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HEALTH RISKS FROM EXPOSURE TO LOW LEVELS OF IONIZING RADIATION

BEIR VII PHASE 2

Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation

Board on Radiation Effects Research

Division on Earth and Life Studies

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Health Risks from Exposure to Low Levels of Ionizing Radiation: Beir VII Phase 2 THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. 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. This study was supported by Environmental Protection Agency Grant #X-826842-01, Nuclear Regulatory Commission Grant #NRC-04-98-061, and U.S. Department of Commerce, National Institute of Standards and Technology Grant #60NANB5D1003. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the organizations or agencies that provided support for the project. Library of Congress Cataloging-in-Publication Data Health risks from exposure to low levels of ionizing radiation : BEIR VII, Phase 2 / Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, Board on Radiation Effects, Research Division on Earth and Life Studies, National Research Council of the National Academies. p. cm. This is the seventh in a series of reports from the National Research Council prepared to advise the U.S. government on the relationship between exposure to ionizing radiation and human health. Includes bibliographical references and index. ISBN 0-309-09156-X (pbk.)—ISBN 0-309-53040-7 (pdf) 1. Ionizing radiation—Toxicology. 2. Ionizing radiation—Physiological effect. 3. Ionizing radiation—Dose-response relationship. I. National Research Council (U.S.). Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation. RA1231.R2H395 2006 363.17'99—dc22 2006000279 Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu. Copyright 2006 by the National Academy of Sciences. All rights reserved. Printed in the United States of America.

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Health Risks from Exposure to Low Levels of Ionizing Radiation: Beir VII Phase 2 COMMITTEE TO ASSESS HEALTH RISKS FROM EXPOSURE TO LOW LEVELS OF IONIZING RADIATION RICHARD R. MONSON (chairman), Harvard School of Public Health, Boston, MA JAMES E. CLEAVER (vice chairman), University of California, San Francisco, CA HERBERT L. ABRAMS, Stanford University, Stanford, CA EULA BINGHAM, University of Cincinnati, Cincinnati, OH PATRICIA A. BUFFLER, University of California, Berkeley, CA ELISABETH CARDIS, International Agency for Research on Cancer, Lyon, France ROGER COX, National Radiological Protection Board, Chilton, Didcot, Oxon, United Kingdom SCOTT DAVIS, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA WILLIAM C. DEWEY, University of California, San Francisco, CA ETHEL S. GILBERT, National Cancer Institute, Rockville, MD ALBRECHT M. KELLERER, Ludwig-Maximilians-Universität, München, Germany DANIEL KREWSKI, University of Ottawa, Ottawa, Ontario, Canada TOMAS R. LINDAHL, Cancer Research UK London Research Institute, United Kingdom KATHERINE E. ROWAN, George Mason University, Fairfax, VA K. SANKARANARAYANAN, Leiden University Medical Centre, Leiden, The Netherlands DANIEL W. SCHAFER, Oregon State University, Corvallis, OR (from May 2002) LEONARD A. STEFANSKI, North Carolina State University, Raleigh, NC (through May 2002) ROBERT L. ULLRICH, Colorado State University, Fort Collins, CO CONSULTANTS JOHN D. BOICE, JR., International Epidemiology Institute, Rockville, MD KIYOHICO MABUCHI, National Cancer Institute, Rockville, MD

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Health Risks from Exposure to Low Levels of Ionizing Radiation: Beir VII Phase 2 Preface BACKGROUND This is the seventh in a series of reports from the National Research Council (NRC) prepared to advise the U.S. government on the relationship between exposure to ionizing radiation and human health. In 1996 the National Academy of Sciences (NAS) was requested by the U.S. Environmental Protection Agency to initiate a scoping study preparatory to a new review of the health risks from exposure to low levels of ionizing radiations. The main purpose of the new review would be to update the Biological Effects of Ionizing Radiation V (BEIR V) report (NRC 1990), using new information from epidemiologic and experimental research that has accumulated during the 14 years since the 1990 review. Analysis of those data would help to determine how regulatory bodies should best characterize risks at the doses and dose rates experienced by radiation workers and members of the general public. BEIR VII—Phase 1 was the preliminary survey to evaluate whether it was appropriate and feasible to conduct a BEIR VII—Phase 2 study. The Phase 1 study determined that it was appropriate and feasible to proceed to Phase 2. The Phase 1 study, Health Effects of Exposure to Low Levels of Ionizing Radiations: Time for Reassessment?, published in 1998, also provided the basis for the Phase 2 Statement of Task that follows. BEIR VII—PHASE 2 STATEMENT OF TASK The

primary objective of the study is to develop the best possible risk estimate for exposure to low-dose, low linear energy transfer (LET) radiation in human subjects. In order to do this, the committee will (1) conduct a comprehensive review of all relevant epidemiologic data related to the risk from exposure to low-dose, low-LET radiation; (2) define and establish principles on which quantitative analyses of low-dose and low-dose-rate effects can be based, including requirements for epidemiologic data and cohort characteristics; (3) consider relevant biologic factors (such as the dose and dose-rate effectiveness factor, relative biologic effectiveness, genomic instability, and adaptive responses) and appropriate methods to develop etiologic models (favoring simple as opposed to complex models) and estimate population determinants; (4) assess the current status and relevance to risk models of biologic data and models of carcinogenesis, including critical assessment of all data that might affect the shape of the response curve at low doses, in particular, evidence for or against thresholds in dose-response relationships and evidence for or against adaptive responses and radiation hormesis; (5) consider, when appropriate, potential target cells and problems that might exist in determining dose to the target cell; and (6) consider any recent evidence regarding genetic effects not related to cancer. In performing the above tasks, the committee should consider all relevant data, even if obtained from high radiation exposures or at high dose rates. With respect to modeling, the committee will (1) develop appropriate risk models for all cancer sites and other outcomes for which there are adequate data to support a quantitative estimate of risk, including benign disease and genetic effects; (2) provide examples of specific risk calculations based on the models and explain the appropriate use of the risk models; (3) describe and define the limitations and uncertainties of the risk models and their results; (4) discuss the role and effect of modifying factors, including host (such as individual susceptibility and variability, age, and sex), environment (such as altitude and ultraviolet radiation), and life-style (such as smoking history and alcohol consumption) factors; and (5) identify critical gaps in knowledge that should be filled by future research. WHAT HAS CHANGED SINCE THE LAST BEIR REPORT ON THE HEALTH EFFECTS OF LOW LEVELS OF LOW-LET IONIZING RADIATION IN THE 15 years since the publication of the previous BEIR report on low-LET radiation (BEIR V), much new informa-

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 Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2 tion has become available on the health effects of ionizing radiation. Since the 1990 BEIR V report, substantial new information on radiation-induced cancer has become available from the Hiroshima and Nagasaki survivors, slightly less than half of whom were alive in 2000. Of special importance are cancer incidence data from the Hiroshima and Nagasaki tumor registries. The committee evaluated nearly 13,000 incidences of cancer and approximately 10,000 cancer deaths in contrast to fewer than 6000 cancer deaths available to the BEIR V committee. Also, since completion of the 1990 report, additional evidence has emerged from studies of the Hiroshima and Nagasaki atomic bomb survivors suggesting that other health effects, such as cardiovascular disease and stroke, can result from radiation exposure. A major reevaluation of the dosimetry at Hiroshima and Nagasaki has recently been completed that lends more certainty to dose estimates and provides increased confidence in the relationship between radiation exposure and the health effects observed in Japanese A-bomb survivors. Additional new information is also available from radiation worker studies, medical radiation exposures, and populations with environmental exposures. Although the cancer risk estimates have not changed greatly since the 1990 report, confidence in the estimates has risen because of the increase in epidemiologic and biological data available to the committee. Progress has also been made since the 1990 report in areas of science that relate to the estimation of genetic (hereditary) effects of radiation. In particular, (1) advances in human molecular biology have been incorporated into the conceptual framework of genetic risk estimation, and (2) it has become possible to project risks for all classes of genetic diseases (i.e., those with more complex as well as simple patterns of inheritance). Advances in cell and molecular biology have also contributed new information on the mechanisms through which cells respond to radiation-induced damage and to the close associations between DNA damage response and cancer development. ORGANIZATION OF THE STUDY The NRC appointed a committee comprised of scientists and educators. Some had particular expertise in conducting research on ionizing radiation, while others were experienced in fields relevant to the committee's work. The NRC vetted all potential members to ensure that the work was free from any apparent or potential conflict of interest with the assistance of the Radiation Effects Research of the Division on Earth and Life Sciences. The committee held 11 meetings over a period of 4.5 years. The long duration of the committee was due largely to a period of reduced activity while awaiting completion of the update of the dosimetry and exposure estimates to atomic bomb survivors of Hiroshima and Nagasaki, Japan (the so-called DS02: Dosimetry System 2002). Six of the meetings included participation of the public for a portion of the meeting, and five of the meetings were conducted exclusively in executive session. Each meeting included extensive deliberations involving the committee as a whole; in addition, two major subcommittees were formed that were termed "biology" and "epidemiology." Dr. Monson convened the epidemiology sessions and Dr. Cleaver convened the biology sessions. Also, a number of loosely organized and nonpermanent working groups were formed to discuss the many issues before the committee. This approach, and the combination of it together and evaluate each other's work. ORGANIZATION OF THE REPORT As noted under its STATEMENT OF TASK, the committee's focus was to develop the best possible risk estimate for exposure to low-dose, low-LET radiation in human subjects. Accordingly, Chapters 1–4 discuss basic aspects of radiation physics and radiation biology, including the known interaction between radiation exposure and genetic material, cellular structures, and whole organisms. Chapters 5–9 discuss basic principles of epidemiology as well as substantive data relating to exposure from the atomic bombs, medical radiation, occupational radiation, and environmental radiation. Chapters 10–12, to the extent possible, integrate the information from biology and epidemiology and develop risk estimates based on this information. Three summary sections provide different levels of description of the report. Chapter 13 is an overall scientific summary and lays out the research needs identified by the committee. The Executive Summary is an abbreviated and reorganized version of Chapter 13 that provides an overview of the report. The Public Summary addresses the findings of the committee and the relevance of the report to public concerns about exposure to ionizing radiation.

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 Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2 Reviewers This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purposes of this review are to provide candid and critical comments that will assist the institution in making the published report as sound as possible and to ensure that the report meets institutional standards of 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 for their participation in the review of this report: Seymour Abrahamson, University of Wisconsin, Madison, WI; John F. Ahearne, Sigma Xi, The Scientific Research Society, Research Triangle Park, NC; Allan Balmain, University of California, San Francisco, CA; Michael Cornforth, University of Texas, Galveston, TX; James F. Crow, University of Wisconsin, Madison, WI; John Easton, University of Chicago Hospitals, Chicago, IL; Eric J. Hall, Columbia University College of Physicians and Surgeons, New York, NY; Richard D. Hichwa, University of Iowa, Iowa City, IA; Hedvig Hricak, Memorial Sloan-Kettering Cancer Center, New York, NY; Glenn F. Knoll, University of Michigan, Ann Arbor, MI; Jack S. Mandel, Emory University Rollins School of Public Health, Atlanta, GA; John P. Murnane, University of California, CA; Hooshang Nikjoo, National Aeronautics and Space Administration, Houston, TX; Jonathan M. Samet, Johns Hopkins University, Baltimore, MD; Susan S. Wallace, University of Vermont, Burlington, VT; Chris G. Whipple, ENVIRON International Corporation, Emeryville, CA. 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 George M. Hornberger, Ernest H. Ern Professor of Environmental Sciences and Associate Dean for the Sciences, University of Virginia, and John C. Bailar III, Professor Emeritus, University of Chicago. Appointed by the National Research Council, they were 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 National Research Council. GENERAL ACKNOWLEDGMENTS The committee thanks the directors and staff of the Radiation Effects Research Foundation (RERF), Hiroshima, Japan, for providing the most current Life Span Study data on the Japanese atomic bomb survivors. These data continue to be the primary source of epidemiologic information on the relationship between exposure to ionizing radiation and its effects on human health. In particular, Dr. Donald Pierce was especially helpful in communication between RERF and the committee; he also added his insightful experience to the work of the committee. The committee was aided in the consideration of its charge not only by comments from the public but also by formal presentations by experts from a number of fields. The following presentations were made as part of the public portion of the meetings (in order of appearance):

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 Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2 Presentations by Sponsors Jerome Puskin, Ph.D. Environmental Protection Agency Vincent Holahan, Ph.D. U.S. Nuclear Regulatory Commission Bonnie Richter, Ph.D. U.S. Department of Energy Scientific Speakers John Boice, Ph.D. International Epidemiology Institute Epidemiology that should be considered by BEIR VII Charles Waldren, Ph.D. Colorado State University Adaptive effects, genomic instability, and bystander effects John Ward, Ph.D. University of California, San Diego Differences between ionizing radiation-induced DNA damage and endogenous oxidative damage Antone Brooks, Ph.D. Washington State University Tri-citys Overview of projects funded by the Department of Energy low-dose program Charles Land, Ph.D. National Institutes of Health (NIH) National Cancer Institute's update of the 1985 NIH Radioepidemiologic Tables L.B. Russell, Ph.D. Oak Ridge National Laboratory Early information derived from radiation-induced mutations in mice R. Chakraborty, Ph.D. University of Texas School of Public Health Mini- and microsatellite mutations and their possible relevance to genetic risk estimation Allan Balmain, Ph.D. University of California, San Francisco High- and low-penetrance genes involved in cancer incidence Al Fornace, Ph.D. Harvard School of Public Health Functional genomics and informatics approaches to categorize radiation response Steve Wing, Ph.D. University of North Carolina Relevance of occupational epidemiology to radiation risk assessment Edward Calabrese, Ph.D. University of Massachusetts radiation hormesis David Utterback, Ph.D. National Institute of Occupational Safety and Health Exposure assessment and radiation worker studies Sharon Dunwoody, Ph.D. University of Wisconsin Challenges in the communication of scientific uncertainties Suresh Moolgavkar, Ph.D., M.B.B.S. Unit of Public Health and Community Medicine, University of Washington and Fred Hutchinson Cancer Research Center Biology-based models We thank these presenters and all other members of the public who spoke on issues related to ionizing radiation. The committee thanks Dr. Isaf Al-Nabulsi for her assistance at the beginning of this study and Doris Taylor and Cathie Berkeley for their administrative assistance in assuring that its members showed up at the right place at the right time. The committee was also aided in its work by a talented group of program assistants. We thank Courtney Gibbs for her assistance in the preparation of this manuscript. We thank Courtney Slack, a Christine Mirzayan Science and Technology Policy Graduate Fellow, who provided additional valuable assistance to NRC staff. We thank Dr. Evan Douple for pulling us in and holding us together. His wise and patient counsel along with his gentle encouragement, when needed, kept the committee focused on its charge. Finally, special thanks are due to Dr. Rick Jostes, the study director. His scientific expertise, persistence, equanimity, and organizational skills were essential to our staying the course. RICHARD MONSON, Chairman

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 Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2 Units Used to Express Radiation Dose Radiation exposures are measured in terms of the quantity absorbed dose, which equals the ratio of energy imparted to the mass of the exposed body or organ. The unit of absorbed dose is joules per kilogram (J/kg). For convenience this unit has been given the special name gray (Gy). Ionizing radiation can consist of electromagnetic radiation, such as X-rays or gamma rays (γ -rays), or of subatomic particles, such as protons, neutrons, and α -particles. X- and γ -rays are said to be sparsely ionizing, because they produce fast electrons, which cause only a few dozen ionizations when they traverse a cell. Because the rate of energy transfer is called linear energy transfer (LET), they are also termed low-LET radiation; low-LET radiations are the subject of this report. In contrast, the heavier particles are termed high-LET radiations because they transfer more energy per unit length as they traverse the cell. Since the high-LET radiations are capable of causing more damage per unit absorbed dose, a weighted quantity, equivalent dose, or its average over all organs, effective dose, is used for radiation protection purposes. For low-LET radiation, equivalent dose equals absorbed dose. For high-LET radiation—such as neutrons, α -particles, or heavier ion particles—equivalent dose or effective dose equals the absorbed dose multiplied by a factor, the quality factor or the radiation weighting factor (see Glossary), to account for their increased effectiveness. Since the weighting factor for radiation quality is dimensionless, the unit of equivalent dose is also joules per kilogram. However, to avoid confusion between the two dose quantities, the special name sievert (Sv) has been introduced for use with equivalent dose and effective dose. Although the BEIR VII report is about low-LET radiation, the committee has had to consider information derived from complex exposures—especially from atomic bomb radiation—that include a high-LET contribution in addition to low-LET radiation. A weighted dose, with a weight factor that differs from the quality factor and the radiation weighting factor, is employed in these computations. The unit sievert is likewise used with this quantity. Whenever the nature of the quantity is apparent from the context, the term dose is used equally in this report for absorbed dose, equivalent dose, effective dose, and weighted dose. With regard to risk assessment, reference is usually to the equivalent dose to specified organs or to the effective dose. The unit sievert is then used, although absorbed dose and equivalent dose are equal for low-LET radiation. In experimental radiation biology and radiotherapy, exact specification of absorbed dose is required and the dose values are frequently larger than in radiation protection considerations. With reference to those fields, therefore, use is made of absorbed dose and the unit is gray. The Public Summary refers to radiation protection, and the dose therefore is given as sieverts throughout that chapter (for a more complete description of the various dose quantities and units used in this report, see the Glossary and the table below). TABLE 1 Units of Dose Units Symbol Conversion Factors Becquerel (SI) Bq 1 disintegration/s = 2.7×10^{-11} Ci Curie Ci 3.7×10^{10} disintegrations/s = 3.7×10^{10} Gray (SI) Gy 1 kg = 100 rads Rad 0.01 Gy = 100 erg/g Sievert (SI) Sv 1 J/kg = 100 rem Rem 0.01 Sv NOTE: Equivalent dose equals absorbed dose times Q (quality factor). Gray is the special name of the unit (J/kg) to be used with absorbed dose; sievert is the special name of the unit (J/kg) to be used with equivalent dose. International Units are designated SI.

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