild, which is unusual from the historical perspective (NRC, 2006).

The new NASA SPE model can be considered to be a major step forward compared to the current NASA SPE model. Nonetheless there are a few minor areas that NASA could consider further addressing in the future, as follows:

- The new NASA SPE model is constructed using a list of events from past measurements. However, the definition of an event is not provided in the 2011 NASA report. Depending on how an event is defined, the underlying distribution function of the events can be different from what is used in the NASA SPE model. There are three areas of SPE climatology research: how to count events that may be correlated, statistics of extreme events, and how SPE characterization varies with the solar cycle. The largest (most extreme) impacts are associated with "clusters" of high-speed CMEs called fast CMEs. Recent studies (Ruzmaikin et al., 2011a,b) indicate that extreme space weather events (i.e., large CMEs and SPEs) are not independent of one another. The most important SPEs for estimating radiation risk to astronauts are these extreme events. A new advanced statistical method (e.g., see Ruzmaikin et al., 2011b, and references therein) recently developed can be used to describe these extreme events. It may change the functional form of the distribution of extreme SPEs, which in turn can affect spacecraft design or mission planning. It will be useful if NASA evaluates the statistics of SPEs using different methods to define better the tail distribution of SPEs, that is, extreme SPEs. Furthermore, since SPE statistics vary dramatically from solar cycle to solar cycle, combining all SPE observations together and saying that they are representative of any given solar cycle introduces additional uncertainty. In this regard, it may be useful for NASA to further investigate the SPE frequency relationship to solar cycles. This may also affect the statistics of extreme events.
- Extension of the energy spectrum of an SPE to 1 GeV using the data only up to approximately 100 MeV seems oversimplified, especially when it has been stressed multiple times that the shape of energy spectrum is an

important parameter when assessing radiation risk from SPEs. Additional measurements of high-energy protons, especially in the energy range of >100 to >500 MeV, will help better define the energy spectra of SPEs.

- There is no mention in the 2011 NASA report of radial and longitudinal variations of the SPE fluence and energy spectrum (e.g., the SPE environments at Earth and at Mars are expected to be different when Earth and Mars are at different solar latitude and longitude). The SEPs preferentially move along the spiral interplanetary magnetic field, and this produces a characteristic coupled longitudinal and radial dependence of the intensity, which depends on the parameters and is difficult to precisely determine. The incorporation of these radial and longitudinal variations of SPE environment may be important for a future mission to Mars. In this regard, actual measurements of SPE environment at Mars would be very useful. The Mars Science Laboratory (MSL) Radiation Assessment Detector (RAD) can provide very valuable data in this sense, which will measure the surface radiation environment at Mars. Furthermore, simultaneous measurements of SPEs on orbit at Mars and at the surface are desired because they can be used to validate radiation transport models for the martian atmosphere and surface.
- There is no mention of a heavy-ion component of SPEs in the 2011 NASA report. Although the committee understands that the SPE heavy-ion flux is low compared to the SPE proton flux, the biological effects of heavy ions is very uncertain at this stage, and it may be premature to exclude the SPE heavy-ion consideration entirely from the overall cancer risk assessment for astronauts. To have a complete SPE model, it is suggested that NASA add a heavy-ion component to the new SPE model.

There are other SPE models available in the community. However, in terms of data sources and model outputs, NASA's proposed model is not much different from other models, although each uses a different mathematical approach: the Jet Propulsion Laboratory model uses a lognormal fit to the observed SEP event fluences (Feynman et al., 1993, 2002), and the emission of solar protons model uses the maximum entropy principle (Xapsos et al., 2004).

Transport Model

Overview

The external radiation environments described above change their properties (in terms of particle type and energy spectra) as they go through spacecraft materials and the body mass surrounding the internal organs. Nuclear interactions between the primary radiation and shielding materials can generate a score of secondary particles through spallation or fragmentation reactions, which include secondary neutrons. These interactions are typically modeled using radiation transport codes, which can employ deterministic or Monte Carlo methods.

Review of the NASA Shielding Transport Models

The transport model used in NASA's proposed model is HZETRN, high charge and energy transport code (and BRYNTRN, a computational model of baryon transport) (Slaba et al., 2010a,b). The fluence for each particle type and energy at each tissue of interest (behind spacecraft and body shielding) is characterized by using radiation transport codes: HZETRN with a quantum multiple scattering fragmentation (QMSFRG) database for GCRs and baryon transport model (BRYNTRN) for SPEs. These radiation transport codes solve the Boltzmann transport equation with the straight-ahead approximation. This is a deterministic approach. Typically, deterministic codes are used for simple geometries for which the Boltzmann equation can be solved numerically—Cartesian, cylindrical, spherical, or toroidal geometries. For complex geometries (e.g., spacecraft and the human body) for which the Boltzmann equation cannot be solved numerically, a Monte Carlo approach is appropriate and would provide more accurate results. However, Monte Carlo simulations take prohibitively long computation time, especially for problems with complex geometry, to obtain the results with a good statistical accuracy. Furthermore, the level of accuracy from the Monte Carlo simulations tends to be negated anyway when a simplified geometry is used in the Monte Carlo simulations.

To deal with this situation, NASA uses the aforementioned deterministic codes with ray-tracing techniques to consider a very detailed geometry in a one-dimensional approach. This approach, along with the numerical techniques used in the proposed NASA transport model, is well accepted in the radiation transport community.

Based on the presentations given by NASA to the committee during the first meeting and materials provided subsequently, it is the committee's opinion that the NASA radiation transport codes have been verified and validated through thin and thick target experimental data and by means of intercomparisons among transport codes widely used in the radiation transport community (HETC-HEDS, FLUKA, PHITS, MANPX, and Geant4). Furthermore, the radiation transport codes used in NASA's proposed space radiation cancer risk assessment model are shown to provide good agreement in most cases with spaceflight measurements from the International Space Station (ISS) and/or Space Transportation System (STS). In this regard, it is concluded that there have been reasonable advances in developing the predictive capability of radiation transport codes used in the NASA cancer risk assessment. However, it is noted that comparisons of HZETRN with spaceflight measurements still show greater than 20 percent difference for several occasions (see Tables 2.5 and 2.6a in the 2011 NASA report).

As discussed in the 2011 NASA report (Cucinotta et al., 2011), a minor source of discrepancy between transport code predictions and measurements is the mesons, electrons, and gamma rays that become important contributors to organ doses for very thick shielding—for example, >50 g/cm^2 shielding. In this sense, the continuous collection of data for different shielding materials and different ion beams is recommended for further validation of transport code, especially for thick targets. The 2011 NASA report also states that the cross-section data are sparse for some projectile-target combinations, especially above 1,000 MeV/u, and improvements are required in how differential cross sections are represented in transports. The committee agrees with this point and suggests that NASA continue compiling experimental thick-target data for code validation.

Final Comments

In general, the committee agrees that the uncertainty associated with the space physics parameters (i.e., environments and transport models) is a minor contributor to the overall space radiation cancer risk assessment, within 15 percent for effective dose comparisons. The knowledge, or lack of it, about the biological effects and responses to space radiation is the single most important factor limiting the prediction of radiation risk associated with human space exploration. NASA's proposed space radiation cancer risk assessment model assigns a slightly higher overall physics model uncertainty than the estimate of 15 percent. It is assumed in the proposed model that light ion ($Z \leq 4$) fluence spectra computed at targets of interest would have a normal distribution with a mean shifted to higher value (M = 1.05) and the standard deviation of 0.33, compared to heavy ions ($Z > 5$) for which the mean and the standard deviation are assigned to be 1.0 and 0.25, respectively. However, it should be noted that the uncertainty of the space physics model is used independently from other uncertainties in the overall radiation risk assessment. Hence, in the Monte Carlo calculations in the overall risk assessment, tissue-specific particle spectra are being used simply as an input.

The radiation environment and transport models used in NASA's proposed space radiation cancer risk assessment model are considered to be a major step forward compared to previous models used (especially the statistical SPE model). The models described in the 2011 NASA report have been developed making extensive use of available data and rigorous mathematical analyses. The uncertainties conservatively allocated to the space physics parameters are deemed adequate at this time, considering that the space physics uncertainty is only a minor contributor to the overall cancer risk assessment. Although further research in this area can reduce the uncertainty, it is not clear at this point whether the extra effort would make enough difference in the space physics uncertainty to reduce the overall risks.

CANCER RISK PROJECTION MODELS

Overview

The cancer risk projection component of NASA's proposed model can be broadly defined as an amalgamation of approaches developed by the 2006 United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2006) and the BEIR VII committee. These committees agree in many respects on how to project lifetime cancer risks following radiation exposure. They both use the latest Japanese atomic bomb survivors life

span study (LSS) as the primary data source. Organ-specific doses are combined with organ-specified cancer risk models, and risks are estimated using both excess relative risk (ERR) and excess absolute risk (EAR) models, which are then combined using a weighted average. (The excess relative risk is the cancer rate in the exposed population divided by the rate in the unexposed population minus 1, whereas the excess absolute risk is the cancer rate in the exposed population minus the rate in the unexposed population.) There are, however, a number of areas in which BEIR VII and UNSCEAR differ in their approach, and these can have a non-negligible impact on risk estimates. The areas are these:

1. The functional form of the ERR and EAR risk models;
2. The estimation of cancer mortality risks;
3. The weights used in the weighted average of the ERR and EAR models, which is the approach used to transfer risk estimates from the Japanese to the U.S. population; and
4. Application of a dose and dose rate effectiveness factor (DDREF) to account for potential differences in cancer risk at low doses and low dose rates.

NASA's proposed model broadly follows UNSCEAR (2006) for the first area listed above, BEIR VII (NRC, 2006) for the second and third, and for the fourth it uses a distribution developed for the National Institutes of Health (NIH) radioepidemiological tables (NIH, 2003). The resulting risk of exposure-induced death (REID) estimates from NASA's proposed model are quite different from those from the current NASA model (developed in 2005). It is difficult, however, to isolate the factors that drive this difference, because NASA's proposed model combines different components of several existing approaches. The UNSCEAR and BEIR VII committees developed their approaches each following a unified philosophy to risk estimation. For example, BEIR VII developed functional forms for the risk models and a specific "LSS DDREF" approach to be combined with those models. Conversely, UNSCEAR evaluated linear-quadratic models for the LSS data as a direct approach to incorporating evidence of lower risks at lower doses. Furthermore, those reports had different emphases. The UNSCEAR report emphasized cancer mortality results, whereas the BEIR VII report emphasized cancer incidence. More effort, therefore, was put into developing the models and evaluating the models for cancer incidence in the BEIR VII report and vice versa for the UNSCEAR report. NASA's proposed model combines the UNSCEAR incidence risk models with the BEIR VII mortality approach, which are probably the least developed aspects of the respective reports. The following of either one of these reports more directly by NASA and the providing of careful justification in its published model description for any minor deviations may result in a model that is more transparent and robust.

A detailed review of the key aspects of the proposed cancer risk projection component of NASA's model is given below, including a comparison with the approach of NASA's current model.

Cancer Mortality Risk Estimation

NASA limits an astronaut's radiation exposures to amounts expected to result in no more than a 3 percent excess risk of exposure-induced death. Therefore, a risk projection model for cancer mortality—as opposed to cancer incidence—is required. The traditional approach to estimating risks of cancer mortality is to use risk coefficients estimated directly from the LSS cancer mortality data. A major proposed change in NASA's proposed model is to use the "incidence-mortality" approach developed by BEIR VII (NRC, 2006) whereby risk coefficients from LSS cancer incidence data are used and then cancer mortality risks are estimated from these incidence risks. For the ERR models the incidence-ERR coefficients are combined directly with current U.S. cancer mortality rates, whereas for the EAR models the EAR cancer incidence coefficients are multiplied by the current ratio of cancer mortality to cancer incidence in the U.S. population. As mentioned earlier these are then combined to provide a single estimate from a weighted average (more details are provided below). This ratio is supposed to approximate the mortality probability for this cancer site.

The incidence-mortality approach is considered an improvement for site-specific cancer mortality estimation because LSS site-specific cancer incidence data are likely to be more accurate than are cancer mortality data (Ron et al., 1994a,b), which suffer from misclassification of causes on death certificates. However, some further

TABLE 2.1 Comparison of Mortality:Incidence Ratio and Survival Probability Approaches to Estimating Probability of Death from Breast Cancer in Women

	Mortality Rate (%)	Incidence Rate (%)	Ratio	10-Year Survival
Ages 20-49	8.6	73.7	0.12	0.21
Ages 50-64	46.6	281.7	0.17	0.18
Ages 65-74	79.5	416.4	0.19	0.16
Ages 75+	137.3	407.2	0.34	0.19

NOTE: Rates are per 100,000 for events occurring from 2003 through 2007 in the U.S. SEER 9 cancer registries. Ten-year survival probability from data from 1988 through 2007 also from SEER 9.
SOURCE: Data from Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, available at http://seer.cancer.gov/.

exploration of the change in approach is warranted because it has a non-negligible impact on the REID estimates, especially with respect to the pattern with age at exposure. For example, an evaluation is required of the epidemiological biases that may be operating in the cancer mortality or cancer incidence data from the LSS that would result in a weaker relationship with age at exposure in the cancer incidence data. One possibility is that the level of misclassification in the cancer deaths may increase with increasing age at exposure. Before a major change is implemented, more research into these epidemiological questions is warranted.

In addition, one aspect of the incidence-mortality approach that requires additional evaluation is the use of the ratio of current cancer mortality to cancer incidence rates in the U.S. general population as an approximation to the probability of mortality. Differential period and cohort effects are likely in cancer incidence and mortality data, and these will be captured in this ratio. Current age-specific 10-year-survival probabilities may be a better approach, but this would need to be examined in more detail before being implemented. An example of the problem is shown in Table 2.1 for female breast cancer. There is a strong age dependence of the ratio of mortality to incidence rates for breast cancer, but this is not evident in the survival probabilities. The Environmental Protection Agency (EPA) committee also highlighted this problem in its recent report (EPA, 2011) and developed an alternative method for breast cancer mortality risk estimation. It is unlikely that this problem is limited to breast cancer, however, and the committee recommends further evaluation of other cancer sites.

Transfer from the Japanese to the U.S. Population

Because underlying cancer incidence rates for some cancer sites differ greatly between the Japanese and the U.S. populations, risk estimation based on an excess relative risk model can give very different REID estimates from those based on an excess absolute risk model. Risk projection committees have used a variety of approaches to transfer radiation-related cancer risk estimates from the life span study of the Japanese atomic bomb survivors to a non-Japanese population. A number of committees have recommended that a weighted average of the ERR and EAR models be used. The choice of weights is not straightforward, however, and the most appropriate weighting may well vary by cancer site. NASA's current (2005) model assigned equal weights to both models for all cancer sites. Most recently the BEIR VII committee (NRC, 2006) assigned subjective weights to each cancer site, mostly weighting the ERR model more heavily than the EAR model. The UNSCEAR (2006) report, however, elected to present the results from the two models separately rather than estimating a weighted average. The proposed NASA approach follows BEIR VII in calculating a weighted average with uncertain weights and generally follows the recommended BEIR VII weights. There are some deviations, however, and the reasons for these deviations need to be justified and the implications of their choices described. For example, BEIR VII recommended a weight of 0.3 for the ERR model for lung cancer because of the evidence that the joint effect of smoking and radiation may be closer to additive than multiplicative (Pierce et al., 2003). In NASA's proposed model, a weight of 0.5 was used for the ERR lung cancer model. For never-smokers (NSs) this choice will result in lower risk estimates than

would the BEIR weight, and so this change needs to be carefully justified. See below for further comments on the never-smoker lung cancer model.

Dose and Dose Rate Effectiveness Factor

A dose and dose rate effectiveness factor is often applied to lifetime cancer risk projections estimated using data from the Japanese atomic bomb survivors because the cancer risk per unit dose from low doses or low-dose-rate protracted radiation exposures may be lower than the risk per unit dose from acute higher-dose exposures. There are considerable uncertainties, however, about whether such a factor is necessary, and the approach by different committees for estimating DDREF varies. The BEIR VII committee conducted an extensive review of the experimental data, analyzed the LSS data, and developed a Bayesian "LSS DDREF" with a central estimate of 1.5. BEIR VII recommended that this LSS DDREF be applied for all protracted doses and for acute doses below 100 mGy. The UNSCEAR (2006) reviewed the various approaches but did not make any recommendations about the application of a DDREF. The proposed NASA approach is to use a discrete uncertainty distribution for the DDREF that was developed for the NIH (2003) radioepidemiological tables, which essentially has a median DDREF of 1.75. This was a subjective uncertainty distribution that approximated continuous subjective distributions from three earlier publications (EPA, 1999; NCRP, 1997; Grogan et al., 2001). The more recent, BEIR VII approach, which is somewhat less subjective, may be preferable to this older approach. An additional consideration is that a number of publications produced since the NIH report are relevant to this issue: for example, the Mayak workers study (Shilnikova et al., 2003), the third analysis of the United Kingdom's National Registry for Radiation Workers (Muirhead et al., 2009), and the 15-country nuclear workers study (Cardis et al., 2005), together with the review of these studies and comparison with the LSS by Jacob et al. (2009). These findings are obviously not reflected in the older, subjective uncertainty distributions referenced above.

Risk Models for Never-Smokers

The issue of the smoking status of the astronauts and the potential implications on risk projections for smoking-related cancers are also important and it is appropriate that the impact of taking smoking status into account should be investigated. Most astronauts are non-smokers, which would likely lower the risk projections for astronauts compared to estimates for the general population (a mixture of never- and ever-smokers). The proposed NASA approach for lung cancer does not take account of variation in lung cancer risk coefficients or competing causes of death with smoking status and should be developed further. The approach is to use the UNSCEAR lung cancer risk coefficients applied to lung cancer rates of those who are never-smokers (typically defined as having smoked fewer than 100 cigarettes ever). These risk coefficients, however, are not smoking-specific. A number of analyses of the joint effect of smoking and radiation on lung cancer risk have been conducted using the LSS data and risk coefficients from these models for never-smokers would be more appropriate (Pierce et al., 2003; Furukawa et al., 2010). Indeed these analyses demonstrate that the risk coefficients do vary by smoking history. There would still need to be consideration of how to transfer the never-smoker risk models from the Japanese to the U.S. population. It may not be as straightforward as just applying the LSS never-smoker ERR coefficients to U.S. never-smoker lung cancer incidence rates, as the pooled analysis by Thun et al. (2008) found that lung cancer rates in never-smokers are much higher in Asians than in Caucasians. NASA's current (2005) model does not include an assessment of the risks for never-smokers.

A second aspect of the risk model for never-smokers that needs to be addressed is that NASA's proposed model does not use competing risk adjustments that are specific to never-smokers in the REID calculation. As the life expectancy of never-smokers is about 10 years longer than that for current smokers, continuing use of the general-population survival probabilities for competing risks will result in underestimates of the REID for never-smokers. One relatively straightforward approach to competing risks for never-smokers is to assume that never-smokers have approximately a 5 years' longer life expectancy than that of the general population (Doll et al., 1994). (The general population is a mixture of never-smokers, past smokers, and current smokers, and so 10 years would be an overestimate of how to adjust the general-population survival curves.)

For the other smoking-related cancers, it is probably premature to estimate the REID for never-smokers. No studies have been conducted to evaluate the joint effect of smoking and radiation for these cancer sites, and reliable estimates of the cancer incidence rates for these sites for never-smokers are not available.

Additional Minor Issues

The UNSCEAR 2006 models included a latency term, but Preston et al. (2007) and BEIR VII did not. For the cancer risk estimates that were based on risk coefficients from those reports, a latency period needs to be added—for example, by assuming that risk is zero for the first 5 years after exposure. It is unclear whether this was done for the cancer risk estimates that were based on risk models from these sources. Secondly, the approach used for the age-centering of the coefficients for breast cancer in the BEIR VII report makes those coefficients inappropriate for use in NASA's proposed model, and therefore coefficients should be taken instead from their original source (Preston et al., 2002). NASA does not consider non-Hodgkins' lymphoma (NHL) as a radiogenic cancer for inclusion in its risk estimates. There are reported studies of the induction of NHL from occupational exposures; however, the issue remains unclear at this time (Preston et al., 1994). NASA may find it useful to follow the literature on this topic for possible future adjustments of its model.

UNCERTAINTIES IN LOW LINEAR ENERGY TRANSFER RISK MODEL

Overview

One of the components in NASA's proposed model (described in Section 4 of the 2011 NASA report: Cucinotta et al., 2011) addresses risk estimates and their uncertainties associated with exposure to low linear energy transfer (LET) radiation. Such radiation includes high-energy gamma radiation found in space environments, the acute gamma radiation received by survivors of the atomic bombings of Hiroshima and Nagasaki in 1945, and medical X rays. Uncertainties are important because risk protection involves safety factors that, as described in the 2011 NASA report, are driven by upper 95 percent uncertainty limits on risk. For example, a space activity that is estimated to be associated with a lifetime excess mortality risk of "about 0.5 percent" would (and should) be viewed very differently depending on whether the upper 95 percent uncertainty limit or confidence bound obtained by NASA on that estimate is 0.6 percent, 1.5 percent, or 4 percent.

Conclusion: Uncertainty limits on radiation-related risk reflect information about anticipated environmental radiation dose levels and accumulated knowledge about the relationship between radiation dose and cancer risk. For the approach used by NASA, more information, if available, might reduce statistical uncertainty and, assuming that the new information did not increase the central risk estimate, lower the upper 95 percent uncertainty bound criterion used by NASA to evaluate the acceptability of activity-related mortality risk.

Epidemiological Basis for Radiation-Related Cancer Risk Estimation

The uncertain relationships between radiation exposure and subsequent, organ-specific cancer risks are best understood for low-LET radiation and, in particular, for the high-energy gamma radiation that dominated the radiation doses received by the Japanese atomic bomb survivors. In contrast with earlier reports—for example, NCRP (1997) Report No. 126 and NCRP (2000) Report No. 132—estimated neutron doses from the bombs are now considerably lower, reflecting new appreciation of the neutron shielding provided by water vapor in the very humid August air of the two cities (Cullings et al., 2006; Preston et al., 2007). As a result, estimated neutron dose, even with a postulated 10-fold relative biological effectiveness (RBE) compared to gamma dose, is now considered to be a less important contributor to risk among atomic bomb survivors and, perhaps more important, it is a risk factor that is difficult to quantify based only on the atomic bomb survivor data (Preston et al., 2007). In NASA's proposed model, the low-LET radiation, and its uncertainties, are based primarily on cancer incidence and mortality data from the LSS cohort of atomic bomb survivors, plus medically or occupationally irradiated populations, as

interpreted in a number of committee reports from the International Commission on Radiological Protection (ICRP, 1991, 2006), NCRP (1997, 2000), NIH (2003), NRC (2006), and UNSCEAR (2008). The statistical uncertainty structure of the estimated parameters of this model is well characterized for the more important cancer sites. The low-LET model pertains directly to cancer risk from high-energy gamma radiation at high dose rates and requires a somewhat controversial, and uncertain, DDREF for such radiation that is fractionated or delivered at low dose rates, as discussed in the section above entitled "Cancer Risk Projection Models." In contrast, cancer risks associated with different types of high-LET radiation characteristic of the radiation environment beyond low-Earth orbit, many of which are rarely if ever encountered at Earth's surface, are more tenuous. It may be, however, that certain simplifying relationships apparent in dose-response models for low-LET radiation, such as common parameter values for attained age as a modifier of dose response (NRC, 2006, Table 12-2), may carry over to high-LET models. The low-LET risk model therefore is an obvious starting point for modeling risk from various types of high-LET radiation, which is discussed in Sections 5 and 6 of the 2011 NASA report (Cucinotta et al., 2011).

Uncertainty-Related Bias

Radiation doses to individual members of epidemiological study populations tend to be uncertain, and such uncertainties may result in biased estimates of risk. This has long been recognized (Gilbert, 1984; Armstrong, 1990), and in recent years and with improved computing power, the correction of biases associated with such uncertainties has increasingly become an essential part of the dose-response analysis (Pierce et al., 1990; Schafer and Gilbert, 2006; Hofer, 2007, 2008; Pierce et al., 2008). Such corrections, which are not covered by NCRP (1997) Report No. 126 or NCRP (2000) Report No. 132, tend to increase the estimated dose-response as well as its uncertainty, a factor that should be mentioned in future descriptions of the risk model.

Radiation Risk Protection

Because Sections 3 and 4 of the 2011 NASA report (Cucinotta et al., 2011) are limited to the consideration of low-LET radiation, inferences are substantially simpler, and better supported by epidemiological data, than are inferences in later sections that deal with the more complex radiation environment beyond low Earth orbit. The 2011 NASA report is concerned with radiation protection, which is intrinsically simpler than the attribution of existing cancer cases to past radiation exposures for compensation or other purposes (NIH, 1985, 2003; Wakeford et al., 1998; Kocher et al., 2008). NASA's decision to consider the cancer site only insofar as it affects the relationship between the radiation dose and overall excess cancer mortality is a further simplification. The proposed model described in the 2011 NASA report continues to depend on the NCRP (1997) Report No. 126 and NCRP (2000) Report No.132 models, but its site-specific risk estimates are based primarily on LSS incidence, which is converted to mortality using U.S. cancer survival rates (NRC, 2006), rather than on mortality data.

Dependence on Atomic Bomb Survivor Data

The LSS data constitute by far the most important single information source for predicting radiation-related cancer risk in exposed or potentially exposed populations, as discussed above. The 2011 NASA report (Cucinotta et al., 2011) expressly relies on LSS incidence data obtained through the Japanese Radiation Effects Research Foundation (RERF) and on U.S. cancer survival statistics in preference to LSS mortality data. The incidence data were obtained through periodic analyses of data from the RERF Tumor Registry, which covers site-specific cancer incidence starting in 1958 and is adjusted for the migration of members of the LSS cohort to other parts of Japan and other places not covered by the registry. Other sources of information include site-specific cancer mortality data beginning from 1950 (Preston et al., 2003) and periodic refinements to the reconstructed radiation doses received by individual survivors (most recently, Pierce et al., 1990, 2008; Preston et al., 1994, 2004, 2007; Cullings et al., 2006; Thompson et al., 1994). The NASA analysis, which generally follows NCRP (2000) Report No. 132, also cites reports by the NRC (2006) and UNSCEAR (2008), and new models for lifetime risk and its uncertainty as employed in UNSCEAR (2006), Little et al. (2008), and an analysis of cancer risk in radiation workers (Jacob et

al., 2009) with emphasis on DDREF. Of these reports, only Jacob et al. (2009) deals mainly with non-LSS data. Although the LSS data have many assets that make them uniquely valuable, they are not without some limitations. For example, they do not cover the entire LSS population but only those resident in Hiroshima and Nagasaki. In addition, the registries start 13 years after the initial exposure. These limitations add a level of uncertainty that is considered in the risk estimates developed by NASA.

The data used by NASA for low-LET risk models are those cited above from the LSS published by RERF, plus additional dose-response data from a pooled analysis of cancers of the thyroid gland by Ron et al. (1995), largely from the Israeli series on children treated by x-ray scalp depilation for tinea capitis, but also from studies of patients treated by radiation for enlarged thymus glands and by tonsil and nasopharyngeal irradiation. Strong evidence of radiation-related risk of female breast cancer is provided by the LSS data, two series of tuberculosis patients given lung collapse therapy monitored by frequent chest fluoroscopies, and a series of children treated in infancy for enlarged thymus. A joint analysis by Preston et al. (2002) found these four series to be consistent with one another. However, in the same joint analysis, data from women given radiation therapy for acute postpartum mastitis and for hemangioma demonstrated increased breast cancer risks, but with dose responses inconsistent with the other four studies and with each other, and so the final estimate was based on a combination of the LSS and tuberculosis and enlarged-thymus studies.

The 2011 NASA report states at the beginning of Section 6 (Cucinotta et al., 2011) that arithmetic weighting of multiplicative and additive risk-transfer models is used to transfer risk estimates to the U.S. population. This appears to be the only mention in the 2011 NASA report of this information, which is crucial, given that, with similar weights, geometric weighting always yields a lower value than arithmetic weighting unless the multiplicative and additive risk-transfer model estimates are identical. It would seem that the above statement in Section 6 of the 2011 NASA report (Cucinotta et al., 2011) might usefully be highlighted by inclusion as well in its Executive Summary.

Miscellaneous Comments

A minor flaw in Formula 4.1 of the 2011 NASA report (Cucinotta et al., 2011), easily repaired, is that the baseline mortality rate λ_0 is written not only as a function of attained age *a,* but also as a function of *E* (energy) and a_E (age at exposure). It would be better to write baseline rate λ_0 as a function only of age and sex; it is the *excess* risk that also depends on energy and exposure age.

The empirical Bayes (EB) shrinkage approach of Pawel et al. (2008) is discussed briefly in Sections 3, 3.1, and 4.2 and in Table 4.1 of the 2011 NASA report (Cucinotta et al., 2011), but it is not mentioned in later sections. The EB approach arguably has advantages for a single-site estimate—for example, cancer of the urinary bladder—to the extent that information pertaining to additional cancer sites may also be relevant to radiation-related bladder cancer risk and may therefore modify that estimate and reduce its uncertainty. For radiation-related mortality from all cancers combined, however, the standard error of the estimate depends on the entire covariance matrix and should be about the same as it would be without shrinkage. The EB discussion is not particularly relevant to radiation-related mortality from all cancers combined, and it might be left out of the 2011 NASA report.

CANCER RISKS AND RADIATION QUALITY IN THE MODEL

Overview

Different types and energies of ionizing radiation (radiation qualities) do not all have the same biological effectiveness per unit absorbed dose. ICRP introduced radiation weighting factors, w_R, for different types of particles to take account of the differences in biological effectiveness (ICRP, 1991). The radiation weighting factors are used to multiply organ- and tissue-absorbed doses in order to obtain equivalent doses for organs. In its current (2005) model, NASA uses quality factors, Q, for the cosmic radiation field instead of radiation weighting factors to obtain equivalent dose, following the recommendation by NCRP (2000) Report No. 132 and NCRP (2002) Report No. 142. In the ICRP system of quantities, Q is used to weight absorbed dose at a point to obtain dose equivalent used for the definition of operational quantities for radiation monitoring. The values

of Q have been selected by ICRP and NCRP as a function of LET on the basis of published data on the RBE for different radiations and for appropriate or relevant biological effects. RBE is the ratio of the absorbed dose of a standard radiation, such as X rays or gamma rays, to the absorbed dose of a radiation in question, that both produce the same level of a given biological effect. Since RBE depends on numerous factors such as the level of effect and the biological effect chosen for comparison, values of Q have been chosen by ICRP as well as by NCRP to represent the factor for low doses of a given radiation most likely to be pertinent for carcinogenesis, the effect of primary concern for most radiation protection considerations, including those of NASA. This is an especially important consideration for the radiation environments in space, where astronauts are exposed to solar protons and heavy ions of high energy and high atomic number (HZE). The vast majority of data relating dose to biological effects in general and to cancer risk in particular, however, relate to sparsely ionizing radiations like X rays or gamma rays.

One property that has been extensively studied in an effort to link a physical description of energy deposition by different ionizing radiations is linear energy transfer, which gives some indication of the average density of ionizations along charged particle tracks. But LET alone does not fully predict RBE for a particular biological effect, and it has become increasingly clear that for radiations encountered in space, a better descriptor is needed. A major focus of the 2011 NASA report, in which NASA's proposed model is described, is to utilize more realistic approaches to defining quality factors and to examine and suggest improved approaches in this regard. However, it should be noted that the 2011 NASA report proposes the replacement of the ICRP-NCRP-defined quality factor, Q (ICRP, 1991, 2007; NCRP, 2000), with a different definition (and different numerical values) of quality factor, QF, for application in the space radiation environment. The 2011 NASA report is not consistent in its usage of the terminology Q and QF, and the report's glossary is unhelpful in this respect: it identifies both Q and QF simply as "quality factor," without indicating a distinction between them. For clarity in reviewing NASA's proposed model, the committee uses the term Q exclusively for the ICRP-NCRP-defined quality factor, and it uses QF exclusively for the space radiation quality factor as defined in the 2011 NASA report (Cucinotta et al., 2011) for NASA's proposed model (see the glossary definitions in Appendix C in the present report). The committee suggests that NASA retain this clear distinction in terminology between ICRP-defined quantities and NASA-defined alternatives.

In NCRP (2000) Report No. 132 and ICRP (1991) Publication 60 and ICRP (2007) Publication 103, it is assumed that particles with the same LET but different spatial distributions of ionization and excitation events produce the same cancer risk even though the complexity of damage and spatial distribution of initial damage may be different. NCRP (2001) Report No. 137 did not consider particle track structure or extrapolation to low dose. Section 5 of the 2011 NASA report (Cucinotta et al., 2011) describing the proposed model builds the case for several major proposed changes to these approaches. First is the use of different values of QF for leukemia and for solid cancers, with substantially higher values for solid cancers than those for leukemia, based on the literature evidence described below. Second is the replacement of the dependence of Q on LET, as the main radiation quality descriptor, with functional dependence of QF on Z^{*2}/β^2, where Z^* is the effective charge number of the particle and β its speed relative to the speed of light. Three empirical parameters, Σ_0/α_γ, m, and κ, are introduced in order to define the proposed QF dependence on Z^{*2}/β^2, as discussed in more detail in the section below entitled "Integration and Completeness of the Model." LET, by definition, is the average energy loss per unit path length of charged particles and does not provide a description of the microscopic distribution of energy deposition around the pathway of the particles including the production of delta rays of varying energies; however, Z^{*2}/β^2 to some degree takes account of energy deposition around the track of the particle. Furthermore, the proposed NASA approach uses a different dependence of QF on Z^{*2}/β^2 for light ($Z \leq 4$) and for heavy ($Z > 4$) charged particles. Third, NCRP (2001) Report No. 137 previously explored the concept of using particle fluence instead of absorbed dose. In that approach, the absorbed dose and quality factor are replaced by particle fluence and a parameter, Σ, denoting risk cross section. In the NASA's proposed model, NASA has proposed empirical functions for Σ guided by considerations of track structure and a biophysical model to extrapolate to HZE particles. Fourth is the consideration of non-targeted effects (NTEs) in the model. These effects, despite the extensive discussion in the NASA report of a possible NTE component, are not incorporated into the proposed NASA risk projection model but do provide a framework for the future incorporation of such extensions of the NASA model.

Quality Factors for Leukemia and Solid Cancers

The epidemiology data available for human populations exposed to high-LET radiation are relatively sparse and have limitations that make them of limited utility for estimating risks. The available data sets together with a discussion of these limitations are provided in the 2011 NASA report in Section 5.1.1, entitled "Relative Biological Effectiveness from Human Epidemiology Studies" (Cucinotta et al., 2011). The committee agrees with NASA's conclusion that most insight on the influences of radiation quality on carcinogenesis comes from limited animal experiments coupled with cellular studies and use of biophysical models. The animal studies available include the Harderian gland studies (Fry et al., 1985; Alpen et al., 1993, 1994), work on skin cancer (Burns et al., 1993, 1994), work on mammary gland carcinogenesis (Dicello et al., 2004), and the recent Weil et al. (2009) work on acute myeloid leukemia (AML) and hepatocellular carcinoma. The results from these animal studies have indicated a large dependence of RBE for heavy ions on tissue and induced cancer type. This was dramatically shown in the study by Weil et al. (2009), in which a very high RBE (in the range of 50) was reported for hepatocellular carcinomas, but low RBE for AML. It should be pointed out that the large RBE is derived from the observation that a barely significant increase in liver tumors was seen for gamma rays even after the highest doses, but a large increase was seen even at the lowest doses for 1 GeV/nucleon Fe ions. The 2011 NASA report also has derived an RBE of 0.48 +/−0.007 for Fe ions relative to gamma rays for induction of AML based on the data presented in Weil et al. (2009). The range of doses and the levels of effect, however, were quite different for the iron ions and gamma rays, and so the establishment of an RBE with this small level of uncertainty will require further work. Nevertheless, the available animal data, coupled with the small amount of human data from Thorotrast studies (Boice, 1993; Grogan et al., 2001), are consistent with the proposed use of low QF for leukemia and substantially higher QF for solid cancers in the NASA model. The committee therefore endorses the use of separate QFs for leukemia and solid tumors and recommends further research using animal models to increase confidence in the numerical values to be used for those QFs.

It is anticipated that human data relevant to the assessment of quality factors for some solid cancers and cardiovascular disease will become available in the near future. Proton irradiation as well as carbon-ion irradiation (with different probabilities of fragment tails for these two radiations) of patients will in the future be a resource for this type of information, especially at different *Z*-values. NASA will need to monitor developments in this area of study.

Delayed effects of irradiation are discussed in Section 5 of the 2011 NASA report (Cucinotta et al., 2011), principally cited are several reports of genomic instability that was measured by a delayed increase in rates of appearance of new chromosomal aberrations or micronuclei in cells several cell generations following irradiation. In these cases, radiations have been shown to trigger a delayed or ongoing instability, apparently due to a decreased capacity for genome maintenance. Radiation-induced instability is potentially very important in connection with current notions of multistep processes involved in carcinogenesis, especially regarding any dependencies on radiation quality that may apply. It would have been useful, for a balanced view on the subject, to include mention in the 2011 NASA report of numerous literature reports in which such instabilities have *not* been seen (e.g., Kodama et al., 2005; Whitehouse and Tawn, 2001; Dugan and Bedford, 2003). Also, interestingly, there are reports of observations on genetic variability among individuals in susceptibility to radiation-induced genomic instability (e.g., Kadhim, 2003) that could have been cited, as well as studies on the lack of a delayed instability in clones of lymphocytes in numerous atomic bomb survivors decades after irradiation. Hence, this topic is in a state in which it can only be suggested as a factor that may be important if a connection to health risk could eventually be established. The whole question of the genetic contribution to variation in individual susceptibilities to radiation-induced cancer would be a fruitful area of further investigation. This is especially pertinent in light of the well-known body of evidence for genetic sources governing the wide variation in carcinogenic radiosensitivity in mouse strains, and more recent evidence for such genetic variation in human populations (e.g., Best et al., 2011; Flint-Richter and Sadetzki, 2007).

To date, the vast majority of Earth-based studies on effects of heavy ions that may be encountered in space involve exposures lasting only seconds or minutes. In light of the fact that exposures received by astronauts will be protracted over weeks, months, or even years in the case of Mars missions, the modification of effects per unit dose resulting from low dose rate exposures received over long periods of time for HZE radiations are briefly dis-

cussed in the 2011 NASA report. The issue of dose and dose rate, or DDREF, is mentioned above. At the cellular level, given the flux of HZE particles in space, the frequency at which cell nuclei are traversed by a particle track will be so low that the issue becomes one of how many cells in a tissue are traversed by a particle track, each of which would deliver a given dose to the cell traversed. As far as dose protraction over an extended time period is concerned, a further question would be whether some forms of time-dependent interactions, as yet unknown, occur among cells or involve other factors that could modify the overall response at the tissue or organ level. Such issues have not been studied adequately, and the fact remains that, with the few exceptions noted below, most Earth-based HZE studies have examined effects for exposures lasting only a few minutes.

A few literature reports (e.g., Burns et al., 1994; Alpen et al., 1994) cited in the 2011 NASA report show that protraction or fractionation of radiation exposures over time has resulted in increased, or in some cases decreased, incidences of induced cancers in animals relative to single exposures of short duration. To emphasize the broad scope and relevance of the issue, the 2011 NASA report mentions many factors aside from cellular and molecular repair processes that can contribute to the modification of carcinogenic or other biological effects, depending on fluence rate or dose fractionation. As mentioned above, further changes in the radiosensitivity of cells or tissues during prolonged exposure, and differences in the way that these changes may depend on radiation quality, greatly increase the uncertainties involved in use of quality factors that are based on data from single, short exposures. Hence, the 2011 NASA report (Cucinotta et al., 2011) correctly points out that there is more to fractionation and dose-rate effects than DNA repair processes might predict for both high- and low-LET radiations. The analysis in Cucinotta et al. (2011) thus summarizes why further studies should be undertaken to account for these several factors, which argue against the indiscriminant application of DDREF in risk estimation. It also emphasizes the need for further studies for HZE radiations.

Replacement of LET-Based Quality Factors with Track-Structure-Based Quality Factors

Cellular studies with end points of chromosome aberrations and neoplastic transformation are presented in the 2011 NASA report as examples of the common observation that RBE depends on LET, with a peak in RBE around 100 to 200 keV/μm. The description of cellular studies of chromosomal aberrations and mutations in the 2011 NASA report could be strengthened considerably by citing other relevant publications from research groups outside of NASA. A few relevant papers from these outside groups are Dugan and Bedford (2003); Cox et al. (1977a,b); Goodhead et al. (1979, 1980); Thacker et al. (1980); Bedford and Goodhead (1989); Anderson et al. (2000, 2005); Goodwin et al. (1996); Loucas and Cornforth (2001); Loucas et al. (2004); Elkind and Whitmore (1967); and Lloyd and Edwards (1983). The number of other relevant publications is limited somewhat because NASA's concerns focus on heavy-ion effects, but even so, there are many references not cited that agree with and strengthen the general conclusions based on those that are cited by NASA.

Importantly, the data (e.g., George and Cucinotta, 2007) also show that the LET value of the RBE peak increases with Z and that RBE increases with decreasing E. As already mentioned, LET is known to provide a poor description of track structure and energy deposition in biomolecules, cells, or tissues due to the different spatial distribution of ionization and excitation events for particles that have the same LET values (as illustrated in Figure 5.4 in the 2011 NASA report [Cucinotta et al., 2011] using data from Plante and Cucinotta [2008]). In part, this reflects the relative contributions of delta rays for different particles of similar LET. NASA's proposed model uses an approach for evaluating energy deposition changes with particle charge and energy that is based on biophysical models that include a description of radial dose (Goodhead, 1989).

The 2011 NASA report describes Monte Carlo methods that relate the stochastic aspects of radiation tracks to energy deposition patterns in nanometer volumes which include secondary electron (delta-ray) tracks. Thus predictions of the energy deposited in nanometer target sizes can be made for particles found in space radiation (Cucinotta et al., 2000). The results of these approaches indicate that the parameter Z^{*2}/β^2 gives a better description of the energy deposition in small nanometer volumes than does LET. Biological data from the literature chosen by NASA for use in its report show that the observed levels of biological effects (survival, mutations) differ significantly for different particles with the same LET (Thacker et al., 1979; Belli et al., 1992, 1993; Schafer et al., 1994;

Baltschukat and Horneck, 1991; Kiefer et al., 1994; Kranert et al., 1990), whereas the fits using the parameter Z^{*2}/β^2 gave better correspondence for particles with the same LET (Cucinotta et al., 1996, 1997).

The data presented in the 2011 NASA report support NASA's rationale for replacing the use of LET as a descriptor of track structure and energy deposition events in biomolecules, cells, or tissues for particle radiation, although the use of LET is not questioned by the radiation protection community for the development of risk estimates for terrestrial radiations. It is acknowledged by this committee that DNA strand breaks, cell death, mutations, and chromosomal aberrations may not be direct measures of cancer risk; however, they may be valuable markers assuming that cancer risk shows similar relative changes with radiation quality. Hence, an increasing amount of data, theory, and literature support is consistent with the idea that at low particle fluences, as present in space, the dependence of biological effects on radiation quality is not well described by LET alone and that instead, both Z and E must be considered in order to give an adequate description of three-dimensional track structure, including both the primary particle and delta rays.

Risk Cross Sections and Quality Factors

The development of risk cross sections, previously discussed in NCRP (2001) Report No. 137, has now been extended using Equations 5.19 through 5.21 in the 2011 NASA report (Cucinotta et al., 2011) to arrive at a QF function (called Q_{NASA} in Equation 5.21 but not elsewhere in the 2011 NASA report). This extension of risk cross sections allows consideration of track structure based on Z^{*2}/β^2 and biophysical models, enabling the extrapolation of experimental data to other particle types and the extrapolation of responses from acute exposures to chronic exposures. The assumption is made without discussion in Equation 5.19 in the 2011 NASA report (Cucinotta et al., 2011) that the risk cross section can be arithmetically partitioned into two independent components describing low- and high-LET-like behavior, respectively. The three variable parameters, Σ_0/α_γ, m, and κ, are estimated from the RBE of HZE particles for various radiobiological end points on Z^{*2}/β^2. Biological end points in mammalian cells for dicentrics, mutations involving the hypoxanthine-guanine phosphoribosyltransferase gene and neoplastic transformations (Figure 5.12 in the 2011 NASA report [Cucinotta et al., 2011]) have been chosen to show the dependence of risk cross sections on Z^{*2}/β^2 since data on solid cancer risk for HZE particles are scarce. The ranges of uncertainty for these three parameters are only estimated from radiobiological data and require more studies using HZE particles of different energy and Z to identify the most effective energy or value of Z^{*2}/β^2 to increase confidence in the use of risk cross sections.

Inspection of the risk cross sections for various biological end points as shown in Figure 5.12 of the 2011 NASA report (Cucinotta et al., 2011) highlights the paucity of data on cancer induction for different HZE particles. The uncertainties in the empirical model parameters, Σ_0/α_γ, m, and κ, estimated from the RBE of HZE particles for various radiobiological end points on Z^{*2}/β^2, and hence the uncertainties in QF, are responsible for the largest component of uncertainty in REID as calculated by NASA's proposed model (see the section below entitled "Integration and Completeness of the Model"). For similar reasons, Q is responsible for the largest component of uncertainty using NASA's current (2005) model. This weakness in both NASA's current and proposed models will continue to be an issue in the absence either of more data relating to cancer risk from HZE particles, or of more data using sufficiently reliable surrogate end points for cancer risk from HZE particles. A limitation of using Z^{*2}/β^2 is the lack of distinguishing track widths for different particles but with identical Z^{*2}/β^2values. Differences in the biological effectiveness of delta rays, especially for energies less than 10 keV (Goodhead and Nikjoo, 1989), have not been considered explicitly, since tracks of some particles—for example, low-energy hydrogen or helium—contain a higher fraction of delta rays at these lower energies. The use of LET, as in NASA's current (2005) model, also suffers from limitations regarding track width and delta-ray energies, as well as from additional limitations as discussed previously. Accordingly, the committee concludes that, given current knowledge, NASA's proposal to use Z^{*2}/β^2, rather than LET, and risk cross sections based on Z^{*2}/β^2 is reasonable and, hence, the committee judges that this change to the model is appropriate.

Non-Targeted Effects in the NASA Model

Section 5 of the 2011 NASA report (Cucinotta et al., 2011) also discusses the possibility of modifying the NASA model by adding a term for non-targeted effects, considered to be biological responses in cells that are not directly irradiated. The existence of such effects in cell culture systems has been widely documented for both high- and low-LET radiations (e.g., reviewed in NRC, 2006; UNSCEAR, 2008; Held, 2009), and the potential relevance of NTEs to space radiation biology has been discussed (Cucinotta and Durante, 2006; Held, 2009). However, there are also published studies in which the effect could not be demonstrated (e.g., Fournier et al., 2009). The existence of NTEs in vivo is less well documented, and the relevance to cancer risk is not known with any degree of certainty. Section 5 of the NASA report presents a clear discussion of the manner in which NTEs could be incorporated mathematically into the proposed risk model, and based on current knowledge, the approach seems reasonable. Furthermore, the section summarizes a recent study (Cucinotta and Chappell, 2010) in which the NTE-containing model, when compared with the so-called targeted effect (TE) model, was shown to improve the fit to data on cancer induction in the Harderian gland (data of Alpen et al., 1993) by a range of heavy charged particles. However, the NTE component is not incorporated into the final version of the proposed NASA risk model because the NASA report authors believe that insufficient data are available to lead to an understanding of the importance of NTEs in cancer risks at this time. The committee endorses the decision that an NTE component not be included in the NASA model at this time.

However, the committee points out that, although it is appreciated that the inclusion of considerations of NTEs in the 2011 NASA report was done to indicate potential future enhancements of NASA's proposed model, such an extensive discussion in the 2011 NASA report seems distracting for an element that is then not incorporated into the final version of the proposed model.

Another issue to consider relates to NTEs with HZE, since delta rays may crossfire into neighboring cells and need to be taken into consideration when defining bystander cells, especially as the energy deposition events due to the delta rays may extend several hundred microns or more. The committee believes that continued research on NTEs and their potential impact on cancer risk projections is highly warranted.

Qualitative Differences Between Low-LET Radiation and Heavy-Ion Biological Effects

The underlying assumption when using quality factors to scale from low- to high-LET risks, and the experimental RBEs on which the factors are based, is that the types of cell damage and response are the same with all radiation qualities. However, substantial evidence suggests that this assumption is not correct. The deposition of energy events for low-LET radiation is more sparsely distributed in cells and tissues, in contrast to the greater localization of energy along the particle track of heavy ions. These different properties result in qualitative differences at various levels of biological complexity, from DNA damage through to cellular and tissue responses. Starting at the DNA level, the distribution of lesions shows an increasing clustering and/or correlation of damage sites with the increasing ionization density of HZE particles, and hence there is an increasingly compromised ability of cells to repair the damage accurately. This can be recognized as increased mutability and changes in the spectrum of mutations (e.g., Zhu et al., 1996; Thacker et al., 1979) and at the chromosome level as increasingly complex chromosome aberrations with high-LET radiations (Anderson et al., 2000, 2005; Loucas and Cornforth, 2001; Loucas et al., 2004; Hande et al., 2003). At the cellular level these differences are reflected in the size of DNA repair-related protein foci and their slower resolution (Costes et al., 2006), differences in gene expression, and increased cellular inactivation.

Although the data are extremely limited, the animal carcinogenesis data are consistent with a different spectrum of cancer types (Weil et al., 2009) and reduced latency of cancer appearance (Burns et al., 1994; Dicello et al., 2004) after high-LET irradiation, suggesting underlying differences in the spectrum of damage types from low- and high-LET radiations.

Despite the limited data, the problems associated with applying universal quality factors based on a ratio such as RBE_{max}, which implies common biochemical and biological responses with low- and high-LET radiation, are clear. While this raises the question of whether universal LET-scaled (or Z^{*2}/β^2-scaled) quality factors are even

appropriate to use, at this time there does not appear to be a better approach. Further, the current position taken by NASA in the proposed model is largely overly conservative, or overprotective rather than underprotective. Hence, this is the most reasonable approach that can be taken at the present time. Thus the committee concludes that the use of the "simplistic" RBE ratios and quality factors in predictive modeling is justified at this time, but an investigation of the qualitative differences in damage and cell or tissue responses dependent on LET and other track structure features is an area in great need of research, with a goal of developing a more mechanistic-based understanding of biological processes for high-LET radiations.

Data or Research That Could Improve This Portion of NASA's Proposed Model

Although use of Z^{*2}/β^2 rather than LET has advantages and is a commendable improvement in NASA's proposed model, there are still deficiencies that include, for example, the lack of allowance for differences in track width between two particles with identical Z^{*2}/β^2, and the absence of a description in the 2011 NASA report of differences in biological effects of delta rays with different energies. To date, the data used have been at an intermediate LET value. To test the validity of the incorporation of Z^{*2}/β^2 instead of LET into NASA's proposed model, research is required to compare the biological effects by using either different particles of the same LET or individual particles at different energies and, hence, different LET values. Secondly, biological data with emphasis on cellular end points of relevance for cancer induction are needed for different particle types and energies, with different energy spreads of delta rays and track widths. The biological data should be obtained under conditions of low particle fluences (less than 1 particle traversal per cell). The biological effectiveness, derived from the data, needs to be interpreted in terms of stochastic track structure models. Additionally, studies are needed to demonstrate whether the end points related to DNA damage that have been widely used in studies of heavy particles are reasonable surrogates for cancer processes.

Due to the scarcity of data on cancer induction by particles relevant to space, research is required to obtain rates of cancer induction and/or a surrogate for cancer induction in animals by particles of different LET or Z^{*2}/β^2.

Studies at low dose rates or with fractionated doses, especially at the low fluences found in space, are needed with high-LET radiations. Recognizing the substantial difficulties, large numbers of animals needed, and the considerable expense in performing such studies in animals, new in vivo models are needed that accurately reflect cancer induction processes relevant to humans.

Recent data are consistent with the idea that the qualitative nature of damage and cell or tissue responses to the damage is different with high- versus low-LET radiations (e.g., reviewed in Held, 2009), as well as at high versus low radiation doses (e.g., Ding et al., 2005; Mezentsev and Amundson, 2011). Studies are needed to evaluate these differences in a systematic fashion and to provide insight on how, or whether, quality factors can appropriately be used if the nature of the damage is different with different radiation qualities.

Increasing evidence indicates that at low particle fluences (doses), dose-response curves may be non-linear due to NTEs. However, it is far from clear that NTEs such as bystander effects are necessarily detrimental, but may, at least in some cases, be beneficial due to removal of damaged cells (Prise et al., 2005; Portess et al., 2007; Schollnberger et al., 2007). Before an NTE component could be added to the risk model described in the 2011 NASA report, additional data are needed on NTEs at low particle fluences, for a range of particle types and energies, using cancer-relevant end points.

INTEGRATION AND COMPLETENESS OF THE MODEL

Background

General

As noted above, NASA's proposed space radiation cancer risk assessment model follows essentially the same overall methodology as that of the current NASA model, developed in 2005, which is based on recommendations by the NCRP (2000) in Report No. 132 and is summarized in Chapter 7 of NCRP (2006) Report No. 153. NASA's proposed model integrates a number of new findings and methods into its components, particularly by taking into

account newer epidemiological data and analyses, new radiobiological data, and an improved method for specifying quality factors in terms of track structure concepts rather than LET. The newer epidemiological information includes the life span study incidence data, transferred to the U.S. population and converted to mortality from U.S. population statistics. In addition, the model provides an alternative analysis applicable to lifetime never-smokers (NSs). Details of the uncertainty analysis have also been improved.

Key Elements of Model

The key input components of NASA's proposed model are summarized in Figure 2.7.

Each key element of NASA's proposed model is discussed in an earlier section of this chapter and is further evaluated below. The key elements are as follows: (1) the LSS cancer incidence rates, which provide tissue-, age-, and gender-specific coefficients of excess relative risk and excess absolute risk per unit dose of low-LET radiation; (2) cancer incidence and mortality and all-cause mortality in the U.S. population and in never-smokers, which enable the dose coefficients to be converted from incidence to mortality risk in the U.S. population or in never-smokers; (3) a dose and dose rate effectiveness factor, to adjust the low-LET risks to low-dose-rate protracted exposures; (4) radiation quality factor (QF) in terms of track structure risk cross sections (representing risk from individual charged particles), with separate specifications for solid tumors and leukemia, to adjust the low-LET coefficients to coefficients for the particle radiations in the space environment; and (5) tissue-specific particle spectra, $F(E,Z)$, and organ doses in the space-exposure radiation environment for which the risk of exposure-induced death is to be evaluated. NASA's proposed model calculates, as its main output, age- and gender-specific REID for the estimation of mission- and astronaut-specific cancer risk and also the associated uncertainties in REID. In addition, the tissue particle spectra and fluences are used together with corresponding quality factors and NASA-chosen tissue weighting factors representative of the space radiation environment to obtain, for that particular environment, a summary quantity that NASA calls effective dose, but which is only partially related to the effective dose defined by ICRP. This summary quantity is for use as an operational measure.

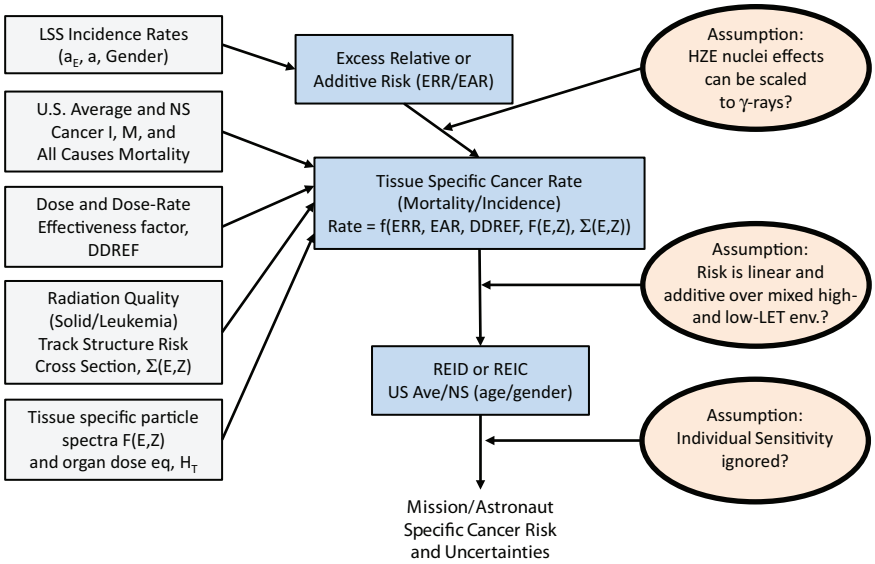

FIGURE 2.7 Flow chart of inputs and computation of risk of exposure-induced death (REID) and risk of exposure-induced cancer (REIC) in NASA's proposed model. The diagram is reproduced from the 2011 NASA report describing the proposed model. NOTE: Acronyms are defined in Appendix C of the present report. SOURCE: F.A. Cucinotta, M.-H.Y. Kim, and L.J. Chappell. 2011. *Space Radiation Cancer Risk Projections and Uncertainties—2010.* NASA/TP-2011-216155. NASA Johnson Space Center, Houston, Tex. July.

As noted in Figure 2.7, the list of major underlying assumptions in NASA's proposed model, and also in NASA's current (2005) model, includes assumptions that (1) cancer risks from space radiation particles can be scaled from risks from low-LET gamma rays, (2) risks from protracted radiation are linear with dose and additive over the components of mixed high- and low-LET radiations, and (3) individual sensitivity is ignored. These are standard simplifying assumptions widely used in radiation protection.

Principal NASA Changes to the Model

The main elements that have been revised or brought up to date in NASA's proposed model compared to its current (2005) model are highlighted in the Executive Summary of the NASA report (Cucinotta et al., 2011). The main elements are as follows:

1. Using the most recent tissue-specific cancer incidence risk coefficients derived from the LSS cohort data in Japan, the risks are transferred to an average U.S. population to estimate the probability of risk of exposure-induced cancer (REIC). Next the risk of exposure-induced death (REID) for cancer is obtained by applying estimated tissue-specific cancer survival rates in the United States and then summing up these individually estimated site-specific cancer mortality estimates.
2. An analysis is made of lung cancer and of other smoking-attributable cancer risks for never-smokers that shows significantly reduced lung cancer risks as well as reduced overall cancer risks compared to risks estimated for the average U.S. population. The lung cancer radiation risks for non-smokers are derived by applying lung cancer rates for never-smokers to the standard LSS risk coefficients.
3. Derivation is made of track-structure-based empirical radiation quality factors that depend on charge number, Z, and kinetic energy, E, in place of a dependence on LET alone.
4. There is specification of a smaller estimated maximum for the quality factor for leukemia than for solid cancers when estimating cancer site-specific risks for high-LET exposures.
5. The use of the ICRP tissue weights is shown to overestimate cancer risks from solar particle events by a factor of two or more. Summing cancer risks for each tissue is proposed in NASA's proposed model as a more accurate approach to the estimating of SPE cancer risks. However, to define a summary metric of space radiation exposures under realistic space environments, which NASA calls effective dose, it is proposed to choose gender-specific tissue weights to represent that environment. This quantity is only partially analogous to the protection quantity that ICRP defines as effective dose.
6. The uncertainty distributions for all model coefficients in the proposed NASA model (physics, low-LET risk coefficients, DDREF, and quality factors) have been updated and revised.
7. A statistical risk assessment model for SPEs is included.

Integration

The elements listed above are combined into an integrated model, which is available for application on a laptop by means of a graphical user interface screen. The low-LET risk coefficients, adjusted to protracted exposures by the DDREF, are folded with the quality factors and the tissue-specific particle fluence spectra so as to obtain age- and tissue-specific risks under the particular exposure conditions. The risks are then summed across attained age, with adjustment for competing causes of death, to obtain REID. Alternative outputs include REIC, so that it is also available for future use if required, and also a summary quantity that NASA calls *effective dose* for a particular radiation environment to use for operational purposes. Tables 6.2.a (females) and 6.2.b (males) in the 2011 NASA report (Cucinotta et al., 2011) provide a comparison of effective dose limits on 1-year missions for a 3 percent REID. In these comparisons, effective dose limits from NASA's current model, from BEIR VII (NRC, 2006), and from NASA's proposed model are provided for ages 30, 40, 50, and 60 years. In addition, dose limits in NASA's proposed model are given separately for the average U.S. population and for never-smokers. Of particular note for practical purposes, there are several differences between the values in NASA's current (2005)

model and those for NASA's proposed model's never-smokers that will impact the number of safe days in deep space (see Table 6.9 in the 2011 NASA report [Cucinotta et al., 2011]).

The tissue-specific cancer mortality risk equation in its track structure-based form for heavy-ion exposures in NASA's proposed model is described in the 2011 NASA report as

$$\lambda_{\mathrm{ZM}}(F_{\mathrm{T}}, a_{\mathrm{E}}, a) = \frac{\lambda_{\gamma\mathrm{M}}(a_{\mathrm{E}}, a)}{DDREF}\left\{D_{\mathrm{T}}(Z,E)\left(1 - P(Z,E)\right) + \frac{\Sigma_0}{\alpha_\gamma}P(Z,E)F_{\mathrm{T}}(Z,E)\right\} \tag{2.1}$$

where $\lambda_{\gamma\mathrm{M}}(a_{\mathrm{E}}, a)$ is the tissue-specific mortality coefficient for low-LET radiation, $D_{\mathrm{T}}(Z,E)$ is the tissue-absorbed dose from particles of charge Z and energy E, and $F_{\mathrm{T}}(Z,E)$ is the corresponding tissue fluence of these particles. The term in curly brackets partitions the risk from each heavy ion into a low-LET component and a high-LET component with relative proportions $(1 - P(Z,E))$ and $P(Z,E)$, respectively. $P(Z,E)$ is dependent on the quality of the radiation and is given by

$$P(Z,E) = \left(1 - \exp(-Z^{*2}/\kappa\beta^2)\right)^m \tag{2.2}$$

where Z^* is the effective charge number of the particle, β is its speed relative to the speed of light, and κ, m, and Σ_0/α_γ are empirical parameters, the values of which have been chosen to give what is deemed to be a suitable QF relationship.

Uncertainties

Table 6.5 of the 2011 NASA report summarizes the components of uncertainty that are quantified in NASA's proposed model. The model expresses uncertainty associated with low-LET radiation dose in terms of site-specific, radiation-related excess absolute risk and excess relative risk treated separately, multiplying them by independent random variables, as follows: $\mathrm{X_S}$, here denoting statistical error, is assumed to be normally distributed with mean 1.0 and standard deviation (SD) 0.15, and $\mathrm{X_B}$, here representing uncertain bias in incidence data, is normal with mean 1.0 and SD 0.05, as in NCRP (1997) Report No. 126. $\mathrm{X_D}$, here representing dosimetry errors, is treated as lognormal with geometric mean (GM) 0.9 and geometric standard deviation (GSD)1.3. For low doses, and for higher doses delivered at low dose rates, the product of $\mathrm{X_S}$, $\mathrm{X_B}$, and $\mathrm{X_D}$ is divided by $\mathrm{X_{DDREF}}$ which is assumed to be equal to 1.75 times a left-truncated (at 0.75) lognormal random variable with GM 1.0 and GSD 1.4 before truncation. For transfer of LSS-based risk estimates to non-smoker U.S. populations, the site-specific LSS EAR estimates were used for breast cancer and the site-specific ERR estimates, times baseline, were used for thyroid cancer; for digestive cancers, differential additive weights of 0.3 for EAR and 0.7 for ERR times baseline were used, whereas for leukemia, cancers of the lung, and other cancer sites, equal additive weights were used (i.e., 0.5 for EAR and 0.5 for ERR times baseline).

Table 6.5 of the 2011 NASA report (Cucinotta et al., 2011) also includes uncertainties related to the quality and doses (or fluences) of space radiation. The quality factors (QFs) are defined as functions of Z^{*2}/β^2 of the particles in terms of three empirical parameters: (1) Σ_0/α_γ, times a lognormal random uncertainty factor with GM = 0.9 and GSD = 1.4; (2) κ, multiplied by an uncertainty factor distributed as N(1,0.2); and (3) m, taking discrete values 1.5, 2, 2.5, 3, 3.5, and 4 with probabilities 0.05, 0.1, 0.2, 0.4, 0.2, and 0.05, respectively. The space environment physics-related uncertainties for high-energy charged particles including protons, neutrons, and heavier atomic nuclei are expressed in table 6.5 by a random multiplier $F(Z^{*2}/\beta^2)$ distributed as N(1.05, 0.333) for $Z < 5$ and distributed as N(1.0, 0.25) for $Z \geq 5$.

The components of uncertainty are combined in NASA's proposed model by Monte Carlo methods, so as to obtain the probability distribution for REID.

Model Completeness, Improvements, and Recommendations

Each of the key elements of NASA's proposed model is discussed in detail in previous sections of this report. In addition, those sections describe how NASA's proposed model differs from its current (2005) model and how

adequately these changes have been incorporated into the proposed model. In this section, the committee provides an evaluation of the completeness of each key element of the model and, in particular, how these elements are integrated to produce NASA's final proposed space radiation cancer risk assessment model. The approach that the committee used is to assess the completeness of each element as presented by NASA and, based on this evaluation, to discuss possible improvements to the model together with recommendations and suggestions for addressing the gaps addressed by the possible improvements. In some cases, additional research might be needed to enhance NASA's proposed model.

On the basis of its review, the committee notes that the general approach to estimating cancer risks from exposure to low-LET radiation follows the approach utilized by ICRP, NCRP, EPA, and BEIR VII, and as such that it is state of the art. The specific data incorporated into NASA's proposed model are generally appropriate, with some exceptions, noted below, relating to new data that have become available since the development of the model or additional data sets that were already available and not selected for use by NASA. In addition, the committee concludes that for the estimation of REID from space radiation, NASA has identified the major issues and, as discussed below, has suitably addressed these, although in a few cases the approach has raised some questions and concerns. These comments are made within the framework that NASA needs for assessing individual risks and providing a summary metric for operational purposes. The following sections discuss the key elements of the proposed NASA model.

Key Element: Cancer Risk Projection Model (Low-LET Radiation)

Model Completeness

The cancer risk projection component of NASA's proposed model is as complete as our current understanding allows, and the general approach follows standard methods also used by national and international radiation protection committees. However, the committee has a number of recommendations for improvements to the model inputs and for modification of aspects of the approach. The key recommendations and conclusions are summarized below. The details are provided in the section above entitled "Cancer Risk Projection Models."

Model Improvements and Recommendations

Cancer Mortality Risk Estimation. A major proposed change in NASA's proposed model is to use the "incidence-mortality" approach developed by BEIR VII (NRC, 2006) whereby risk coefficients from LSS cancer incidence models are used, and then cancer mortality risks are estimated from these incidence risks. The approach results in considerable changes in the REID estimates, particularly in the pattern with age at exposure. The committee considers the approach to be an improvement for site-specific cancer mortality estimation because LSS site-specific cancer incidence data are likely to be more accurate than are cancer mortality data, which suffer from misclassification of causes on death certificates.

Recommendation: Before NASA implements its proposed major change to the "incidence-mortality" approach, the committee recommends that NASA conduct more research into the specific patterns of the underlying epidemiological biases that drive these changes. The committee also highlights a specific problem with the method of estimating the mortality probability from the ratio of cancer mortality to incidence as developed by the BEIR VII report published by the National Research Council in 2006 and proposed for use by NASA. In response, the committee recommends that NASA consider alternative methods for improved estimation of mortality probabilities for each cancer site. For example, as presented in its 2011 report *EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population,* the Environmental Protection Agency has developed an alternative approach for breast cancer mortality estimation, and this could serve as a suitable approach to be applied by NASA.

Transfer of Risk Estimates from the Japanese to the U.S. Population. Because underlying cancer incidence rates for some cancer sites differ greatly between the Japanese and the U.S. populations, risk estimates based on

an excess relative risk model can give very different REID values from those based on an excess absolute risk model. A number of organizations and committees have recommended that a weighted average of the ERR and EAR models be used. The proposed NASA approach follows BEIR VII (NRC, 2006) in calculating a weighted average with uncertain weights and generally follows the recommended BEIR VII weights.

Recommendation: Because there are some deviations in NASA's proposed model from the weights recommended by BEIR VII for the excess relative risk and excess absolute risk models, the committee recommends that NASA provide additional justification for these alternative weights. (See additional comments below on never smokers.)

Dose and Dose Rate Effectiveness Factor. A DDREF value is applied to adjust the LSS-based cancer risk coefficients to apply to low-dose-rate protracted exposures, following conventional practice. In NASA's proposed model, it is assumed that the DDREF applies only to gamma rays and that there is no dose-rate dependence of risks from space radiation. Differences between space radiation charged particles and gamma rays at low dose-rate are encompassed entirely within the quality factor (QF) discussed below. This is a standard assumption for high-LET radiations in the field of radiation protection. NASA's proposed model uses an uncertain DDREF with a median value of 1.75, which was based on subjective uncertainty distributions developed for the NIH radioepidemiological tables (NIH, 2003). A number of publications produced since the NIH report are relevant to this issue.

Conclusion: Although the proposed NASA approach for estimating a DDREF describes a number of limitations in these newer epidemiological studies and in the BEIR VII DDREF methodology, the justification given for preferring the older NIH approach is that it is close to the average of various recommended values of slightly less than 2. The use of this average value is somewhat problematic given that the recommended values that are used to derive this average are not independent and thus applying equal weights to these is not justifiable.

Recommendation: The committee agrees with the use of an uncertainty approach for estimating DDREF, but it recommends that NASA use a central value and distribution that better accounts for the recent epidemiological and laboratory animal data.

Risk Models for Never-Smokers. The issue of the smoking status of the astronauts and the potential implications on risk projections for smoking-related cancers are important, and it is appropriate that this should be investigated. Most astronauts are non-smokers, which would likely lower the risk projections for astronauts compared to estimates for the general population (a mixture of never- and ever-smokers).

Recommendation: The proposed NASA approach for estimating lung cancer risks for astronauts who are never-smokers is limited and does not consider competing risks. Thus, the committee recommends that the NASA approach be developed further, given the important impact that it has on reducing estimated risk. The revised approach should use survival probabilities for competing risks that are specific to never-smokers. Further, the committee recommends that NASA make no changes at this time in the proposed model to include other smoking-related cancers. The data are not sufficiently robust for use in the modification of the REID estimate.

Key Element: Radiation Quality and Track Structure Risk Cross Section

Model Completeness

As in the current NASA model, quality factors in NASA's proposed model are applied to convert the low-dose low-LET cancer risk coefficients to risk coefficients for the variety of charged particles from space radiation. The underlying assumption is that the age- and tissue-specific risks can be simply scaled from low-LET radiation to HZE particles. Although there are known to be qualitative differences between the biological damage inflicted by

high-LET and low-LET radiations at the molecular and higher levels and there are possibly also different spectra of cancer types and latency, the committee agrees that simple scaling of risks is reasonable, given the current limited state of knowledge of qualitative differences in health effects (see also the section below entitled "Key Element: Other Issues").

The main radiation quality parameter is Z^{*2}/β^2, and this largely takes the place of LET, although three additional parameters (κ, Σ_0/α_γ, and m) are also introduced by Equation 2.2 above to define $P(Z,E)$ in the quality factor relationships for risk as a function of Z^{*2}/β^2. According to Equation 5.21 of the 2011 NASA report (Cucinotta et al., 2011):

$$QF = \left(1 - P(Z,E)\right) + \frac{6.24(\Sigma_0/\alpha_\gamma)}{LET} P(Z,E). \tag{2.3}$$

Thus, QFs are created for NASA's proposed model on the basis of a number of empirical relationships and parameters that have been judged to give a reasonable description of the RBEs for a variety of available radiobiological data for heavy ions. These available radiobiological data are from animal and cellular systems but are quite limited in scope and in their relationship to carcinogenesis, as described in the section above entitled "Cancer Risks and Radiation Quality in the Model." The parametric forms of the QF relationships have been guided by aspects of track structure and by aspects of a specific biophysical model, but it is stated that the interpretation of the parameters is not tied to any particular model. These empirical relationships replace the Q(L) relationship used in the current NASA risk model. The committee considers NASA's proposed definition of QF to be reasonable and agrees that the parametric forms should be regarded as essentially empirical and not as having been formally derived from biophysical first principles.

Conclusion: In the proposed model, different maximum values of quality factor, QF, are assumed for leukemia (maximum 10) and for solid tumors (maximum 40). This is a change from the current NASA risk model. The committee agrees that it is reasonable to make such a distinction on the basis of the limited animal and human data available.

The concepts underlying this new parameterization of QF and the rationale for their use are discussed in the section above entitled "Cancer Risks and Radiation Quality in the Model." Overall, the committee considers that the new parameterization, although more complicated, provides an improvement over the previous LET descriptions, particularly for the wide diversity of HZE and lower-energy charged particles to which astronauts are exposed in space. Not only are the new QF relationships likely to be more accurate for the proposed risk model, but they are also more amenable to uncertainty analysis and can guide future research aimed at reducing the parameter uncertainties and improving the form of parameterization.

At a purely empirical level, plotting the relative biological effectiveness of charged particles against Z^{*2}/β^2 does tend to bring the RBE data closer toward a single curve (for a given biological system) compared to the plotting of RBE against LET. However, as is noted in the 2011 NASA report, the uncertainties related to the quality factor are still the largest contributor to the overall uncertainty of REID.

Model Improvements and Recommendations

For NASA's proposed model, values for the three parameters that define QF have been selected by comparison with experimentally observed variations in biological effectiveness with radiation type for some cellular biological effects and by considering the few available data on the induction of cancer by high-LET radiation. However, it is not clear from the 2011 NASA report how the particular values were decided, including the ad hoc selection of different values for parameters κ and Σ_0/α_γ for ions of $Z \leq 4$ compared to all ions of higher charge, and what analyses were carried out.

Recommendation: The committee recommends that NASA make a detailed comparison of the relative biological effectiveness versus Z^{*2}/β^2 dependence of the experimental data with the proposed form and parameters of the quality factor, QF, equation in order to improve the transparency of the basis for the selection of the proposed parameter values for the model and to provide guidance for future research to test, validate, modify, and/or extend the parameterization. This analysis needs to include the defined selection of different values for parameters κ and Σ_0/α_γ for ions of $Z \leq 4$ compared to all ions of higher charge.

The risk equation of NASA's proposed model (see Equation 2.1 above) follows directly from the proposed risk cross-section Equation 5.19 of the 2011 NASA report (Cucinotta et al., 2011), namely:

$$\Sigma(Z,E) = \Sigma_0 P(Z,E) + \frac{\alpha_\gamma LET}{6.24}(1 - P(Z,E)). \tag{2.4}$$

This equation partitions the risk from a single heavy ion into two components, one of which behaves exclusively as the low-LET component of energy deposition and the other exclusively as the high-LET component, with no radiobiological interaction between the two components. This important assumption is introduced in the 2011 NASA report as Equation 5.19 (Cucinotta et al., 2011), but without any clear attempt to justify it or to present a rationale for its use. The committee recommends that work be carried out to validate this assumption.

Key Element: Effective Dose

Model Completeness

The ICRP defines the quantity "effective dose" for use in radiation protection and states that it is intended mainly for use in "prospective dose assessment for planning and optimisation in radiological protection, and demonstration of compliance with dose limits for regulatory purposes" (ICRP, 2007, p. 13). Its computation includes tissue weighting factors (w_T), the specific normalized values of which are defined by ICRP for the individual tissues of the body as an approximate gender-averaged representation of the relative contribution of each tissue to the radiation detriment of stochastic effects from uniform whole-body low-LET irradiation.

The 2011 NASA report defines its own quantity, which it also calls effective dose, and it states that this quantity is strictly for internal NASA use. This NASA quantity is analogous to ICRP effective dose but is based on NASA's own gender-specific sets of relative tissue weights (w_T) for the space radiation environment and NASA's definition of quality factor for the space radiation environment. Values for w_T are chosen in the 2011 NASA report to match the estimated tissue-specific components of REID from the various tissues in representative space radiation environments, including the high-LET radiation components. Values of w_T are calculated by NASA's proposed model. These NASA w_T values can differ substantially from the ICRP values for a variety of reasons, particularly due to gender-specificity, inclusion of only radiation-induced death from cancer and not other forms of health detriment, the low penetration of some components of space radiation (such as the lower-energy SPE protons), and different QFs for leukemia compared to solid cancers. The committee considers NASA's proposed model to be an appropriate tool for calculating this summary metric.

It should be noted that the partly substantial changes in weighting factors that NASA uses for evaluating *its* effective dose in comparison to the ICRP effective dose do not lead to major differences under many space radiation environments, as illustrated in Figures 6.4 and 6.5 in the 2011 NASA report (Cucinotta et al., 2011). In circumstances in which there are large differences, such as from SPE exposures, it is explained in the report that these are due to the relatively much larger doses to superficial organs compared to the more cancer-prone deep-seated organs. It would be useful to make clear that the main driver of these differences in effective dose is the chest/breast, which alone is responsible for about 40 percent of the total ICRP effective dose in the case of the SPE

example given in Table 2.7 of the 2011 NASA report (Cucinotta et al., 2011), due to the large superficial dose to this tissue and to its large ICRP tissue weighting factor (0.12).

Model Improvements and Recommendations

As described above, NASA proposes to use its own summary quantity for mission operational purposes, and in the 2011 NASA report this quantity is simply called effective dose. However, "effective dose" is, strictly speaking, a quantity defined by ICRP, including ICRP-defined specification of numerical values for weighting factors and gender-averaging. If different tissue weighting factors and radiation quality specifications are used and effective dose is evaluated without gender-averaging, it is problematical for the resulting quantity still to be called effective dose and the unit sievert given to its numerical values. The committee believes that the NASA description of the proposed model would be improved by the use of terminology and notation that distinguish NASA-defined quantities (especially effective dose) from those defined by ICRP. Wide dissemination of the definition of "effective dose" within NASA and the research community would reduce confusion about what exactly is being measured or limited.

It is not clear from the 2011 NASA report in what ways the NASA-defined effective dose will be implemented as a summary variable for mission operations. The provision of further information would be useful, including what quantity or quantities are used for the calibration of area and personal monitors in space vehicles and how these calibration quantities compare with the NASA versions of effective dose.

Key Element: Tissue-Specific Particle Spectra, F(E,Z)

Model Completeness

The assessment of cancer risk due to space radiation begins with defining the external (or ambient) radiation environments, which in turn are inputs to transport-shielding calculations to obtain the local radiation environment, modified by spacecraft and body shielding, at tissues of concern. GCR and particles from SPE are two major components[3] of the space radiation environment. Hence, tissue-specific particle fluence spectra, denoted by $F(E,Z)$, are obtained as input to the cancer risk calculation, together with all of the components described above. The committee concludes that NASA's proposed model uses standard and well-studied methods for the specification of the space radiation environment and computation of the tissue-specific particle spectra.

Model Improvements and Recommendations

The radiation environment and shielding transport models in NASA's proposed model are considered by the committee to be a major step forward compared to previous models used (especially the introduction of the statistical SPE model to NASA's proposed model in place of the current SPE model). The proposed SPE model is not actually a probabilistic risk assessment (PRA), as is suggested in the Executive Summary of the 2011 NASA report (Cucinotta et al., 2011), but rather a statistical model developed using a data set from past measurements.

The committee agrees that the proposed radiation environment and shielding transport models have been developed with the extensive use of available data and rigorous mathematical analyses. The uncertainties conservatively allocated to the space physics parameters (i.e., environment and transport models) are deemed adequate at this time, considering that the space physics uncertainty is only a minor contributor to the overall cancer risk assessment. The currently used paradigm for both galactic cosmic rays and solar energetic particles is based entirely on the statistics obtained from past measurements. The committee agrees that the specification of the space physics parameters is done as well as it can be with this approach, and it may well be adequate for NASA's purpose given other uncertainties in REID. However, the committee suggests that estimates could be improved by adding physics-based studies of particle transport using the current picture of the heliosphere and its electric and magnetic fields. Particle transport in the interplanetary medium is determined by the electric and magnetic fields

[3]As stated in footnote 1 at the beginning of this chapter, trapped-particle models are not covered here because they contribute very little to the organ dose for missions aboard the International Space Station or missions to the Moon or Mars.

in the solar wind. Theoretical and numerical studies of particle trajectories should certainly result in improved transport models and smaller uncertainties in the environmental estimates. However, this would involve a major effort and change in modeling approach and may not be warranted in view of the relatively minor contribution of space physics uncertainties.

Key Element: Uncertainties

Model Completeness

The committee considers that the handling and combining of uncertainties in the NASA's proposed organ-site-specific models, as presented in Table 6.5 of the 2011 NASA report (Cucinotta et al., 2011), are logical and appropriate as applied to statistical errors, bias in cancer incidence data, dosimetry errors, transfer model weights, and DDREF for low-LET radiation, and for radiation quality factors and risk cross sections for space radiation, as well as for the physics uncertainties of space radiation.

It is not clear, however, that the use of empirical Bayes estimates for the calculation of cancer risks for multiple organ sites, as discussed in Sections 3, 3.1, and 4.2 and in Table 4.1 of the 2011 NASA report, offers any advantage for estimating cancer mortality risk for all organ sites combined, as discussed in the following section.

Model Improvements and Recommendations

NASA's proposed model does not include an upward bias correction for dosimetric uncertainty in the underlying life span study data (Pierce et al., 2008); however, the correction would be small at the dose levels anticipated for astronauts in the near future. In the 2011 NASA report, the discussion of the use of a maximum likelihood estimate (MLE) and empirical Bayes (EB) estimate of site-specific ERR per sievert in Section 4.2 and Table 4.1 is somewhat confusing. For example, as shown in the table, the site-specific EB estimate of ERR per sievert for kidney cancer (0.40) would be similar to the MLE (also 0.40 for this particular organ site), with a lower estimated standard error (0.19) compared to the MLE standard error of 0.32. This difference is due to the fact that the site-specific EB estimate uses additional risk information from organ sites other than the kidney, and the MLE estimate does not. However, the variance (and therefore the standard error) of the summed site-specific estimates of ERR per sievert over all cancer site groupings in the table should be similar for the MLE and EB approaches, because the EB error calculation would include information from the (mostly positive) off-diagonal elements of the covariance matrix as well as the estimated variances. It is not clear whether the EB approach has been used in NASA's proposed model.

Recommendation: On the assumption that the empirical Bayes approach has been used in NASA's proposed model, the committee recommends that the authors ensure that the off-diagonal covariance information has been taken into account. If the EB approach has not been used, either this fact should be stated in the text of the 2011 NASA report (Cucinotta et al., 2011) or the references to the EB approach should be removed from the text.

The uncertainty analysis in NASA's proposed model reveals that the value of QF is the largest contributor to the uncertainty of REID, alone introducing about 3.4-fold uncertainty in risk. Additionally, it is found that this component is reduced to 2.8-fold uncertainty if two of the track structure parameters are constrained to a fixed algebraic relationship to one another (such that the Z^{*2}/β^2-position of the maximum value of QF is held fixed).

Conclusion: NASA's proposed model discusses the observation that the use of a fixed relationship between two track structure parameters reduces the uncertainty as being a potentially valuable finding that may provide a method to reduce uncertainty in estimations of the REID. However, little indication is given in the 2011 NASA report as to why such a fixed position might be justified or expected. The

committee suggests that further investigations into the validity and usefulness of this approach would be worthwhile.

Key Element: Other Issues

Non-Cancer Effects (Tissue Reactions)

In its proposed approach to estimating the safe days in deep space, NASA has used a 3 percent REID for fatal cancer as the limit. In its current (2005) model, NASA also considers dose limits for non-cancer effects—lens, skin, blood-forming organs, heart and central nervous system. For example, "career limits for the heart are intended to limit the REID for heart disease to be below approximately 3 to 5 percent, and are expected to be largely age and sex independent" (NASA, 2005, p. 65). It was further assumed by NASA that the limits established would restrict mortality values for these non-cancer effects to less than the risk level for cancer mortality. The cancer and non-cancer risks were not combined into a single REID. More recent data have led ICRP to reconsider the threshold dose values, particularly for the cardiovascular system (and cataracts) (see ICRP, 2011). It is concluded by ICRP (2011) that a threshold absorbed dose of 0.5 Gy should be considered for cardiovascular disease (and cataracts) for acute and for fractionated/protracted exposures. It is appreciated by ICRP that these values have a degree of uncertainty associated with them. For example, several reports suggest that effects on the cardiovascular system occur only at much higher dose levels (Mulrooney et al., 2009; Davis et al., 1989).

Conclusion: The revised value for the threshold dose value proposed by ICRP suggests that NASA may need to consider how it might account for cardiovascular disease in their calculations of dose limits. However, it is noted that to date there is very little information on RBE for non-cancer effects that is needed for risk estimates for space radiation exposures.

By continuing to monitor developments in the area of potential cardiovascular effects at low doses of radiation, NASA would have the opportunity to determine if there is a need to modify the proposed estimates of REID.

Delayed Effects

Delayed effects pertinent to the assessment of risk principally relate to observations whereby radiation-induced genomic instabilities have been reported, as measured by the appearance of a delayed increase in the rates of new chromosomal aberrations, mutations, or micronuclei in cells several cell generations after irradiation. Such effects could have important implications for radiation protection in view of current notions of the multistep mutational processes involved in carcinogenesis. An early induced change in subsequent and ongoing mutation rates in irradiated somatic cells could accelerate this process.

Conclusion: There are conflicting reports on the generality of the phenomenon of radiation-induced delayed genomic instability and some question about variation in susceptibilities of cells from different individuals with regard to this effect. Thus, the committee concludes that it is appropriate that genomic instability not be incorporated into the model, in agreement with the proposed NASA approach. However, the committee considers that further investigation of the phenomenon is certainly warranted.

Non-Targeted Effects

Non-targeted effects largely refer to the so-called bystander effects, by which responses can be produced in an unirradiated cell as a result of the transfer of a signal from an irradiated cell. For HZE radiations, doses that may be received by astronauts are very non-uniform in the sense that some cells will be traversed by the primary particle itself, whereas other cells will not be traversed; thus, an NTE is also a phenomenon that is of considerable interest.

Conclusion: While the 2011 NASA report contains an extended discussion on non-targeted effects (NTEs) and their potential impact on risk estimates, they appropriately chose not to include these NTEs in their proposed model at this time. Little is known in qualitative or quantitative terms of the contribution of these NTEs directly related to radiation-induced carcinogenesis, but the committee believes that studies to elucidate any such relevance should be encouraged.

Qualitative Differences

It is recognized that there are qualitative differences in the nature of the initial energy depositions and hence in initial chemical, biochemical, and biological damages from different types of ionizing radiation. Differences are particularly great between low-LET gamma rays and the wide variety of high-LET heavy ions in space radiation. This may lead to observed differences in responses of cells, tissues or organisms such as different spectra of mutations and chromosome aberrations, altered gene-expression patterns, and different types and latencies of cancer. There is experimental evidence for qualitative differences at each of the above levels of biological effect. As a result, it may not be entirely appropriate to apply universal QFs as quantitative scaling factors, based on quantities such as RBE that assume similar underlying biological processes. This is an area in which experiments quantifying types, frequencies, and latencies of various cancers—for example, lung, colon, and breast cancer—as well as the studies of leukemia and liver cancer mentioned above, are sorely needed for radiations of varying LET, especially at low particle fluences such as in space. Furthermore, the tumor studies would need to be coupled with appropriate mechanistic investigations to provide understanding of the underlying carcinogenic processes.

Probabilistic Risk Assessment

The performance of a probabilistic risk assessment of spaceflight cancer risk implies the consideration of a comprehensive set of radiation exposure scenarios involving an array of radiation hazards over a long period of time and an assessment of the vulnerability of a complex engineered system under a variety of threats. Although it was not the intent of NASA's proposed model to be comprehensive in terms of the risk scenarios, as the focus was limited to the health effects component of a total system risk model, it is important to recognize the limitations of the model in reference to best practices in total-system PRA. Details were lacking in the 2011 NASA report regarding the PRA context of NASA's current (2005) model and the planned steps toward an eventual total-system cancer risk model.

Eventual movement to a total-system cancer risk model would require the development of scenario sets that include not only the quantification of the health effects but the details of the dynamics of the radiation source term and consideration of the "what can go wrong" scenarios associated with specific missions. Examples of such scenarios are unexpected solar particle events and a failure of radiation protection systems. The extent to which NASA's current (2005) model accommodates multiple scenarios is not clear. Experience suggests that several exposure and shielding scenarios will have to be considered should the decision be made to perform comprehensive, mission-specific risk assessments.

The 2011 NASA report (Cucinotta et al., 2011) does make clear that there are only two radiation sources of interest, GCR and SPE. The report includes data suggesting that the GCR radiation environment is well characterized and nearly constant over time during solar-cycle activity minima. The report also includes data suggesting that SPEs may not contribute significantly to risk during solar-cycle activity minima and may be mitigated by shielding. This may be the case with respect to the radiation source term, although it is doubtful, but it is certainly not the case with respect to quantifying "what can go wrong" scenarios. It is possible that a single radiation hazard scenario is sufficient for a comprehensive PRA, but it would be a unique circumstance in the practice of PRA, and there is a lack of evidence to support such a condition.

It is always possible that many "what can go wrong" scenarios can be recovered from during a mission, but if that is part of the process, then recovery activities, such as the possible need for extravehicular activity, also have to be evaluated for their contribution to the overall risk. Evidence was not presented to indicate that such scenarios were actually considered or, that if they were, how they entered into the risk assessment.

A major strength of comprehensive PRA is the quantification of the uncertainties and the importance ranking of the contributors to risk. The absence of the importance ranking of the contributors, including their uncertainties, compromises the comprehensiveness and possibly the capability of NASA's proposed model. To be sure, the NASA methodology for characterizing uncertainty in the health effects model is comprehensive, but the point is that there is much more to a comprehensive risk assessment of the cancer risk of a space mission than the health effects model. In order to perform total-system and comprehensive risk assessments, much more attention to detail is required, particularly with respect to quantifying other factors contributing to risk, such as the engineering driven *"what can go wrong"* scenarios that experience indicates to be major contributors to risk.

REFERENCES

Alpen, E.L., Powers-Risius, P., Curtis, S.B., and DeGuzman, R. 1993. Tumorigenic potential of high-Z, high-LET charged particle radiation. *Radiation Research* 88:132-143.

Alpen, E.L., Powers-Risius, P., Curtis, S.B., DeGuzman, R., and Fry, R.M.J. 1994. Fluence-based relative biological effectiveness for charged particle carcinogenesis in mouse Harderian gland. *Advances in Space Research* 14:573-581.

Anderson, R.M., Marsden, S.J., Wright, E.G., Kadhim, M.A., Goodhead, D.T., and Griffin, C.S. 2000. Complex chromosome aberrations in peripheral blood lymphocytes as a potential biomarker of exposure to high-LET alpha-particles. *International Journal of Radiation Biology* 76:31-42.

Anderson, R.M., Tsepenko, V.V., Gasteva, G.N., Molokanov, A.A., Sevan'kaev, A.V., and Goodhead, D.T. 2005. mFISH analysis reveals complexity of chromosome aberrations in individuals occupationally exposed to internal plutonium: A pilot study to assess the relevance of complex aberrations as biomarkers of exposure to high-LET alpha particles. *Radiation Research* 163:26-35.

Armstrong, B.G. 1990. The effects of measurement errors on relative risk regressions. *American Journal of Epidemiology* 132(6):1176-1184.

Baltschukat, K., and Horneck, G. 1991. Response to accelerated heavy ions of spores of *Bacillus subtilis* of different repair capacity. *Radiation and Environmental Biophysics* 30:87-104.

Barth, J. 1997. "Modeling Space Radiation Environments," presentation at the IEEE Nuclear and Space Radiation Effects Conference Short Course: Applying Computer Simulation Tools to Radiation Effects Problems, July 21, 1997, IEEE NPSS Radiation Effects Committee. NASA Goddard Space Flight Center, Greenbelt, Md.

Bedford, J.S., and Goodhead, D.T. 1989. Breakage of human interphase chromosomes by alpha particles and X-rays. *International Journal of Radiation Biology* 55:211-216.

Belli, M., Goodhead, D.T., Ianzini, F., Simone, G., and Tabocchini, M.A. 1992. Direct comparisons of biological effectiveness of protons and alpha-particles of the same LET. II. Mutation induction at the HPRT locus in V79 cells. *International Journal of Radiation Biology* 61:625-629.

Belli, M., Cera, F., Cherubini, R., Haque, A.M.I., Ianzini, F., Moschini, G., Sapora, O., Simone, G., Tabocchini, M.A., and Tiverton, P. 1993. Inactivation and mutation induction in V79 cells by low energy protons: Re-evaluation of the results at the LNL facility. *International Journal of Radiation Biology* 63:331-337.

Best, T., Li, D., Skol, A.D., Kirchhoff, T., Jackson, S.A., Yasui, Y., Bhatia, S., Strong, L.C., Domchek, S.M., Nathanson, K.L., Olopade, O.I., et al. 2011. Variants at 6q21 implicate PRDM1 in the etiology of therapy-induced second malignancies after Hodgkin's lymphoma. *Natural Medicine* 17:941-943.

Boice, J.D. 1993. Leukemia risk in thorotrast patients. *Radiation Research* 136:301-302.

Burns, F., Yin, Y., Koenig, K. L., and Hosselet, S. 1993. The low carcinogenicity of electron radiation relative to argon ions in rat skin. *Radiation Research* 135:178-188.

Burns, F., Yin, Y., Garte, S.J., and Hosselet, S. 1994. Estimation of risk based on multiple events in radiation carcinogenesis of rat skin. *Advances in Space Research* 14:507-519.

Cardis, E., Vrijheid, M., Blettner M., Gilbert, E., Hakama, M., Hill, C., Howe, G., Kaldor, J., Muirhead, C.R., Schubauer-Berigan, M., Yoshimura, et al. 2005. Risk of cancer after low doses of ionising radiation: Retrospective cohort study in 15 countries. *British Medical Journal* 331(7508):77.

Costes, S.V., Boissière, A., Ravani, S., Romano, R., Parvin, B., and Barcellos-Hoff, M.H. 2006. Imaging features that discriminate between foci induced by high- and low-LET radiation in human fibroblasts. *Radiation Research* 165:505-515.

Cox, R., Thacker, J., Goodhead, D.T., and Munson, R.J. 1977a. Mutation and inactivation of mammalian cells by various ionizing radiations. *Nature* 267:424-427.

Cox, R., Thacker, J., Goodhead, D.T., and Munson, R.J. 1977b. Response of 2 different mammalian-cell types to high LET radiations. *British Journal of Radiology* 50:537-537.

Cucinotta, F.A., and Durante, M. 2006. Cancer risk from exposure to galactic cosmic rays: Implications for space exploration by human beings. *Lancet Oncology* 7:431-435.

Cucinotta, F.A., and Chappell, L.J. 2010. Non-targeted effects and the dose response for heavy ion tumor induction. *Mutation Research* 687:49-53.

Cucinotta, F.A., Wilson, J.W., Shavers, M.R., and Katz, R. 1996. Effects of track structure and cell inactivation on the calculation of heavy ion mutation rates in mammalian cells. *International Journal of Radiation Biology* 69:593-600.

Cucinotta, F.A., Wilson, J.W., Shavers, M.R., and Katz, R. 1997. *The Calculation of Heavy Ion Inactivation and Mutation Rates in the Track Structure Model.* NASA TP-1997-3630. NASA Johnson Space Center, Houston, Tex.

Cucinotta, F.A., Nikjoo, H., and Goodhead, D.T. 2000. Model of the radial distribution of energy imparted in nanometer volumes from HZE particles. *Radiation Research* 153:459-468.

Cucinotta, F.A., Kim, M.-H.Y., and Chappell, L.J. 2011. *Space Radiation Cancer Risk Projections and Uncertainties—2010.* NASA/TP-2011-216155. NASA Johnson Space Center, Houston, Tex. July.

Cullings, H.M., Fujita, S., Funamoto, S., Grant, E.J., Kerr, G.D., and Preston, D.L. 2006. Dose estimation for atomic bomb survivor studies: Its evolution and present status. *Radiation Research* 166:219-254.

Davis, F.G., Boice, J.D., Jr., Hrubec, Z., and Monson, R.R. 1989. Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. *Cancer Research* 49(21):6130-6136.

Dicello, J.F., Christian, A., Cucinotta, F.A., Gridley, D.S., Kathirithamby, R., Mann, J., Markham, A.R., Moyers, M.F., Novak, G.R., Piantadosi, S., Ricart-Arbona, R., et al. 2004. In vivo mammary tumorigenesis in the Sprague-Dawley rat and microdosimetric correlates. *Physics in Medicine and Biology* 49:3817-3830.

Ding, L.-H., Shingyoji, M., Chen, F., Hwang, J.-J., Burma, S., Lee, C., Cheng, J.-F., and Chen, D.J. 2005. Gene expression profiles of normal human fibroblasts after exposure to ionizing radiation: A comparative study of low and high doses. *Radiation Research* 164:17-26.

Doll, R., Peto, R., Wheatley, K., Gray, R., and Sutherland, I. 1994. Mortality in relation to smoking: 40 years' observations on male British doctors. *British Medical Journal* 309(6959):901-911.

Dugan, L.C., and Bedford, J.S. 2003. Are chromosomal instabilities induced by exposure of cultured normal human cells to low- or high-LET radiation? *Radiation Research* 159:301-311.

Elkind, M.M., and Whitmore, G.F. 1967. *The Radiobiology of Cultured Mammalian Cells*. Gordon and Breach, New York.

EPA (Environmental Protection Agency). 1999. *Estimating Radiogenic Cancer Risks.* Report 402-R-00-003. Washington, D.C.

EPA. 2011. *Radiogenic Cancer Risk Models and Projections for the U.S. Population.* EPA 402-R-11-001. Washington, D.C.

Feynman, J., and Gabriel, S., eds. 1988. Interplanetary Particle Environment: Proceedings of Conference. NASA-CR-185461. JPL Publication 88-28. Jet Propulsion Laboratory, Pasadena, Calif.

Feynman, J., Armstrong, T., Dao-Gibner, L., and Silverman, S. 1990. New interplanetary proton fluence model. *Journal of Spacecraft and Rockets* 27:403-410.

Feynman, J., Spitale, G., and Wang, J. 1993. Interplanetary proton fluence model. *Journal of Geophysical Research* 98:13281-13294.

Feynman, J., Ruzmaikin, A., and Berdichevsky, V. 2002. The JPL proton fluence model: An update. *Journal of Atmospheric and Solar-Terrestrial Physics* 64:1679-1686.

Flint-Richter, P., and Sadetzki, S. 2007. Genetic predisposition for the development of radiation-associated meningioma: An epidemiological study. *Lancet Oncology* 8:403-410.

Fournier, C., Barberet, P., Pouthier, T., Ritter, S., Fischer, B., Voss, K.O., Funayama, T., Hamada, N., Kobayashi, Y., and Taucher-Scholz, G. 2009. No evidence for DNA and early cytogenetic damage in bystander cells after heavy-ion microirradiation at two facilities. *Radiation Research* 171:530-540.

Fry, R.J.M., Powers-Risius, P., Alpen, E.L., and Ainsworth, E.J. 1985. High LET radiation carcinogenesis. *Radiation Research* 104:S188-S195.

Furukawa, K., Preston, D.L., Lönn, S., Funamoto, S., Yonehara, S., Matsuo, T., Egawa, H., Tokuoka, S., Ozasa, K., Kasagi, F., Kodama, K., and Mabuchi, K. 2010. Radiation and smoking effects on lung cancer incidence among atomic bomb survivors. *Radiation Research* 174(1):72-82.

George, K.A., and Cucinotta, F.A. 2007. The influence of shielding on the biological effectiveness of accelerated particles for the induction of chromosome damage. *Advances in Space Research* 39:1076-1081.

Gilbert, E.S. 1984. Some effects of random dose measurement errors on analyses of atomic bomb survivor data. *Radiation Research* 98:591-605.

Goodhead, D.T. 1989. Relationship of radiation track structure to biological effect: A re-interpretation of the parameters of the Katz model. *Nuclear Tracks and Radiation Measurements* 116:177-184.

Goodhead, D.T., and Nikjoo, H. 1989. Track structure analysis of ultrasoft X-rays compared to high- and low-LET radiations. *International Journal of Radiation Biology* 55:513-529.

Goodhead, D.T., Thacker, J., and Cox, R. 1979. Effectiveness of 0.3 keV carbon ultrasoft X-rays for the inactivation and mutation of cultured mammalian-cells. *International Journal of Radiation Biology* 36:101-115.

Goodhead, D.T., Munson, R.J., Thacker, J., and Cox, R. 1980. Mutation and inactivation of cultured mammalian cells exposed to beams of accelerated heavy ions. IV. Biophysical interpretation. *International Journal of Radiation Biology* 37:135-167.

Goodwin, E.H., Bailey, S.M., Chen, D.J., and Cornforth, M.N. 1996. The effect of track structure on cell inactivation and chromosome damage at a constant LET of 120 keV/micrometer. *Advances in Space Research* 18:93-98.

Grogan, H.A., Sinclair, W.K., and Voilleque, P.G. 2001. Risks of fatal cancer from inhalation of 239,240 plutonium by humans: A combined four-method approach with uncertainty evaluation. *Health Physics* 80:447-461.

Hande, M.P., Azizova, T.V., Geard, C.R., Burak, L.E., Mitchell, C.R., Khokhryakov, V.F., Vasilenko, E.K., and Brenner, D.J. 2003. Past exposure to densely ionizing radiation leaves a unique permanent signature in the genome. *American Journal of Human Genetics* 72:1162-1170.

Held, K.D. 2009. Effects of low fluences of radiations found in space on cellular systems. *International Journal of Radiation Biology* 85:379-390.

Hofer, E. 2007. Hypothesis testing, statistical power, and confidence limits in the presence of epistemic uncertainty. *Health Physics* 92(3):226-235.

Hofer, E. 2008. How to account for uncertainty due to measurement errors in an uncertainty analysis using Monte Carlo simulation. *Health Physics* 95(3):277-290.

ICRP (International Commission on Radiological Protection). 1991. *1990 Recommendations of the ICRP.* ICRP Publication 60. Pergamon Press, Elsevier Science, Oxford, U.K.

ICRP. 2006. *Low-Dose Extrapolation of Radiation-Related Cancer Risk.* ICRP Publication 99. ICRP. Pergamon Press, Elsevier Science, Oxford, U.K.

ICRP. 2007. *The 2007 Recommendations of the International Commission on Radiological Protection.* ICRP Publication 103. Pergamon Press, Elsevier Science, Oxford, U.K.

ICRP. 2011. Early and Late Effects of Radiation in Normal Tissues and Organs: Threshold Doses for Tissue Reactions in a Radiation Protection Context. Draft Report for Consultation. ICRP Ref 4844-6029-7736. International Commission on Radiological Protection, Ottawa, Ontario, Canada. January 20.

Jacob, P., Rühm, W., Walsh, L., Blettner, M., Hammer, G., and Zeeb, H. 2009. Is cancer risk of radiation workers larger than expected? *Occupational and Environmental Medicine* 66(12):789-796.

Jokipii, J.R. 2010. The heliosphere and cosmic rays. Pp. in *Heliophysics—Evolving Solar Activity and the Climates of Space and Earth* (C.J. Schrijver and G.L. Siscoe, eds.). Cambridge University Press, New York, 2010.

Kadhim, M.A. 2003. Role of genetic background in induced instability. *Oncogene* 22:6994-6999.

Kiefer, J., Stoll, U., and Schneider, E. 1994. Mutation induction by heavy ions. *Advances in Space Research* 14:257-265.

Kim, M.-H.Y., Wilson, J.W., Cucinotta, F.A., Simonsen, L.C., Atwell, W., Badari, F.F., and Miller, J. 1999. *Contribution of High Charge and Energy (HZE) Ions During Solar-Particle Events of September 29, 1989.* NASA/TP-1999-209320. NASA, Washington, D.C.

Kim, M.Y., Hayat, M.J., Feiveson, A.H., and Cucinotta, F.A. 2009. Prediction of frequency and exposure level of solar particle events. *Health Physics* 97:68-81.

Kim, M.Y., Angelis, G.D., and Cucinotta, F.A. 2011. Probabilistic assessment of radiation risk for astronauts in space mission. *Acta Astronautica* 68:747-759.

King, J.H. 1974. Solar proton fluences for 1977-1983 space missions. *Journal of Spacecraft* 11:401-408.

Kocher, D., Apostoaei, A.I., Henshaw, R.W., Hoffman, F.O., Schubauer-Berigan, M.K., Stancescu, D.O., Thomas, B.A., Trabalka, J.R., Gilbert, E.S., and Land, C.E. 2008. Interactive Radioepidemiological Program (IREP): A web-based tool for estimating probability of causation/assigned share for radiogenic cancers. *Health Physics* 95(1):119-147.

Kodama, Y., Ohtaki, K., Nakano, M., Hamasaki, K., Awa, A.A., Lagarde, F., and Nakamura, N. 2005. Clonally expanded T-cell populations in atomic bomb survivors do not show excess levels of chromosome instability. *Radiation Research* 164:618-626.

Kranert, T., Schneider, E., and Kiefer, J. 1990. Mutation induction in V79 Chinese hamster cells by very heavy ions. *International Journal of Radiation Biology* 58:975-987.

Little, M.P., Hoel, D.G., Molitor, J., Boice, J.D., Jr., Wakeford, R., and Muirhead, C.R. 2008. New models for evaluation of radiation-induced lifetime cancer risk and its uncertainty employed in the UNSCEAR 2006 report. *Radiation Research* 169:660-676.

Lloyd, D.C., and Edwards, A.A. 1983. Chromosome aberrations in human lymphocytes: Effect of radiation quality, dose, and dose rate. *Radiation Research,* 98(3):23-49.

Loucas, B.D., and Cornforth, M.N. 2001. Complex chromosome exchanges induced by gamma rays in human lymphocytes: An mFISH study. *Radiation Research* 155:660-671.

Loucas, B.D., Eberle, R.L., Durante, M., and Cornforth, M.N. 2004. Complex chromatid-isochromatid exchanges following irradiation with heavy ions? *Cytogenetic Genome Research* 104:206-210.

Lubin, J.H., Schafer, D.W., Ron, E., Stovall, M., and Carroll, R.J. 2004. A reanalysis of thyroid neoplasms in the Israeli Tinea capitis study accounting for dose uncertainties. *Radiation Research* 161:359-368.

McCracken, K.G., Dreschhoff, G.A.M., Zeller, E.J., Smart, D.F., and Shea, M.A. 2001. Solar cosmic ray events for the period 1561-1994. 1. Identification in polar ice, 1561-1950. *Journal of Geophysical Research* 106:21585-21598.

Mewaldt, R.A., Cohen, C.M.S., Labrador, A.W., Leske, R.A., Mason, G.M., Desai, M.I., Looper, M.D., Mazur, J.E., Selesnick, R.S., and Haggerty, D.K. 2005. Proton, helium, and electron spectra during the large solar particle events of October-November 2003. *Journal of Geophysical Research* 110:A09S18.

Mezentsev, A., and Amundson, S.A. 2011. Global gene expression responses to low- or high-dose radiation in a human three-dimensional tissue model. *Radiation Research* 175:677-688.

Muirhead, C.R., O'Hagan, J.A., Haylock, R.G., Phillipson, M.A., Willcock, T., Berridge, G.L., and Zhang, W. 2009. Mortality and cancer incidence following occupational radiation exposure: Third analysis of the National Registry for Radiation Workers. *British Journal of Cancer* 100(1):206-212.

Mulrooney, D.A., Yeazel, M.W., Kawashima, T., Mertens, A.C., Mitby, P., Stovall, M., Donaldson, S.S., Green, D.M., Sklar, C.A., Robison, L.L., and Leisenring, W.M. 2009. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: Retrospective analysis of the Childhood Cancer Survivor Study cohort. *British Medical Journal* 339:B4606.

NASA. 2005. *NASA Space Flight Human System Standard. Volume 1: Crew Health.* NASA Technical Standard NASA-STD-3001 (Approved 03-05-2007). NASA, Washington, D.C.

NCRP (National Council on Radiation Protection and Measurements). 1989. *Guidance on Radiation Received in Space Activities.* Report No. 98. Bethesda, Md.

NCRP. 1997. *Uncertainties in Fatal Cancer Risk Estimates Used in Radiation Protection.* Report No. 126. Bethesda, Md.

NCRP. 2000. *Radiation Protection Guidance for Activities in Low-Earth Orbit.* Report No. 132. Bethesda, Md.

NCRP. 2001. *Fluence-based Microdosimetric Event-based Methods for Radiation Protection in Space.* Report No. 137. Bethesda, Md.

NCRP. 2002. *Operational Radiation Safety Program for Astronauts in Low-Earth Orbit: A Basic Framework.* NCRP Report No. 142. Bethesda, Md.

NCRP. 2006. *Information Needed to Make Radiation Protection Recommendations for Space Missions Beyond Low-Earth Orbit.* NCRP Report No. 153. Bethesda, Md.

NIH (National Institutes of Health). 1985. Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables. National Institutes of Health, Bethesda, Md.

NIH. 2003. Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables. NIH Publication No. 03-5387. Bethesda, Md.

NRC (National Research Council). 2006. *Health Risks from Exposure to Low Levels of Ionizing Radiation, BEIR VII Phase 2.* The National Academies Press, Washington, D.C.

Nymmick, R.A., Panasyuk, M.I., and Suslov, A.A. 1996. Galactic cosmic ray flux simulation and prediction. *Advances in Space Research* 17(2):19-30.

O'Neill, P.M. 2006. Badhwar-O'Neill galactic cosmic ray model update based on advanced composition explorer (ACE) energy spectra from 1997 to present. *Advances in Space Research* 37:1727-1733.

Parzen, E.J. 1967. *Stochastic Processes.* Holden-Day, Inc., San Francisco, Calif.

Pawel, D., Preston, D., Pierce, D., and Cologne, J. 2008. Improved estimates of cancer site-specific risks for A-bomb survivors. *Radiation Research* 169:87-98.

Pierce, D.A., Stram, D.O., and Vaeth, M. 1990. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. *Radiation Research* 123(3):275-284.

Pierce, D.A., Sharp, G.B., and Mabuchi, K. 2003. Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. *Radiation Research* 159(4):511-520.

Pierce, D.A., Vaeth, M., and Cologne, J.B. 2008. Allowance for random dose estimation errors in atomic bomb survivor studies: A revision. *Radiation Research* 170:118-126.

Plante, I., and Cucinotta, F.A. 2008. Ionization and excitation cross sections for the interaction of HZE particles in liquid water and application to Monte-Carlo simulation of radiation tracks. *New Journal of Physics* 10:125020.

Portess, D.I., Bauer, G., Hill, M.A., and O'Neill, P. 2007. Low dose irradiation of non-transformed cells stimulates the selective removal of pre-cancerous cells via intercellular induction of apoptosis. *Cancer Research* 63:1246-1253.

Preston, D.L., Kusumi, S., Tomonaga, M., Izumi, S., Ron, E., Kuramoto, A., Kamada, N., Dohy, H., Matsuo, T., Nonaka, H., Thompson, D.E., Soda, M., and Mabuchi, K. 1994. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. *Radiation Research* 137:S68-S97.

Preston, D.L., Mattsson, A., Holmberg, E., Shore, R., Hildreth, N.G., Boice, Jr., J.D. 2002. Radiation effects on breast cancer risk: A pooled analysis of eight cohorts. *Radiation Research*, 158(2):220-235.

Preston, D.L., Shimizu, Y., Pierce, D.A., Suyama, A., and Mabuchi, K. 2003. Studies of the mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiation Research* 160(4):381-407.

Preston, D.L., Pierce, D.A., Shimizu, Y., Cullings, H.M., Fujita, S., Funamoto, S., and Kodama, K. 2004. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. *Radiation Research* 162:377-389.

Preston, D.L., Ron, E., Tokuoka, S., Funamoto, S., Nishi N., Soda, M., Mabuchi, K., and Kodama, K. 2007. Solid cancer incidence in atomic bomb survivors: 1958-1998. *Radiation Research* 168:1-64.

Prise, K.M., Schettino, G., Folkard, M., and Held, K.D. 2005. New insights on cell death from radiation exposure. *Lancet Oncology* 6:520-528.

Ron, E., Carter, R., Jablon, S., and Mabuchi, K. 1994a. Agreement between death certificate and autopsy diagnoses among atomic bomb survivors. *Epidemiology* 5:48-58.

Ron, E., Preston, D.L., Mabuchi, K., Thompson, D.E., and Soda, M. 1994b. Cancer incidence in atomic bomb survivors. Part IV: Comparison of cancer incidence and mortality. *Radiation Research* 137:S98-S112.

Ron, E., Lubin, J.H., Shore, R.E., Mabuchi, K., Modan, B., Pottern, L., Schneider, A.B., Tucker, M.A., and Boice, J.D. 1995. Thyroid cancer after exposure to external radiation: A pooled analysis of seven studies. *Radiation Research* 141:259-277.

Ruzmaikin, A., Feynman, J., and Jun, I. 2011a. Distribution of extreme solar energetic proton fluxes. *Journal of Atmospheric and Solar-Terrestrial Physics* 73:300-307.

Ruzmaikin, A., Feynman, J., and Stoev, S.A. 2011b. Distribution and clustering of fast coronal mass ejections. *Journal of Geophysics Research* 116:A04220.

Schafer, M., Schmitz, C., and Bucker, H. 1994. DNA double strand breaks induced in *Escherichia coli* cells by radiations of different quality. *Radiation Protection Dosimetry* 52:233-236.

Schafer, D.W., and Gilbert, E.S. 2006. Some statistical implications of dose uncertainty in radiation dose-response analyses. *Radiation Research* 166(1 Pt 2):303-312.

Schneider, A.B., Ron, E., Lubin, J., Stovall, M., and Gierlowski, T.C. 1993. Dose-response relationships for radiation-related thyroid cancer and thyroid nodules: Evidence for the prolonged effects of radiation on the thyroid. *Journal of Clinical Endocrinology and Metabolism* 77:362-364.

Schollnberger, H., Mitchel, R.E.J., Redpath, J.L., Crawford-Brown, D.J., and Hofmann, H. 2007. Detrimental and protective bystander effects: A model approach. *Radiation Research,* 168:614-626.

SEER (Surveillance Epidemiology and End-Result) Program of the National Cancer Institute. Version 6.4.4. 2011. Available at http://seer.cancer.gov/seerstat.

Shea, M.A., and Smart, D.A. 1990. A summary of major solar proton events. *Solar Physics* 127:297-320.

Shea, M.A., and Smart, D.F. 1995. History of solar proton event observations, *Nuclear Physics B* (Proc. Suppl.) 39A:16-25.

Shilnikova, N.S., Preston, D.L., Ron, E., Gilbert, E.S., Vassilenko, E.K., Romanov, S.A., Kuznetsova, I.S., Sokolnikov, M.E., Okatenko, P.V., Kreslov, V.V., and Koshurnikova, N.A. 2003. Cancer mortality risk among workers at the Mayak nuclear complex. *Radiation Research* 159(6):787-798.

Shore, R.E. 1992. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. *Radiation Research* 131:98-111.

Shore, R.E., Woodward, E., Hildreth, N., Dvoretsky, P., Hempelmann, L., and Pasternack, B. 1985. Thyroid tumors following thymus irradiation. *Journal of the National Cancer Institute* 74:1177-1184.

Slaba, T.C., Blattnig, S.R., and Badavi, F.F. 2010a. Faster and more accurate transport procedures for HZETRN. *Journal of Computational Physics* 229:9397-9417.

Slaba, T.C., Blattnig, S.R., Aghara, S.K., Townsend, L.W., Handler, T., Gabriel, T.A., Pinsky, L.S., and Redell, B. 2010b. Coupled neutron transport for HZETRN. *Radiation Measurements* 45:173-182.

Thacker, J., Cox, R., and Goodhead, D.T. 1980. Do carbon ultrasoft X-rays induce exchange aberrations in cultured mammalian-cells? *International Journal of Radiation Biology* 38:469-472.

Thacker, J., Stretch, S., and Stephens, M.A. 1979. Mutation and inactivation of cultured mammalian cells exposed to beams of accelerate heavy ions. II. Chinese hamster V79 cells. *International Journal of Biological Sciences* 38:137-148.

Thompson, D.E., Mabuchi, K., Ron, E., Soda, M., Tokunaga, M., Ochikubo, S., Sugimoto, S., Ikeda, T., Terasaki, M., Izumi, S., and Preston, D.L. 1994. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958-1987. *Radiation Research* 137:S17-S67.

Thun, M.J., Hannan, L.M., Adams-Campbell, L.L., Boffetta, P., Buring, J.E., Feskanich, D., Flanders, W.D., Jee, S.H., Katanoda, K., Kolonel, L.N., Lee, I.M., et al. 2008. Lung cancer occurrence in never-smokers: An analysis of 13 cohorts and 22 cancer registry studies. *PLoS Medicine* 5(9):E185.

Tylka, A.J., Adams, J.H., Boberg, P.R., Brownstein, B., Dietrich, W.F., Flueckiger, E.O., Petersen, E.L., Shea, M.A., Smart, D.F., and Smith, E.C. 1997. CREME96: A revision to cosmic ray effects on microelectronics code. *IEEE Transactions on Nuclear Science* 44:2150-2160.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). 2006. *Studies of Radiation and Cancer.* Report to the General Assembly, with Scientific Annexes A and B. United Nations, New York.

UNSCEAR. 2008. *Epidemiological Studies of Radiation and Cancer.* Volume I, Scientific Annex A. United Nations, New York.

Wakeford, R., Antell, B.A., and Leigh, W.J. 1998. A review of probability of causation and its use in a compensation scheme for nuclear industry workers in the United Kingdom. *Health Physics* 74(1):1-9.

Weil, M.M., Bedford, J.S., Bielefledt-Ohmann, H., Ray, A.F., Gernick, P.C., Ehrhart, E.J., Falgren, C.M., Hailu, F., Battaglia, C.L.R., Charles, C., Callan, M.A., and Ullrich, R.L. 2009. Incidence of acute myeloid leukemia and hepatocellular carcinoma in mice irradiated with 1 GeV/nucleon ^{56}Fe ions. *Radiation Research* 172:213-219.

Whitehouse, C.A., and Tawn, E.J. 2001. No evidence for chromosomal instability in radiation workers with in vivo exposure to plutonium. *Radiation Research* 156:467-475.

Xapsos, M.A., Stauffer, C., Gee, G.B., Barth, J.L., Stassinopoulos, E.G., and McGuire, R.E. 2004. Model for solar proton risk assessment. *IEEE Transactions on Nuclear Science* 51:3394-3398.

Zhu, L.X., Waldren, C.A., Vannias, D., and Hei, T.K. 1996. Cellular and molecular analysis of mutagenesis induced by charged particles of defined linear energy transfer. *Radiation Research* 145(3):251-259.

Appendixes

Appendix A

Statement of Task

BACKGROUND

NASA's current missions to the International Space Station (ISS) and potential future exploration missions involving extended stays by astronauts on the lunar surface, as well as the possibility of Near-Earth Objects (NEO) or Mars missions, present challenges in protecting astronauts from radiation risks. These risks arise from a number of sources, including solar particle events (SPE), galactic cosmic rays (GCR), secondary radiation from surface impacts, and even nuclear isotope power sources transported with the astronauts. The serious early and late radiation health effects potentially posed by these exposures are equally varied, ranging from prodromal radiation sickness to cancer induction. Other possible effects include central nervous system damage, cataracts, heritable effects, impaired wound healing and infertility. Since opening in October 2003, the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Lab has enabled NASA to sponsor research focused on understanding and quantifying the radiation health risks posed by space radiation environments. While most aspects of the space radiation environments are now relatively well characterized, important uncertainties still exist regarding biological effects and thus the level and types of risks faced by astronauts.

CURRENT STATUS

In response to reviews and recommendations, NASA has developed an integrated research program that consists of openly solicited peer reviewed research to investigate the biomedical effects of simulated space radiation and provide the needed knowledge base on GCR and SPE radiobiology. While the main focus is on understanding cancer risks, the program also includes studies on potential degenerative risks to the central nervous system, the cardiovascular system and other tissues. In cooperation with the U.S. Department of Energy (DoE), NASA operates the NSRL, the only place in the U.S. where sophisticated biomedical experiments can be conducted using the heavy ions encountered in the space radiation environment.

For projecting cancer risk for ISS crews and to support trade study assessments of potential lunar, NEO, and Mars missions, NASA uses the model recommended by the National Council of Radiation Protection and Measurements (NCRP) Report No. 132. NASA also makes an uncertainty assessment in the NCRP model coefficients that describes errors in low LET human radio-epidemiology data, dose- and dose-rate effectiveness factors (DDREFs), radiation quality factors, and space physics. For astronaut occupational exposures, the 95 percent confidence level is used as a supplementary requirement as part of the Permissible Exposure Limit (PEL) of a no greater than

3 percent increase in the Risk of Exposure Induced Death (REID). The PEL standards are approved by the NASA Chief Health and Medical Officer.

NASA has updated its Space Radiation Cancer Risk Model based on recent developments including the following:

- BEIR-VII, UNSCEAR-2006, and other reports in the scientific literature have made new assessments of human radio-epidemiology data and DDREFs;
- New research results from NSRL have begun to modify the understanding of radiation quality and dose-rate effects; and
- NASA's revised evaluation of uncertainty factors.

Because it is used to project the cancer risk for current ISS crews and future explorations missions, this NASA update to its Space Radiation Cancer Risk Model requires independent review and validation.

PROPOSED STUDY

1. The committee will evaluate proposed updates to the NASA cancer projection model taking into consideration the following:

- Current knowledge of low-LET radiation cancer epidemiology,
- Effects of tissue weighting factors, radiation weighting factors, and DDREFs used in projecting risks, and
- Current uncertainties in Quality Factors, DDREFs and organ dose assessment.

This will be done taking into consideration possible qualitative differences between low LET and heavy ion biological effects to determine if the use of quality factors are appropriate or inappropriate for GCR risk assessments.

2. The committee will identify gaps in NASA's current research strategy for reducing the uncertainties in cancer induction risks.

Appendix B

Committee and Staff Biographical Information

R. JULIAN PRESTON, *Chair,* is the associate director for health for the National Health and Environmental Effects Research Laboratory of the Environmental Protection Agency (EPA). He also has served as director of the Environmental Carcinogenesis Division at the EPA and as senior science adviser at the Chemical Industry Institute of Toxicology. He has been employed at the Biology Division of the Oak Ridge National Laboratory and has served as associate director for the Oak Ridge–University of Tennessee Graduate School for Biomedical Sciences. Dr. Preston's research and current activities have focused on the mechanisms of radiation and chemical carcinogenesis and the approaches for incorporating these types of data into cancer risk assessments. Currently Dr. Preston is chair of Committee 1 of the International Commission on Radiological Protection (ICRP), a member of the ICRP Main Commission, and a member of the U.S. delegation to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). He is an associate editor of *Environmental and Molecular Mutagenesis, Mutation Research, Chemico-Biological Interactions,* and *Health Physics.* Dr. Preston has had more than 200 peer-reviewed papers and chapters published. He received his B.A. and M.A. from Peterhouse, Cambridge University, England, in genetics and his Ph.D. from Reading University, England, in radiation genetics. He has served on the National Research Council's (NRC's) Committee to Assess the Scientific Information for the Radiation Exposure Screening and Education Program and the Task Group on the Biological Effects of Space Radiation.

JOEL S. BEDFORD is a professor of environmental and radiological health sciences and is on the graduate faculty of Cell and Molecular Biology at Colorado State University. He was an associate professor in radiology at Vanderbilt University. He received a D.Phil. degree from Oxford University. Dr. Bedford's areas of interest and expertise for more than 45 years have been in cellular radiobiology, radiation cytogenetics, radiation genetics, dose-rate effects, and the genetic control of radiosensitivity. During the past decade his research interest has also focused on variations in radiosensitivity related to processes involved in cancer development. His research has been funded continuously by the National Institutes of Health (NIH), the Department of Energy, or NASA. Dr. Bedford served as a member of the NIH Radiation Study Section and as its chair. He was a member of Grant Review Panel H of the National Cancer Institute of Canada. He was president of the Radiation Research Society and received the Failla Award from that society, as well as the Excellence in Mentoring Award. He has also served as a regular member of other national or international committees such as the NRC's Board on Radiation Effects Research and the Nuclear and Radiation Studies Board. He was a member of the Scientific Council of the Radiation Effects Research Foundation in Hiroshima and is a member of the National Council on Radiation Protection and Measurements (NCRP).

AMY BERRINGTON DE GONZALEZ is an investigator in the Radiation Epidemiology Branch at the National Cancer Institute (NCI) and adjunct faculty at the Johns Hopkins Bloomberg School of Public Health. At NCI, Dr. Berrington de Gonzalez has led the development of the NCI Radiation Risk Assessment Tool, which is interactive computer software designed to estimate the lifetime risk of cancer (with uncertainty intervals) following complex exposure histories. She has also used this software to conduct a research program projecting cancer risks from a large number of medical exposure scenarios including CT scans, nuclear medicine tests, and mammography screening. Her research interests include methods to improve radiation risk projection and the conduct of epidemiological studies of cancer risks from both low- and high-dose medical radiation exposures. She has served on the U.K. Health Protection Agency's Advisory Group on Ionizing Radiation and Solid Cancer, as a special adviser on radiation and health to the World Health Organization, and as a committee member on the U.K. government's Advisory Committee on Breast Cancer Screening. She was a member of the organizing committee for the 2009 Conference on Uncertainties in Radiation Dosimetry and Their Impact on Risk Analysis. Dr. Berrington de Gonzalez earned her Ph.D. in radiation epidemiology from the University of Oxford.

B. JOHN GARRICK is an independent consultant with Garrick Consulting. He was a co-founder of PLG, Inc., an international engineering, applied science, and management consulting firm, from which he retired as president and chief executive officer. His professional interests include risk assessment in nuclear energy, space and defense, chemicals and petroleum, and transportation. He is a member of the National Academy of Engineering and a past president of the Society for Risk Analysis and has received the society's Distinguished Achievement Award. Dr. Garrick was appointed to the U.S. Nuclear Regulatory Commission Advisory Committee on Nuclear Waste and served for 10 years, 4 years as chair. President George W. Bush appointed Dr. Garrick to the U.S. Nuclear Waste Technical Review Board with the designation of chairman in 2004. Dr. Garrick received his B.S. in physics from Brigham Young University and his M.S. and Ph.D. in engineering and applied science from the University of California, Los Angeles. He is also a graduate of the Oak Ridge School of Reactor Technology. He served on many NRC committees, including several associated with the space program.

DUDLEY T. GOODHEAD is retired from the Medical Research Council's (MRC's) Radiation and Genome Stability Unit, Harwell, United Kingdom, where he served as director. The Genome Stability Unit carried out basic research on the relationship of genome stability to human health, including how DNA may be damaged by radiation and other agents and how the cellular repair systems act to restore normality. Dr. Goodhead continues as a visitor at MRC Harwell and assists the European Commission's research program as well as a number of agencies in the United States and the United Kingdom. His research has been mainly on the biophysics of radiation effects, with particular emphasis on microscopic features of radiation track structure at the atomic, molecular, and cellular levels and their consequent radiobiological and health effects. He has held positions at the University of California, Los Angeles; St. Bartholomew's, London; and Natal, as well as the Radiobiology Unit at MRC Harwell. Dr. Goodhead has served on a variety of national and international committees on the evaluation of radiation risks, including the Committee on Medical Aspects of Radiation in the Environment in the United Kingdom; consultancies to UNSCEAR and the International Atomic Energy Agency (IAEA), and working groups of the International Agency for Research on Cancer (on carcinogenic risk of gamma rays, neutrons, and internally deposited radionuclides) and the Royal Society (on risks from depleted uranium). He was chair of the Committee Examining Radiation Risks of Internal Emitters in the United Kingdom until its final report. In the Queen's Birthday Honours List, Dr. Goodhead was awarded the Order of the British Empire for services to medical research. He has been the recipient of various other awards, including the Weiss Medal from the Association for Radiation Research, the Failla Medal from the Radiation Research Society, the Douglas Lea Lecturer from the Institute of Physics and Engineering in Medicine and Biology, the Bacq and Alexander Award from the European Society of Radiation Biology, an Honorary Fellowship of the Society of Radiological Protection, the Warren K. Sinclair Lecturer from the NCRP, and the Gray Medal (August 2011) from the International Committee on Radiation Units and Measurements. He earned his D.Phil. in particle physics at the University of Oxford, United Kingdom. He served on the NRC Committee on Health Risks of Exposure to Radon (BEIR VI), Phase II.

BERNARD A. HARRIS, JR., is currently the chief executive officer and managing director of Vesalius Ventures, Inc., a venture capital firm that invests in early- to mid-stage health care technology companies, particularly in the area of telemedicine. Prior to joining Vesalius Ventures, Dr. Harris was at NASA for 10 years, where he conducted research in musculoskeletal physiology and clinical investigations of space adaptation and developed in-flight medical devices to extend astronaut stays in space. A veteran astronaut for more than 18 years, he has logged more than 438 hours and traveled over 7.2 million miles in space. He holds several faculty appointments, including those of associate professor in internal medicine at the University of Texas Medical Branch and assistant professor at Baylor College of Medicine. Additionally, he is the author and co-author of numerous scientific publications. Currently, Dr. Harris serves on the board for the Houston Angel Network, the Houston Technology Center, BioHouston, SCORE, and the National Space Biomedical Research Institute's board of scientific counselors. He is the recipient of numerous awards, including honorary doctorates from the State University of New York at Stony Brook, the Morehouse School of Medicine, and the University of Hartford. He has been awarded two NASA Space Flight Medals and the NASA Award of Merit. Dr. Harris is a fellow of the American College of Physicians and was the recipient of the 2000 Horatio Alger Award. He earned a B.S. in biology from the University of Houston, an M.S. from the University of Texas Medical Branch at Galveston, an M.B.A. from the University of Houston, and an M.D. from Texas Tech University School of Medicine. He has served on the NRC Committee on Aerospace Medicine and Medicine of Extreme Environments and the the Institute of Medicine's Committee on Creating a Vision for Space Medicine During Travel Beyond Earth Orbit.

KATHRYN D. HELD is an associate radiation biologist in the Department of Radiation Oncology, Massachusetts General Hospital (MGH), and an associate professor of radiation oncology (radiation biology) at Harvard Medical School (HMS). At MGH, Dr. Held leads a team that is involved in research on molecular mechanisms for the induction of bystander effects by high-energy particles in cells and tissues, characterization of proton-beam-induced DNA damage responses, the development of a cancer screening platform for personalized radiation medicine, mechanisms for the regulation of DNA damage response by cell-cell communication (NCI Federal Share-funded), and the development of novel agents for mitigation of radiation-induced pulmonary injury (National Institute of Allergy and Infectious Diseases [NIAID]-funded). Dr. Held also teaches radiation biology to radiation oncology medical and physics residents and graduate students. She has served on review panels for numerous federal agencies including NIH, NASA, and the U.S. Army Medical Research and Materiel Command. She is currently the past president of the Radiation Research Society and serves on the board of directors of the NCRP, having served as chair of the program committee for the 2011 Annual Meeting of the NCRP on Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions. Dr. Held earned her Ph.D. in biology from the University of Texas, Austin.

DAVID G. HOEL is a distinguished university professor in the Department of Medicine at the Medical University of South Carolina. He also is a principal scientist at Exponent, Inc. Dr. Hoel was at the National Institute of Environmental Health Sciences of NIH for more than 20 years as director of the Division of Environmental Risk Assessment, which was responsible for developing methods for quantitatively estimating health risks from low-dose chemical exposures. He has particular interest in estimating the health effects of radiation exposures and has spent a total of 3 years working at the Radiation Effects Research Foundation in Hiroshima, Japan, as one of the program directors. His current research is focused on low-dose adverse health effects of gamma, neutron, and alpha radiation as well as plutonium in particular. His research support has included a 5-year project on the analysis of the potential health risks from high linear energy transfer (LET) radiation for NASA. International committees on which Dr. Hoel has served include a radiation exposure advisory committee for the IAEA and the World Health Organization's International Agency for Research on Cancer. He is a member of the Institute of Medicine and a fellow of the American Association for the Advancement of Science. He earned a B.A. in mathematics from the University of California, Berkeley, and a Ph.D. in mathematical statistics from the University of North Carolina, Chapel Hill, and completed postdoctoral training in preventive medicine from Stanford University. Dr. Hoel has served on the NRC Committee on Evaluation of Radiation Shielding for Space Exploration and the Nuclear and Radiation Studies Board.

JACK R. JOKIPII is a Regents' Professor in the Department of Planetary Sciences and Lunar and Planetary Laboratory at the University of Arizona. His research in the areas of theoretical astrophysics and space physics is primarily related to the transport and acceleration of cosmic rays and energetic particles in the solar wind and in the Galaxy. Dr. Jokipii and his research group have been guest investigators on several NASA missions and specialize in theoretical interpretation and modeling of the observations. Specifically, Dr. Jokipii's group is currently in the midst of an extensive program of theoretical research to study the mutual interactions of shock waves, turbulence, and energetic particles. He is a member of the National Academy of Sciences and a lifetime associate of the National Research Council. He received his B.S. from the University of Michigan and his Ph.D. from the California Institute of Technology. He currently serves on the NRC Committee on Solar and Space Physics and is chair of the Panel Review Board of the NRC Policy and Global Affairs Division's Associateship Program.

INSOO JUN is a principal scientist and the technical group supervisor of the Mission Environments Group for the Jet Propulsion Laboratory at the California Institute of Technology. Previously he worked with the Fusion Engineering Group at the University of California, Los Angeles (UCLA) and with the Hughes Space and Communications Company. His experience includes the modeling of planetary and interplanetary space environments (radiation, meteoroid, and plasma, etc.) and their impact analyses on spacecraft systems and components, as well as interactions with bodies in the solar system. Dr. Jun's main interests are in the computational physics of space radiation interactions with materials (spacecraft structure, planetary atmospheres, or surface materials, etc.) using Monte Carlo and deterministic radiation transport tools. His expertise also includes nuclear instrumentation, simulation of spaceborne instruments or detectors, and data reduction and analysis. Dr. Jun has received several awards, including various NASA achievement awards. He is also a member of the American Geophysical Union. He received his B.S. in nuclear engineering from the University of Massachusetts and his M.S. and Ph.D. in mechanical, aerospace, and nuclear engineering from UCLA.

CHARLES E. LAND retired as senior investigator in the Division of Epidemiology and Genetics following more than 30 years at the National Cancer Institute, Radiation Epidemiology Branch. He is a statistician who has specialized in the epidemiology of radiation-related cancer risk in exposed populations. He became interested in the topic during a 2-year tour with the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki, Japan, and returned for another tour after teaching statistics for 5 years at Oregon State University. Dr. Land served on a number of expert committees concerned with radiation-related cancer risk, including the NIH Ad Hoc Working Group to Develop Radioepidemiological Tables and the NCI-CDC [Centers for Disease Control and Prevention] Working Group, which updated the tables with an interactive computer program to determine the attributability of a given cancer diagnosis to a given history of radiation exposure. After 24 years on the NCRP, he retired as a Distinguished Emeritus Member and presented the 2010 Lauriston Taylor Lecture. Dr. Land served for 20 years on Committee 1, on Risk, of the International Commission on Radiation Protection, chairing the working group that produced ICRP Report 99, on low-dose extrapolation of radiation-related cancer risk. At present he serves on an UNSCEAR working group dealing with uncertainty in radiation-related risk estimation. Dr. Land received his B.A. from the University of Oregon and his M.A. and Ph.D. from the University of Chicago. He served on the NRC's Committee on NASA's Research on Human Health Risks, the Committee on Health Risks from Exposure to Low Levels of Ionizing Radiation, and the Committee on NASA's Bioastronautics Critical Path Roadmap.

HANS-GEORG MENZEL is currently an honorary staff member of CERN, the European Organization for Nuclear Research in Geneva, Switzerland. His professional career began at the European Joint Research Centre, Ispra, Italy, and continued at the German Cancer Research Centre, Heidelberg, Germany, and at the University of Saarland, Germany. Previously, he worked as scientific program manager at the European Commission in Brussels, Belgium, and was then appointed the head of the Radiation Protection Group at CERN. His main research activities are in the fields of dosimetry and microdosimetry of high-energy radiation, basic nuclear data and instrumentation for dosimetry and applications for high-LET radiation therapy, radiation protection, medical physics, and radiation biology. Dr. Menzel has been teaching physics and medical physics at the University of Saarland and has been

a member of the physics and medical faculty of Université Catholique de Louvain, Belgium. Currently he is the chair of the International Commission on Radiation Units and Measurements (ICRU), chair of Committee 2, and member of the Main Commission of the ICRP. Dr. Menzel has served on numerous international scientific committees of the ICRU, the ICRP, the IAEA, and the European Commission. More recently, he was a co-chair of an ICRU report on cosmic radiation exposure of aircrew, and he is currently a member of an ICRP Task Group on Assessment of Radiation Exposure of Astronauts in Space. Dr. Menzel was the William G. Morgan Lecturer of the Health Physics Society. He earned his Ph.D. in physics from the University of Saarland.

PETER O'NEILL is a professor of radiation biology and the deputy director and head of the DNA Damage Group at the Gray Institute of Radiation Oncology and Biology, University of Oxford, United Kingdom. He is a fellow of the Royal Society of Chemistry and a chartered chemist. His research focuses on the chemistry of the types of DNA damage induced by ionizing radiation, from the early free-radical processes to the complexities of damage, and how these may contribute to carcinogenesis or radiation cytotoxicity. More recently his major research interests have focused on understanding the challenges that radiation-induced clustered DNA damage sites present to the repair pathways and, as a consequence, contribute to carcinogenesis at environmental radiation levels or to the killing of tumor cells. Among the several grants that he holds, he is funded through the Department of Energy/NASA low-dose radiation program. Dr. O'Neill is currently the president of the North American Radiation Research Society. He received the Weiss Medal for his contributions to radiation biology and the health effects of ionizing radiation. He was awarded his B.Sc. in chemistry and Ph.D. from the University of Leeds, United Kingdom. At present he serves as a member of the Topical Team IBER for the European Space Agency to review and update scientific knowledge in space radiation biology and dosimetry and is a member of the EU MELODI Group developing the Strategic Research Agenda for Radiation Protection Program for the next 20 to 30 years. He is or has been a member on several Research Council committees in the United Kingdom.

Staff

SANDRA J. GRAHAM, *Study Director,* has been a senior program officer at the National Research Council's Space Studies Board (SSB) since 1994. During that time Dr. Graham has directed a large number of major studies, many of them focused on space research in biological and physical sciences and technology. More recent studies include an assessment of servicing options for the Hubble Space Telescope, a study of the societal impacts of severe space weather, and a review of NASA's Space Communications Program while she was on loan to the NRC's Aeronautics and Space Engineering Board (ASEB). Prior to joining the SSB, Dr. Graham held the position of senior scientist at the Bionetics Corporation, where she provided technical and science management support for NASA's Microgravity Science and Applications Division. She received her Ph.D. in inorganic chemistry from Duke University, where her research focused primarily on topics in bioinorganic chemistry, such as rate modeling and reaction chemistry of biological metal complexes and their analogs.

CATHERINE A. GRUBER, editor, joined the Space Studies Board as a senior program assistant in 1995. Ms. Gruber first came to the NRC in 1988 as a senior secretary for the Computer Science and Telecommunications Board and also worked as an outreach assistant for the National Science Resources Center. She was a research assistant (chemist) in the National Institute of Mental Health's Laboratory of Cell Biology for 2 years. She has a B.A. in natural science from St. Mary's College of Maryland.

AMANDA R. THIBAULT, research associate, joined the Aeronautics and Space Engineering Board in 2011. Ms. Thibault is a graduate of Creighton University where she earned her B.S. in atmospheric science in 2008. From there she went on to Texas Tech University where she studied lightning trends in tornadic and non-tornadic supercell thunderstorms and worked as a teaching and research assistant. She participated in the VORTEX 2 field project from 2009-2010 and graduated with a M.S. in atmospheric science from Texas Tech in August 2010. She is a member of the American Meteorological Society.

RODNEY N. HOWARD joined the Space Studies Board as a senior project assistant in 2002. Before joining SSB, most of his vocational life was spent in the health profession as a pharmacy technologist at Doctor's Hospital in Lanham, Maryland, and as an interim center administrator at the Concentra Medical Center in Jessup, Maryland. During that time, he participated in a number of Quality Circle Initiatives that were designed to improve relations between management and staff. Mr. Howard obtained his B.A. in communications from the University of Maryland, Baltimore County, in 1983.

MICHAEL H. MOLONEY is the director of the Space Studies Board and the Aeronautics and Space Engineering Board at the National Research Council. Since joining the NRC in 2001, Dr. Moloney has served as a study director at the National Materials Advisory Board, the Board on Physics and Astronomy (BPA), the Board on Manufacturing and Engineering Design, and the Center for Economic, Governance, and International Studies. Before joining the SSB and ASEB in April 2010, he was the associate director of the BPA and study director for the Astro2010 decadal survey for astronomy and astrophysics. In addition to his professional experience at the NRC, Dr. Moloney has more than 7 years' experience as a Foreign Service officer for the Irish government and served in that capacity at the Embassy of Ireland in Washington, D.C., the Mission of Ireland to the United Nations in New York, and the Department of Foreign Affairs in Dublin, Ireland. A physicist, Dr. Moloney did his graduate Ph.D. work at Trinity College Dublin in Ireland. He received his undergraduate degree in experimental physics at University College Dublin, where he was awarded the Nevin Medal for Physics.

Appendix C

Glossary and Acronyms

Σ	Risk cross section.
absolute risk (AR)	The rate of disease among a population.
absorbed dose (D)	The fundamental dose quantity is absorbed dose, D, defined as the quotient of $\mathrm{d}\bar{\varepsilon}$ by $\mathrm{d}m$, where $\mathrm{d}\bar{\varepsilon}$ is the mean energy imparted by ionizing radiation to matter of mass $\mathrm{d}m$; thus $$D = \frac{\mathrm{d}\bar{\varepsilon}}{\mathrm{d}m}.$$ Unit: J kg^{-1}. The special name for the unit of absorbed dose is gray (Gy). A formerly used (non-SI) unit is rad. 1 Gy = 1 J/kg = 100 rad. 1 rad = 0.01 J/kg. In radiation protection and epidemiology, absorbed dose averaged over organs and tissues is used.
activity (A)	Variation $\mathrm{d}N$ of number of nuclei N in a particular energy state, in a sample of a radionuclide, due to spontaneous nuclear transitions from this state during an infinitesimal time interval, divided by its duration $\mathrm{d}t$, thus: $$A = -\mathrm{d}N/\mathrm{d}t.$$ Unit: s^{-1}. The special name for the unit of activity is becquerel (Bq). A formerly used (non-SI) unit is curie (Ci). 1 Bq = 1 s^{-1} = 2.7 × 10^{-11} Ci. 1 Ci = 3.7 × 10^{10} Bq.
additive effect	When two agents do not interact, the combined effect is equal to the sum of the effects of the two agents acting alone.

AML	Acute myeloid leukemia.
apoptosis	Programmed cell death. The cell death is characterized by a distinctive fragmentation of DNA that is regulated by cellular functions.
artificial radioactivity	Man-made radioactivity produced by fission, fusion, particle bombardment, or electromagnetic irradiation.
attributable risk (AR)	The estimated rate of a disease (such as lung cancer) that could, in theory, be prevented if all exposures to a particular causative agent (such as radon) were eliminated.
AU	Astronomical unit.
background radiation	The radiation to which a member of the population is exposed from natural sources, composed of terrestrial radiation due to naturally occurring radionuclides in the soil and building material, cosmic radiation originating in outer space, and naturally occurring radionuclides in the human body.
baseline rate of cancer	The annual cancer incidence observed in a population in the absence of the specific agent being studied; the baseline rate includes cancers from a number of other causes, such as smoking and occupational exposures to chemicals.
becquerel (Bq)	SI unit of activity. 1 Bq = 1 s^{-1} = 2.7 × 10^{-11} Ci.
BEIR	Biological Effects of Ionizing Radiation. Refers to the reports by the National Research Council's Committee on Biological Effects of Ionizing Radiation and its successor committees. The most recent of these reports is BEIR VII, published in 2006.
beta particle	An electron or positron emitted from a nucleus during radioactive decay.
bias	Factors that influence the outcome of data collection, such as causing certain measurements to have a greater chance of being included than others.
Boltzmann transport equation	Describes the trajectory and interactions of particles traversing a medium. So called because of its similarity to the expression obtained by Boltzmann in connection with the kinetic theory of gases.
BRYNTRN	Computational model of baryon transport.
cancer	A malignant tumor of potentially unlimited growth, capable of invading surrounding tissue or spreading to other parts of the body by metastasis.
carcinogen	An agent that can cause cancer. Ionizing radiation is a physical carcinogen; there are also chemical and biological carcinogens; biological carcinogens may be extrinsic (e.g., viruses) or intrinsic (genetic defects).
carcinoma	A malignant tumor (cancer) of epithelial origin.
case-control study	An epidemiologic study in which people with disease and a similarly composed control group are compared in terms of exposures to a putative causative agent.
cell culture	The growing of cells in vitro (in a glass or plastic container, or in suspension) in such a manner that the cells are no longer organized into tissues.

CME	Coronal mass ejection.
CNS	Central nervous system.
cohort study	An epidemiologic study in which groups of people (the cohort) are identified with respect to the presence or absence of exposure to a disease-causing agent, and in which the outcomes of disease rates are compared; also called a follow-up study.
collective effective dose	For a specified group of individuals: the sum of individual effective doses from a specified source within a specified time period. Unit: j/kg; special name used for unit: person-Sv.
competing risks	Causes other than the agent under study that contribute to the mortality rate. The mortality rate from these other causes is not included in the risk of dying from the factor under study.
confidence interval (CI)	An interval estimate of an unknown parameter, such as a risk. A 95 percent confidence interval, as an example, is constructed from a procedure that is theoretically successful in capturing the parameter of interest in 95 percent of its applications. Confidence limits are the end points of a confidence interval.
constant relative risk (CRR)	A risk model which assumes that the ratio of the risk at a specific dose and the risk in the absence of the dose remains constant after a certain time.
coronal mass ejections	Large regions of plasma ejected outward from the Sun by an electromagnetic process in the solar atmosphere.
curie (Ci)	Former special unit of radioactivity. 1 Ci = 3.7×10^{10} Bq.
DDREF (dose and dose rate effectiveness factor)	A judged factor by which the radiation effect, per unit of dose, caused by a given high or moderate dose of radiation received at high dose rates is reduced when doses are low or are received at low dose rates.
deletion	Type of mutation in which sections of DNA are removed; term can refer to the removal of a single base or many bases.
detriment	The total harm to an exposed group (and its descendants) as a consequence of exposure of the group to radiation. The principal components of detriment are probability of fatal cancer attributable to radiation, weighted probability of non-fatal cancer attributable to radiation, weighted probability of severe heritable effects, and length of life lost from any harm induced.
detriment-adjusted risk	The probability of the occurrence of cancer or heritable effect, adjusted to allow for the different components of detriment to express the severity of the consequences.
DNA	Deoxyribonucleic acid; the genetic material of cells.
dose-effect (dose-response) model	A mathematical formulation and description of the way that the effect (or biological response) depends on the dose.

dose equivalent — The dose equivalent, H, at a point is given by

$$H = Q\,D,$$

where D is the absorbed dose and Q is the quality factor at that point. The unit of dose equivalent is joules per kilogram (J kg^{-1}), and its special name is the sievert (Sv).

This quantity is used by the ICRU (see *ICRU*) in the definition of operational quantities, including ambient dose equivalent and personal dose equivalent, applied in radiation monitoring.

dose range — Definitions of low, medium, and high doses vary widely in the literature. For the purposes of this report, dose ranges are defined as follows: Low dose: 0 to 100 mGy (mSv). Medium dose: in excess of 100 mGy up to a maximum of 1 Gy. High dose: in excess of 1 Gy up to the very high total doses used in radiation therapy (on the order of 20 to 60 Gy).

dose rate — The absorbed dose delivered per unit time.

dose rate effectiveness factor (DREF) — The factor by which the effect per unit dose caused by a specific type of radiation changes at low doses or low dose rates (protracted or fractionated delivery of dose) as compared to high doses delivered at high (or acute) dose rates.

dosimetric model — A method for estimating risk based on the use of physical models for doses to target cells and the use of results from epidemiologic studies of exposures to humans from other types of radiation.

EB — Empirical Bayes.

ecological fallacy — The fact that two populations differ in many factors other than the one being evaluated and that one or more of these other factors may be the underlying reason for any difference noted in their morbidity or mortality experience.

ecologic study — A method of epidemiologic study in which rates of health effects outcome based on population rather than individual data are related to the measure of population radiation exposure.

effective dose — As defined by the ICRP (see *ICRP*): the sum of the equivalent doses H_T in all specified tissues and organs T of the body of a reference person, each weighted by w_T, the tissue weighting factor after sex-averaging of the equivalent doses.

$$E = \sum_T w_T \sum_R w_R\, D_{T,R} = \sum_T w_T\, H_T\,,$$

where

$$D = \frac{\mathrm{d}\bar{\varepsilon}}{\mathrm{d}m}\cdot$$

Unit: J kg^{-1}.

The special name for the unit of effective dose is sievert (Sv). Effective dose is used to set exposure limits for radiation protection of stochastic effects and for implementing the optimization principle (ALARA, or "as low as reasonably achievable") in radiation protection. The quantity enables the summation of doses from internal emitters and external radiation fields in order to provide a single numerical value.

electron volt (eV) A special unit of energy: 1 eV = 1.6×10^{-19} J = 1.6×10^{-12} erg; 1 eV is equivalent to the energy gained by an electron in passing through a potential difference of 1 V; 1 keV = 1,000 eV; 1 MeV = 1,000,000 eV.

empirical model Derived from measurements in populations, as opposed to a theoretical model.

EPA Environmental Protection Agency.

epidemiology The study of the determinants of the frequency of disease in humans. The two main types of epidemiologic studies of chronic disease are cohort (or follow-up) studies and case-control studies.

equivalent dose The equivalent dose in an organ or tissue, H_T, defined by

$$H_T = \sum_R w_R D_{TR},$$

where

$$D = \frac{d\bar{\varepsilon}}{dm}.$$

and w_R is the radiation weighting factor for radiation R. The sum is performed over all types of radiations involved.

Unit: J kg^{-1}.

The special name for the unit of equivalent dose is sievert (Sv).

1 Sv = 1 J/kg = 100 rem. 1 rem = 0.01 Sv ("rem" was the formerly used special name for equivalent dose).

ESP Emission of solar protons.

etiology The science or description of cause(s) of disease.

EVA Extravehicular activity.

excess absolute risk (EAR) The rate of disease in an exposed population minus the rate of disease in an unexposed population. Also termed "attributable risk" or "risk difference."

excess relative risk (ERR) The rate of disease in an exposed population divided by the rate of disease in an unexposed population minus 1.0.

exposure (E) The condition of having contact with a physical or chemical agent.

fibrosis	Damage to normal tissue that results in the formation of excess fibrous connective tissue in an organ or tissue.
fractionation	The delivery of a given dose of radiation as several smaller doses separated by intervals of time.
galactic cosmic ray (GCR)	Very energetic charged particles that have their origin inside our Galaxy and have speeds approaching the speed of light, propagating in the rarefied plasmas of space.
gamma radiation	Also gamma rays; short-wavelength electromagnetic radiation originating from the decay of radioactive nuclei, from bremsstrahlung, and from cosmic sources.
GCR	Galactic cosmic ray.
geometric mean	The geometric mean of a set of positive numbers is the exponential of the arithmetic mean of their logarithms. The geometric mean of a lognormal distribution is the exponential of the mean of the associated normal distribution.
geometric standard deviation (GSD)	The geometric standard deviation of a lognormal distribution is the exponential of the standard deviation of the associated normal distribution.
germ cells	Reproductive cells such as the sperm and egg and their progenitor cells.
GMIR	Global merged interaction regions.
GOES	Geostationary operational environmental satellite.
gray (Gy)	Special name of the SI unit for absorbed dose (see *unit of dose*). 1 Gy = 1 J/kg = 100 rads.
half-life, biological	Time required to eliminate half of an incorporated amount of any substance from a body by metabolic processes of elimination; it is approximately the same for both stable and radioactive isotopes of a particular element.
half-life, radioactive	Period of time that it takes for the amount of a radioactive substance to decrease by half by decay.
heliosphere	A vast, spheroidal cavity, approximately 200 times the mean Sun-Earth distance, created in the interstellar gas by the outflowing solar wind.
high-LET radiation	Heavy, charged particles, such as protons or alpha-particles or heavier ions (such as are encountered in galactic cosmic radiation), that produce ionizing events densely spaced on a molecular scale (e.g., $L > 10$ keV/μm). Neutrons are also considered as high-LET radiation because the charged particles released in neutron interactions with matter are high-LET particles.
HMF	Heliospheric magnetic field.
HRP	Human Research Program (NASA).
HZE	High atomic number (Z) and energy (E).
HZETRN	High charge and energy transport code.

ICRP (International Commission on Radiological Protection)	An independent international organization that provides recommendations and guidance on protection against ionizing radiation.
ICRU (International Commission on Radiation Units and Measurements)	An independent international organization that provides recommendations and guidance on radiation quantities, units, and measurements for all applications of ionizing radiation.
incidence	Also, incidence rate; the rate of occurrence of a disease within a specified period of time, often expressed as a number of cases per 100,000 individuals per year.
in utero	In the womb: i.e., before birth.
inverse dose-rate effect	An effect in which, for a given exposure, the probability of effect per unit dose increases as the dose rate is lowered.
in vitro	Cell culture conditions in glass or plastic containers.
in vivo	In the living organism.
ionizing radiation	Particles or electromagnetic radiation sufficiently energetic to dislodge electrons from an atom or molecule, thereby creating an ion pair. Ionizing radiation includes x and gamma radiation, electrons (beta radiation), alpha particles (helium nuclei), and heavier charged atomic nuclei. Neutrons ionize indirectly by first interacting with components of atomic nuclei.
ISS	International Space Station.
kerma	The kerma (kinetic energy released in matter) for ionizing uncharged particles (photons, neutrons) is the quotient of the mean sum of the initial kinetic energies of all charged particles liberated in a unit mass of a material by the uncharged particles incident on that mass. Unit: J kg^{-1}. The special name for the unit of kerma is gray (Gy). If all of the kinetic energy is absorbed "locally," the kerma is approximately equal to the absorbed dose.
latent period	The period of time between exposure and expression of the disease. After exposure to a dose of radiation, there typically is a delay of several years (the latent period) before any cancer is observed.
LET	The linear energy transfer (LET) for charged particles of a given type and energy in a given material is the quotient of the mean energy lost by the charged particles due to electronic interactions in traversing a unit track length. The unit often used for LET is keV μm^{-1}.
life table	Shows the number of persons of a given number born or living at a specified age who live to attain successive higher ages, together with the numbers who die in each interval.

linear model or relationship (also linear dose-effect relationship)	The linear model is a special case of the linear-quadratic model, with the quadratic coefficient equal to zero; the linear model expresses the effect (e.g., cancer or mutation) as proportional to the dose (linear function of the dose).
linear-quadratic model	Also, linear-quadratic dose-effect relationship; expresses the effect (e.g., cancer) as the sum of two components, one proportional to the dose (linear term) and one proportional to the square of the dose (quadratic term). The linear term predominates at low doses; the quadratic term, at high doses.
LNT model	Linear no-threshold dose response for which any dose greater than zero has a finite probability of producing an effect (e.g., mutation or cancer). The probability is calculated either from the slope of a linear model or from the limiting slope, as the dose approaches zero, of a linear-quadratic model.
lognormal distribution	When the logarithms of a randomly distributed quantity have a normal (Gaussian) distribution.
low-LET radiation	X rays and gamma rays, charged particles, such as electrons or high-energy protons that produce low ionization density (e.g., $L < 10$ keV/μm).
LSS	Life span study. Long-term study of health effects in the Hiroshima and Nagasaki atomic bomb survivors.
mechanistic basis	An explanation derived from a knowledge of the individual stages leading to an effect.
meta-analysis	An analysis of epidemiologic data from several studies based on data included in publications.
MLE	Maximum likelihood estimate.
model	A schematic description of a system, theory, or phenomenon that accounts for its known or inferred properties and that may be used for further study of its characteristics.
Monte Carlo calculation	The method for evaluation of a probability distribution by means of random sampling.
mortality (rate)	The frequency at which people die from a disease (e.g., a specific cancer), often expressed as the number of deaths per 100,000 population per year.
MSL RAD	Mars Science Laboratory Radiation Assessment Detector.
multiplicative effects	The combined effect of two agents is equal to the product of the effects of the two agents acting alone.
natural radioactivity	The property of radioactivity exhibited by more than 50 naturally occurring radionuclides.
NCRP (National Council on Radiation Protection and Measurements)	U.S. Council commissioned to formulate and disseminate information, guidance, and recommendations on radiation protection and measurements.
NEO	Near-Earth object.

neoplasm	Any new and abnormal growth, such as a tumor; neoplastic disease refers to any disease that forms tumors, whether malignant or benign.
NIH	National Institutes of Health (U.S.).
nonstochastic	A description of effects whose severity is a function of dose; for these, a threshold may occur; some examples of somatic effects believed to be non-stochastic are cataract induction, nonmalignant damage to the skin, hematological deficiencies, and impairment of fertility.
normal distribution	The so-called bell-shaped curve of randomly distributed quantities; also referred to as a "Gaussian distribution."
NS	Never-smoker.
NSRL	NASA Space Radiation Laboratory.
NTE	Non-targeted effect. Biological response occurring in unirradiated cells as a result of radiation exposure in other cells. Generally taken to include bystander responses, in which biological changes are seen in unirradiated cells communicating with irradiated ("targeted") cells, and genomic instability in progeny of irradiated cells.
odds ratio (OR)	The odds of being exposed among diseased persons divided by the odds of being exposed among non-diseased persons.
oncogene	An overexpressed or mutated version of a normal gene that can, in a dominant fashion, release a cell from normal restraints controlling its proliferation and convert it into a tumor cell, by itself or in combination with other cellular changes. (This should be contrasted to a tumor suppressor gene whose product acts to suppress malignant transformation of cells and operates in a recessive manner, where in classical terms, both alleles must be lost or mutated to stop or curtail the supply of the growth suppressor gene product.)
PEL	Permissible exposure limit.
phenotype	The genetically and environmentally determined physical appearance of an organism.
photon	An electromagnetic quantum whose energy (Eph) equals the product of the Planck constant (h) and its frequency (v). With the convenient units eV and s, and with the wavelength λ in μm: $E_{ph} = 4.136\ 10^{-15}\ v = 1.24/\lambda$.
plasma	A gas in which a significant number of the atoms and molecules have lost one or more electrons and in which, therefore, electromagnetic effects are important.
pooled analysis	An analysis of epidemiologic data from several studies based on original data from the studies.
PRA	Probabilistic risk assessment.
prevalence	The number of cases of a disease in existence at a given time per unit of population, usually 100,000 persons.
probability of causation	A number that expresses the probability that a given cancer, in a specific tissue, has been caused by a previous exposure to a carcinogenic agent, such as radiation.

projection model	A mathematical model that simultaneously describes the excess cancer risk at different levels of some factor such as dose, time after exposure, or baseline level of risk, in terms of a parametric function of that factor. It becomes a projection model when data in a particular range of observations are used to assign values to the parameters in order to estimate (or project) excess risk for factor values outside that range.
promoter	An agent that is not by itself carcinogenic but which can amplify the effect of a true carcinogen by increasing the probability of late-stage cellular changes needed to complete the carcinogenic process.
proportional mortality ratio	The ratio of the percentage of a specific cause of death among all deaths in the population being studied divided by the comparable percentage in a standard population.
protraction	The spreading out of a radiation dose over time by continuous delivery at a lower dose rate.
QMSFRG	Quantum multiple scattering fragmentation.
quadratic-dose model	A model that assumes that the excess risk is proportional to the square of the dose.
quality factor (Q)	A LET-dependent factor by which the absorbed dose is multiplied to obtain (for radiation protection purposes) the dose equivalent. The currently used values of Q were chosen by the ICRP on the basis of published RBE (see *relative biologic effectiveness*) values for a range of radiation and biological end points. Absorbed dose in Gy × Q dose equivalent in Sv.
quality factor (QF)	A track structure-dependent factor, for use in NASA's proposed model, by which the absorbed dose is multiplied to scale the cancer risk coefficients for low-LET radiation so as to apply to space radiation. The proposed values of QF are chosen in the 2011 NASA report on the basis of an empirical relationship and available data on RBE values for HZE particles for a range of biological end points.
rad	The formerly used special name for the unit of absorbed dose, now replaced by the SI unit Gy (see *unit of dose*). 1 rad = 0.01 Gy = 100 erg/g.
radiation weighting factor	w_R, used by the ICRP to weight absorbed dose of an organ or tissue to obtain equivalent dose for the organ or tissue.
radioactivity	The property of nuclide decay in which particles or gamma radiations are usually emitted.
radiogenic	Caused by radiation.
radioisotope	A radioactive atomic species of an element with the same atomic number and usually identical chemical properties.
radionuclide	A radioactive species of an atom characterized by the constitution of its nucleus.
random errors	Errors that vary in a nonreproducible way around a limiting mean. These errors can be treated statistically by use of the laws of probability.
REIC	Risk of exposure-induced cancer.

REID	Risk of exposure-induced death. The difference in a cause-specific death rate for exposed and unexposed populations of a given sex and a given age at exposure, as an additional cause of death introduced into a population.
relative biological effectiveness (RBE)	The ratio D_{ref}/D, where D is the absorbed dose of a specified radiation and D_{ref} is the absorbed dose of a sparsely ionizing reference radiation (gamma rays or X rays) that produces the same level of effect. When the magnitude of the dose D is not specified, the RBE is meant to be the low-dose limit of the ratio D_{ref}/D (this low-dose RBE equals the low-dose effectiveness [initial slope] of the specified radiation to that of the reference radiation).
relative risk (RR)	The rate of disease in an exposed population divided by the rate of disease in an unexposed population. Also termed "rate ratio."
rem	(rad equivalent man). A special unit of dose equivalent, now replaced by the SI unit sievert (see *unit of dose*). 1 rem = 0.01 Sv.
RERF	Radiation Effects Research Foundation (Japan).
risk	A chance of injury, loss, or detriment. A measure of the deleterious effects that may be expected as the result of an action or inaction.
risk assessment	The process by which the risks associated with an action or inaction are identified and quantified.
risk coefficient	The increase in the annual incidence or mortality rate per unit dose: (1) absolute risk coefficient is the increase of the incidence or mortality rate per unit dose; (2) relative risk coefficient is the fractional increase above the baseline incidence or mortality rate per unit dose.
risk estimate	The increment of the incidence or mortality rate projected to occur in a specified exposed population per unit dose for a specified exposure regime and expression period.
SEP	Solar energetic particle.
SI units	Units of the International System of Units as defined by the General Conference of Weights and Measures in 1960. They are the base units, such as meter (m), kilogram (kg), second (s), and their combinations, which have special names (e.g., the unit of energy, 1 J = 1 kg m^2/s^2, or absorbed dose, 1 Gy = 1 J/kg. (See *unit of dose.*)
sievert (Sv)	Special name of the SI unit of dose equivalent, equivalent dose, and effective dose (see *unit of dose*). 1 Sv = 1 J/kg = 100 rem.
solar cycle	A periodic change of the Sun's activity with a period of approximately 11 years; typically, consists of 7 years of solar maximum and 4 years of solar minimum.
solar particle event	Very energetic process from the Sun produced both by solar flares and by shocks driven by fast coronal mass ejections; occurs when very strong magnetic fields in the solar photosphere reach a critical instability.
solid cancers	All malignant neoplasms other than those of the lymphatic and hematopoietic tissue.
somatic cells	Non-reproductive cells.

SPE	Solar particle event.
specific activity	Activity of a given nuclide per unit mass of a compound, element, or radioactive nuclide.
specific energy (z)	The energy per unit mass actually deposited in a microscopic volume in a single energy deposition event or at a given absorbed dose. This is a stochastic quantity as opposed to its average, the absorbed dose, *D*. The mean energy imparted by ionizing radiation to a medium per unit mass. Unit: 1 Gy = 1 J/kg.
standardized mortality ratio (SMR)	The ratio (multiplied by 100) of the mortality rate from a disease in the population being studied divided by the comparable rate in a standard population. The ratio is similar to a relative risk times 100.
stochastic	Effects whose probability of occurrence in an exposed population (rather than severity in an affected individual) depends on dose; stochastic effects are commonly regarded as having no threshold; hereditary effects are stochastic; some somatic effects, especially cancers, are regarded as being stochastic.
STS	Space Transportation System.
suppressor gene	A gene that can suppress another gene such as an oncogene. Changes in suppressor genes can lead to expression by genes such as oncogenes.
synergistic effect	Increased effectiveness results from an interaction between two agents, so that the total effect is greater than the sum of the effects of the two agents acting alone.
systemic errors	Errors that are reproducible and tend to bias a result in one direction. Their causes can be assigned, at least in principle, and they can have constant and variable components. Generally, these errors cannot be treated statistically.
target cells	Cells in a tissue that have been determined to be the key cells in which changes occur in order to produce an end point such as cancer.
TE	Targeted effect; occurrence of biological responses in irradiated cells (in contrast to NTE; see above).
threshold hypothesis	The assumption that no radiation injury occurs below a specified dose.
transformed cells	Tissue culture cells changed from growing in an orderly pattern exhibiting contact inhibition to growing in a pattern more like that of cancer cells.
transport	The term used in the study of energetic particles (GCR, SEP, etc.) to describe quantitatively the motion of the particles and their interaction with matter. Generally, transport calculations use an equation (see *Boltzmann transport equation*) that depends on the medium (e.g., shielding material, structural material, human body, interplanetary space) and particles being studied.
turbulence	The essentially random fluctuations that often occur in a large-scale fluid.
u	Atomic mass unit. Kinetic energies are often expressed in units of MeV per atomic mass unit (u), MeV/u, because particles with identical *E* then have the same β.

uncertainty	The range of values within which the true value is estimated to lie. It is a best estimate of possible inaccuracy due to both random and systemic errors.
units of dose	Dosimetric units. Unit conversion factors: Gray (SI): 1 Gy = 1 J/kg = 100 rad: used for absorbed dose and kerma. Sievert (SI): 1 Sv = 1 J/kg = 100 rem: used for equivalent dose, effective dose, and dose equivalent. Rem: 1 rem = 0.01 Sv.
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation; publishes periodic reports on sources and effects of ionizing radiation.
variability	The variation of a property or a quantity among members of a population. Such variation is inherent in nature and is often assumed to be random; it can then be represented by a frequency distribution.
weighted dose (d)	The dose to the atomic bomb survivors, roughly adjusted to account for the increased effectiveness of the small neutron absorbed dose contribution. The weighted dose equals the gamma-ray absorbed dose to a specified organ plus the neutron absorbed dose multiplied by a weighting factor that has usually been set equal to 10 in the analyses by RERF (see *RERF*).
x radiation	Also x rays; penetrating electromagnetic radiation, usually produced by bombarding a metallic target with fast electrons in a high vacuum.