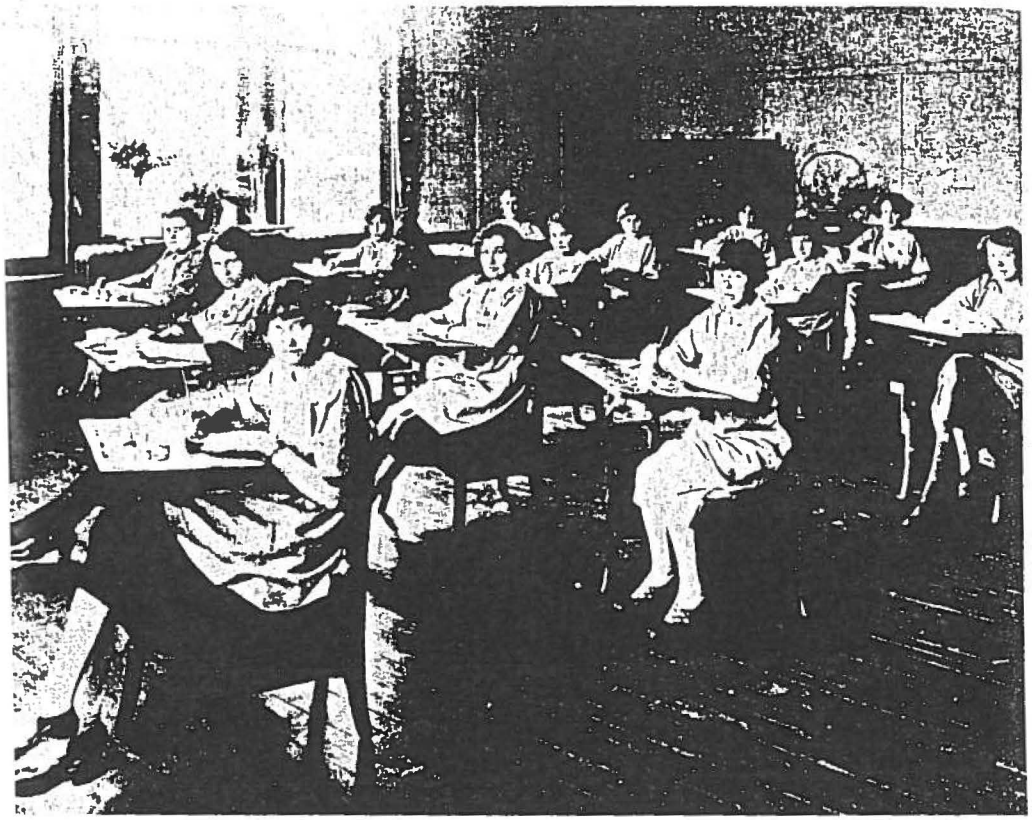

HEALTH RISKS OF RADON AND OTHER INTERNALLY DEPOSITED ALPHA-EMITTERS

BEIR IV

Committee on the Biological Effects
of Ionizing Radiations
Board on Radiation Effects Research
Commission on Life Sciences
National Research Council

NATIONAL ACADEMY PRESS
Washington, D.C. 1988

National Academy Press • 2101 Constitution Avenue, N.W. • Washington, D. C. 20418

The study summarized in this report was supported by the U.S. Environmental Protection Agency and the U.S. Nuclear Regulatory Commission under Contract No. 68-02-3895.

Library of Congress Cataloging-in-Publication Data
Health risks of radon and other internally deposited alpha-emitters.

This report was supported by the U.S. Environmental Protection Agency and the U.S. Nuclear Regulatory Commission under Contract No. 68-02-3895.

Includes bibliographies and index.

1. Alpha rays—Health aspects. 2. Radioisotopes in the body—Health aspects. 3. Radon—Health aspects. 4. Health risk assessment. I. National Research Council (U.S.). Committee on the Biological Effects of Ionizing Radiations. II. United States. Environmental Protection Agency. III. U.S. Nuclear Regulatory Commission. [DNLM: 1. Probability. 2. Radiation Effects. 3. Radioactive Pollutants—adverse effects. 4. Radon—adverse effects. 5. Risk WN 620 H4345]
RC95.A42H43 1987 616.9'897 87-31280
ISBN 0-309-03789-1, soft cover; ISBN 0-309-03797-2, hard cover

FRONTISPIECE: *Radium dial painters.*

Printed in the United States of America

First Printing, January 1988
Second Printing, June 1988
Third Printing, January 1989

COMMITTEE ON THE BIOLOGICAL EFFECTS OF IONIZING RADIATIONS

Jacob I. Fabrikant (*Chairman*), Donner Laboratory, University of California, Berkeley, California
William J. Bair (*Vice-Chairman*), Battelle Pacific Northwest Laboratories, Richland, Washington
Michael A. Bender, Brookhaven National Laboratory, Upton, New York
Carmia G. Borek, College of Physicians and Surgeons, Columbia University, New York, New York
Peter G. Groer, Center for Epidemiologic Research, Oak Ridge Associated Universities, Oak Ridge, Tennessee
Jay H. Lubin, National Cancer Institute, Bethesda, Maryland
David C. F. Muir, McMaster University, Hamilton, Ontario, Canada
Donald A. Pierce, Department of Statistics, Oregon State University, Corvallis, Oregon
William C. Roesch, Richland, Washington
Jonathan M. Samet, University of New Mexico Cancer Center, Albuquerque, New Mexico
Robert A. Schlenker, Argonne National Laboratory, Argonne, Illinois
Richard J. Waxweiler, Centers for Disease Control, Atlanta, Georgia

National Research Council Staff

William H Ellett, Project Director, Board on Radiation Effects Research, Commission on Life Sciences
Raymond D. Cooper, Senior Program Officer, Board on Radiation Effects Research, Commission on Life Sciences

Sponsors' Project Officers

Neal Nelson, U.S. Environmental Protection Agency
Shlomo Yaniv, U.S. Nuclear Regulatory Commission

Preface

BACKGROUND

In June 1984, the Environmental Protection Agency (EPA) and the Nuclear Regulatory Commission (NRC) asked the National Academy of Sciences,to submit a proposal in response to EPA Solicitation DU-84-C165 for a study of the "biological effects of internally deposited alpha-emitting radionuclides and their decay products." The proposal constituted an extension of the work of the National Research Council's Committees on the Biological Effects of Ionizing Radiations (BEIR), which began in the early 1970s and most recently culminated in the report *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980.* That report, the so-called BEIR III report, dealt mainly with the effects of radiation of low linear energy transfer (low LET), primarily external x rays and gamma rays.

At the time of the BEIR III deliberations, the human and animal studies on high-LET radiation effects were limited, and epidemiological surveys were only beginning to provide reliable data on potential health effects. The reported epidemiological and laboratory animal studies pointed to a need to extend the series of BEIR reports, to appraise the state of scientific knowledge concerning the biological and health effects of alpha radiation (internally deposited alpha-emitting radionuclides and their decay products). This will enable government officials and the public to make decisions about the potential community and workplace health hazards associated with exposure

to internal alpha-emitters, such as those from indoor radon and uranium mining.

The task before the current BEIR committee was specified in detail in the contract agreement between the National Academy of Sciences and the EPA and NRC signed on October 1, 1984.

CHARGE TO THE COMMITTEE

In response to the EPA and NRC request, the Committee on the Biological Effects of Ionizing Radiations was established within the National Research Council's Commission on Life Sciences. This committee, the fourth in a series originally established in 1969, was asked for a comprehensive assessment of available knowledge of the risks associated with internally deposited alpha-emitters. Radiobiological and animal data were to be reviewed, but relevant epidemiological data were also to be used to the greatest possible extent in estimating the risks.

The first phase of the study was to be a review of current knowledge of the somatic and genetic effects of internal alpha-emitters, including clinical and epidemiological evidence of human effects, results of animal studies, alpha-particle damage at the cellular level, metabolic pathways for internal alpha-emitters, dosimetry and microdosimetry of alpha-emitters deposited in specific tissues, and the possible chemical toxicity of low-specific-activity alpha-emitters. The committee was also asked to review the evidence of dependence of the biological effects on age, sex, route of entry, dose, dose rate, physical and chemical properties of the radioactive materials, and similar factors.

During the second phase of the study, the committee was requested to suggest methods for estimating the risks to human health, with their related uncertainties, associated with internally deposited alpha-emitters and then to apply the methods to the principal alpha-emitters in the environment. This phase was to include the provision of formulas and coefficients to estimate individual and population risks associated with single and chronic exposure to internal alpha-emitters and, where appropriate, threshold formulas and coefficients for nonstochastic effects. This information was to be applied to estimating numbers of genetic effects, risks to unborn children, and risks of carcinogenic effects. The committee was asked to describe the metabolic models they used and provide examples of the methods to

be used in applying their risk estimates to exposed populations. Finally, the committee was asked to discuss the uncertainty in their risk estimates and provide recommendations for further research based on the limitations in the data available for assessing the risks which the committee identified.

The third phase of the committee's work was preparation and submission of a report covering the results and findings of the first two phases.

The committee's review and evaluation of the current epidemiological and basic research involved not only an assessment of the relevant research data and their analyses in the scientific literature, but also an independent evaluation and analysis of relevant epidemiological data considered essential to the committee's charge. The committee critically reviewed the scientific literature on the biological and health effects of internally deposited alpha-emitting radionuclides, relying wherever possible on original scientific publications and on current data that were generously provided by investigators in the United States, Canada, Western Europe, and Japan.

ORGANIZATION OF THE STUDY

To carry out the charge, the NRC appointed a committee of scientists experienced in radiation epidemiology, radiobiology, genetics, biostatistics, metabolism and pharmacokinetics, pathology, radiation dosimetry, inhalation physics, chemistry, biology, radiology and nuclear medicine, and mathematical modeling and risk assessment. The study was conducted under the general guidance of the Board on Radiation Effects Research of the Commission on Life Sciences.

To facilitate its work and to augment its expertise so as to encompass a wider spectrum of scientific subjects, the committee solicited specific contributions from a number of scientific experts other than its own members. These experts participated in the committee's deliberations throughout the course of its work.

The committee held eight meetings over a period of 24 months—six in Washington, D.C., one in Berkeley, California, and one in Woods Hole, Massachusetts. The second meeting, on May 15, 1985, included a public meeting, at which open discussion and contributions from interested scientists and the public at large were invited. Several additional meetings of subgroups of the committee were held, to plan and outline specific work assignments.

The committee organized its work according to the main objectives of the charge and divided the study into the following main categories:

- Genetic, teratogenic, and fetal effects of internally deposited alpha-emitting radionuclides.
- Carcinogenic and other health effects of radon, radium, thorium, polonium, uranium, and the transuranic radionuclides.
- The scientific basis and mechanisms underlying the biological and health effects, including the relevant physics and dosimetry, radiobiology, anatomy and physiology, and method of risk analysis.

The structure, composition, and expertise of the committee, including its invited participants, permitted considerable overlapping of assignments among the different categories, ensuring the interaction of scientific disciplines.

The committee also conducted two informal workshops that focused on radon. These workshops were designed to review with a number of investigators the current scientific knowledge with respect to uranium-miner epidemiology, lung modeling and dosimetry, and risk estimation.

JACOB I. FABRIKANT
Chairman
Committee on the Biological Effects
of Ionizing Radiations

Acknowledgments

During this study the committee was aided by many experts from the scientific community. Scientific data, advice, and help in the preparation of the text were freely offered, and the committee wishes to acknowledge this very important assistance. Special thanks are due to Richard Hornung, Geoffrey Howe, Jan Muller, and their respective government authorities in the United States and Canada, and Edward Radford for providing their data tapes on the followup of miners exposed to radon progeny for reanalysis by this committee. The resulting combined data base of radon effects in uranium miners is the largest that has been analyzed.

The preparation of the report required expertise in many disciplines. The committee gratefully acknowledges the help it received from Victor P. Bond, Anthony L. Brooks, Fred Cross, Carter Denniston, William H. DuMouchel, Marvin Goldman, Douglas Grahn, Webster Jee, Robert E. Rowland, Charles L. Sanders, Melvin R. Sikov, Newell Stannard, and McDonald E. Wrenn. These invited participants provided invaluable aid in the preparation and review of specific chapters; they are not responsible for errors that might have crept in to the final report. In addition, several other scientists, including Bernard Cohen, Richard Cuddihy, Leonard Hamilton, and Charles Land, provided useful information on lung dosimetry, epidemiological studies, and risk modeling. The analyses of the radon-exposed cohorts presented in this report were made possible by the

use of the AMFIT program developed by Dale Preston and his colleagues at the Radiation Effects Research Foundation, Hiroshima.

We wish to acknowledge also the help and support of Stephen L. Brown and William L. Lappenbusch, formerly of the National Research Council, who were instrumental in getting this study started. Special appreciation is extended to Colette A. Carmi and Doris E. Taylor for handling the myriad administrative details associated with this committee's work and for preparing the many drafts of the report. Their patience and good cheer helped the committee over the innumerable difficulties that inevitably arise during the course of its work.

Contents

PRINCIPAL TABLES

HEALTH RISKS OF RADON AND OTHER INTERNALLY DEPOSITED ALPHA-EMITTERS

BEIR IV

1
Overview

INTRODUCTION

This report addresses demonstrated and potential health effects of exposure of human populations to internally deposited alpha-emitting radionuclides and their decay products. It emphasizes carcinogenic effects and, where possible, presents quantitative risk estimates for cancer induction. The largest part of the report deals with health effects of exposure to radon and its progeny, primarily because of a need to characterize the lung-cancer risk associated with exposure to radon and its short-lived daughters in indoor domestic environments. The report also addresses health effects of exposure to other groups of radionuclides and their progeny that emit alpha particles—the isotopes of polonium, radium, thorium, uranium, and the transuranic elements.

Several alpha-emitting radionuclides occur naturally in our environment; others are produced for industrial, military, and medical applications. Recent attention has focused on the alpha-emitting radioisotopes because of their presence in drinking water, in indoor air in buildings, and in mines and because of their potential release into the environment from the nuclear fuel cycle (including radioactive waste disposal) and from accidents during space exploration. The radionuclides of concern are mainly radon-222 and radium-226 and their alpha-emitting daughter products and the transuranic elements plutonium-238 and -239.

Alpha-emitting radionuclides can be absorbed into the tissues of the body and irradiate adjacent cells after inhalation or ingestion, after entry through a wound in the skin, or after injection for diagnostic or therapeutic purposes. Radiation effects depend not only on the physical properties of emitted radiation, but also on the physiology and biochemistry of the exposed person and the physical and chemical characteristics of the radionuclides, which control their deposition, transport, metabolism, excretion, and reuse in the body. The health effects of radiation in humans include cancer induction, genetic disease, teratogenesis (induction of developmental abnormalities), and degenerative changes. The most important target tissues for cancer induction and degenerative changes are the respiratory tract, bone, liver, and the reticuloendothelium system.

Both natural and man-made alpha-emitting radionuclides in our environment can pose a risk to human health, but the natural sources currently make the largest contribution to human exposure. Among the natural sources, inhaled radon and radon decay products indoors are the largest contributors to population exposure and might be responsible for a large number of lung-cancer deaths each year.[3] That has led to recommendations, now being implemented, for national studies to assess the magnitude of the problem, for adopting remedial action levels of radon progeny in the indoor environment, and for introducing mitigation procedures to take effect at or below such levels to reduce population exposures from this source.[8,9]

For estimation of risks associated with exposure to the alpha-emitting radionuclides, the most important human populations examined are the underground miners who are exposed to widely differing concentrations of radon-222 progeny,[3] the American radium-dial workers who ingested various amounts of long-lived radium-226 and radium-228,[6] the German patients who received injections of short-lived radium-224[11] with different activities, and the German patients who received injections of graded volumes of Thorotrast (colloidal thorium-232 dioxide).[10] Human data on cancer induction by alpha-particle irradiation are sparse, but preliminary risk estimates have been calculated for some sites and tissues—lung, bone, head sinus and mastoid, and liver.

All of these epidemiological surveys are presently in progress, none is completed, and the person-years of follow-up are still relatively small, so that the lifetime carcinogenic risks of alpha-radiation exposure remain uncertain. Sufficient human data are not available for assessing the late health effects of the transuranic elements, e.g.,

plutonium-239; and here it has been necessary to estimate risks from these internally deposited alpha-emitters in humans by simplified mathematical and dosimetric models[1] or from comparison of effects with other radionuclides, where both direct experimental observation in laboratory animals and knowledge of radiation effects in humans are available. Complications arise in evaluating such comparisons because of such factors as different time patterns of deposition and resorption of the various radionuclides, e.g., radium vis à vis plutonium in bone.[2]

This report attempts to respond to a broad range of scientific questions related to current public health issues. Not all the questions can be addressed directly. There is considerable variation in the amount of data on each radionuclide from epidemiological studies and animal investigations. Epidemiological data are available on some alpha-emitting radionuclides, such as radon and its daughters, radium, and thorium. Little human information is available, however, on the transuranic elements, so dependence must be placed on animal experiments. As in all experimental animal studies, the extent to which the results can be extrapolated to humans and the confidence that can be placed on such extrapolation are uncertain. Even when human data were available, the committee has tried to rely on its own studies using newly developed methods for the analysis of occupational cohort data rather than relying solely on published information. The committee has also used novel statistical methods to analyze interspecies comparisons of the risks associated with different radionuclides when human data were insufficient. The committee recognizes that these analyses are preliminary and that large uncertainties are inherent in such extrapolations. Nevertheless, the committee believes that the methods introduced here will help to point the way to more detailed comparisons as additional data from epidemiological and animal studies become available.

This report consists of eight chapters and eight appendixes. The remainder of this chapter presents a summary of the committee's findings and its recommendations for future research. The next six chapters review the epidemiological and experimental evidence of the biological and health effects of the internally deposited alpha-emitting radionuclides and their daughter products. Chapter 8 summarizes the scientific evidence on genetic and fetal effects. The eight appendixes provide much of the scientific basis for the committee's conclusions, dealing primarily with radon and its progeny and with molecular and cellular radiobiology. Throughout the committee's

deliberations, the sources of uncertainty that should be recognized in connection with radiation risk estimation are discussed; they are particularly important with regard to the effects of radon and its progeny.

The committee found it necessary, because of constraints on time and resources, to narrow its charge to an examination only of alpha-emitting radionuclides known to induce health effects in exposed human populations and to concentrate its efforts on specific subjects in each case. The committee's focus and efforts were strongly influenced by the need to address the health effects of inhaled radon progeny, because of the concern over lung-cancer risk associated with increased indoor concentrations of radon. When results of epidemiological surveys were available (e.g., on radon, radium, and thorium), analysis of human data was preferred to analysis of laboratory animal data (e.g., on polonium, uranium, and the transuranic elements) for quantitative human risk estimation.

As in earlier reports from the Committee on the Biological Effects of Ionizing Radiations, the so-called BEIR reports, the committee cautions that the risk estimates derived from epidemiological and experimental animal data should not be considered precise. They are derived from analyses of incomplete data and involve numerous uncertainties. The risk estimates presented here will change as new information and analytical methods become available.

Finally, the committee notes that it assumes no responsibility to address the subject of regulatory guidance on exposure levels or societal cost-benefit issues that involve the radionuclides of concern. Clearly, such issues are beyond the scope of the committee's task and beyond its expertise.

SUMMARY OF FINDINGS

Most primordial radionuclides are isotopes of heavy elements and belong to the three radioactive series headed by uranium-238, thorium-232, and uranium-235. These contribute significantly to the general population collective dose equivalent. The relevant radionuclides in the body include the isotopes of uranium, radium, radon, polonium, bismuth, and lead; these enter the body by inhalation or by ingestion of food and water and only rarely through wounds in the skin. They follow normal chemical metabolism, and the concentrations of the long-lived radionuclides are usually maintained at

equilibrium or increase slowly with age. The shorter-lived radionuclides disappear by decay, but might be continually replenished by renewed intake.

The annual dose equivalent to the bronchial epithelium from inhaled alpha-emitting radionuclides and their progeny approaches 2,500 mrem/yr (25 mSv/yr),[3] due almost entirely to the radon progeny polonium-218–polonium-214 pair. The important tissue is the bronchial epithelium, which is the site of most lung cancers thought to be induced by radiation. The major contributors are the short-lived decay products of radon, measurements of which show an apparent log-normal distribution of concentrations in indoor air. For smokers, the additional exposure to the lungs from naturally occurring radionuclides in tobacco increases the dose to the bronchial epithelium.[4] For other soft tissues, bone surfaces, and bone marrow, the largest contributors to the dose equivalent from the alpha-emitters are the lead-210–polonium-210 pair in bone. Exposure of the general and worker populations from man-made or enhanced sources comes primarily from consumer products (e.g., tobacco), the nuclear fuel cycle, and emissions from government and industrial facilities, including those from mineral extraction. In the past, enhanced materials produced for medical applications, such as colloidal thorium dioxide, were injected or instilled directly into body tissues and resulted in high doses to some organs.

RADON

The evaluation of the lung-cancer risk associated with radon and its progeny has been the most challenging task of the committee. Numerous studies of underground miners exposed to radon daughters in the air of mines have shown an increased risk of lung cancer in comparison with nonexposed populations. Laboratory animals exposed to radon daughters also develop lung cancer. The abundant epidemiological and experimental data have established the carcinogenicity of radon progeny. Those observations are of considerable importance, because uranium, from which radon and its progeny arise, is ubiquitous in the earth's crust, and radon in indoor environments can reach relatively high concentrations. Although the carcinogenicity of radon daughters is established and the hazards of exposure during mining are well recognized, the hazards of exposure in other environments have not yet been adequately quantified. Risk estimates of the health effects of long-term exposures at relatively low levels are

required, to address the potential health effects of radon and radon daughters in homes and to refine estimates of the risk in occupational environments.

Two approaches are being used to characterize the lung-cancer risks associated with radon-daughter exposure: mathematical representations of the respiratory tract that model radiation doses to target cells and epidemiological investigation of exposed populations, mainly underground miners. The dosimetric approach used by other investigators and committees provides an estimate of lung-cancer risk related to radon-daughter exposure that is based specifically on modeling of the dose to target cells. The various dosimetric models all require assumptions, some of which are not subject to direct verification, as to breathing rates; the deposition of radon daughters in the respiratory tract; and the type, nature, and location of the target cells for cancer induction. Accordingly, the committee chose not to use dosimetric models for calculating lung-cancer risk estimates in this report. However, the results of dose models were used to extrapolate lung-cancer risks derived from the epidemiological studies of underground miners to the general population in indoor environments. The lung-cancer risk estimates for radon-daughter exposure derived by the committee in this report are based solely on epidemiological evidence.

The committee preferred a direct epidemiological approach, because the studies of radon-daughter-exposed miners provided a direct assessment of human health effects. Although each of the epidemiological studies that the committee assessed has limitations, the approach of a combined analysis of major data sets permitted a comprehensive assessment of the health risks associated with radon-daughter exposure and of other factors that influence the risk, such as age and time since exposure. In analyzing the data, the committee used a descriptive analytical approach, rather than statistical methods based on conceptual models of carcinogenesis. The committee obtained data from four of the principal studies of radon-exposed miners (Ontario uranium miners, Saskatchewan uranium miners, Swedish metal miners, and Colorado Plateau uranium miners) and developed risk models for lung cancer based on analyses of these data. By means of statistical regression techniques appropriate for survival-time data, the committee found that the probability of dying of lung cancer at age a in the combined cohorts was best described by the following expression:

$$r(a) = r_0(a)[1 + 0.025\gamma(a)(W_1 + 0.5W_2)], \qquad (1\text{-}1)$$

where $r(a)$ is the lung-cancer mortality rate at age a; $r_0(a)$ is the baseline lung-cancer mortality rate in the 1980–1984 U.S. population; $\gamma(a)$ is 1.2 for ages less than 55 yr, 1.0 for ages 55–64 yr, and 0.4 for age 65 yr or greater; W_1 is the cumulative radiation exposure, in WLM,* from 5 to 15 yr before age a; and W_2 is the cumulative exposure, in WLM, 15 yr or more before age a.

In this model, the excess relative risk varies with time since exposure, rather than remaining constant, and depends on age at risk; the expression, therefore, is a departure from most previous risk models, which have assumed that the relative risk is constant over both age and time. In the committee's modified relative-risk model, radon exposures more distant in time have a smaller impact on the age-specific excess relative risk than more recent exposures. Moreover, the age-specific excess relative risk is higher for younger persons and declines at higher ages. The committee's analysis did not assume a priori that analysis based on the relative risk was necessarily more appropriate than alternatives, such as analysis based on absolute risk. However, an absolute-risk model would have involved a complex power function of age. Since it requires fewer variables, the relative-risk form adopted by the committee provides a simpler description of observed lung-cancer risks in the miner cohorts.

Recognition that radon and its daughter products can accumulate to high concentrations in homes has led to concern about the potential lung-cancer risk associated with indoor domestic exposure. Although such risks can be estimated with the mathematical expression in Equation 1-1 for excess relative risks, it must be recognized that the committee's model is based on occupational exposure data. Several assumptions are required to transfer risk estimates from an occupational setting to the indoor domestic environment. Accordingly, the committee assumed that the epidemiological findings in the underground miners could be extended across the entire life span, that cigarette smoking and exposure to radon daughters interact multiplicatively, that exposure to radon progeny increases the risk of lung cancer in proportion to the sex-specific ambient risk of lung cancer associated with other causes, and that, to a reasonable

*Working level month (WLM) is a unit of exposure to radon progeny. It is defined in Chapter 2 and in the Glossary. The current occupational limit is 4 WLM/yr.

TABLE 1-1 Comparisons of Estimates of Lifetime Risk of Lung-Cancer Mortality due to a Lifetime Exposure to Radon Progeny

Study	Excess Lifetime Lung-Cancer Mortality (deaths/10^6 person WLM)
BEIR IV (1987, this report)	350[a]
NCRP[3] (1984)	130
BEIR III[5] (1980)	730
UNSCEAR[7] (1977)	200–450

[a]See Chapter 2 of this report.

approximation, a WLM yields an equivalent dose to the bronchial epithelium in both occupational and environmental settings. This last assumption is tentative, as it is based on very limited information. The committee concluded that more complete specifications of aerosol characteristics in mines and homes and the relevant physiological parameters are needed to permit quantitative assessment of the comparative dosimetry of radon daughters in the occupational and environmental settings.

On the basis of the estimates of excess relative risks per WLM of exposure to radon progeny derived from analysis of the four miner cohorts examined and the assumptions outlined above, the committee projected lung-cancer risks for U.S. males and females. The committee's risk projections estimate the ratio of lifetime risks relative to baseline risks, the probability of lung-cancer mortality, and average years of life lost for various exposure rates and durations of exposure. The report includes tables for estimating risks conditional on survival to a particular age and for smokers and nonsmokers of either sex.

The risk projections cover exposure situations of current public-health concern. Lifetime exposure to 1 WLM/yr is estimated to increase the number of deaths due to lung cancer by a factor of about 1.5 over the current rate for both males and females in a population having the current prevalence of cigarette smoking. Occupational exposure to 4 WLM/year from ages 20 to 40 is projected to increase male lung-cancer deaths by a factor of 1.6 over the current rate in this age cohort in the general population. In all these cases, most of the increased risk is in smokers in whom the risk is 10 or more times greater than that in nonsmokers.

Comparisons of estimates of the lifetime risk of lung-cancer mortality due to a lifetime exposure to radon progeny in terms of WLM made by this and other scientific committees yield the data presented in Table 1-1.

The BEIR IV (this report) committee's modified relative-risk model differs from the others, in that it incorporates dependence of the relative risk of lung-cancer mortality on both time since exposure and age at risk. Unlike the modified relative-risk model developed by this committee, risk estimates by the 1980 BEIR III committee[5] were based on the assumption of an additive risk of lung-cancer mortality due to exposure to radon progeny that increased with age.

Users must be aware of the uncertainties that affect the estimates of the lung-cancer risk due to exposure to radon progeny given in this report. The uncertainties include sampling variation in the primary data, random and possibly systematic errors in the original data on exposure and lung-cancer occurrence, inappropriate statistical models for analysis or misspecification of the components of the models, and incorrect description of the interaction between radon-daughter exposure and cigarette smoking. In addition, the actual computed lifetime risk and expected life-shortening depend on the age-specific disease rates in the referent population—in the committee's examples, the 1980–1984 U.S. population mortality rates. Projections based on a different referent population would be expected to differ, although the ratios of lifetime risks and years of life lost to baseline values are believed to be more stable across populations.

In its review and analysis, the committee found gaps in information related to some aspects of radiation carcinogenesis by radon daughters. The cells of the respiratory tract that give rise to radon-daughter-associated lung cancer are still not known. A unique link between radon-daughter exposure and small-cell carcinoma of the lung was not found; in the studies of underground miners, this histological type occurred in greatest excess, but other cancer-cell types were also increased.

Review of the literature and the committee's own analyses of the relevant data did not lead to a conclusive description of the interaction between radon daughters and cigarette smoking for the induction of lung cancer. Several data sets were analyzed, and although the committee chose a multiplicative interaction for its risk projections on a relative-risk scale, it recognizes that a submultiplicative model is also consistent with the data analyzed. Neither an additive nor a subadditive model appears consistent with these data.

Health effects of exposure to radon daughters other than respiratory cancer are also of concern, but the data are sparse and associations are weak. Reductions in lung function in some uranium miners cannot be attributed directly to radon-daughter exposure.

The data on increased occurrence of chromosomal aberrations in lymphocytes and on adverse reproductive outcomes in uranium miners are inconclusive.

Research in the United States and other countries has provided data on concentrations of radon and radon progeny in homes. The studies have also described the sources of radon and determinants of its concentration. A few exploratory epidemiological investigations of the lung-cancer risk associated with radon-daughter exposure in homes have been carried out, but the study populations have been small and the results inconclusive. The committee judged these exploratory studies to be inadequate for the purposes of risk estimation. Its risk projections for the general population are therefore based on the studies of miners. The committee concluded that estimates of lung-cancer risks based on studies on miners can be used to estimate the potential lung-cancer risk associated with increased concentrations of indoor radon; however, the estimates derived are imprecise. The committee recognizes that the differences between risks in mining and domestic environments and the interaction between smoking and exposure to radon progeny remain incompletely resolved.

POLONIUM

Polonium isotopes occur in nature; they appear in tissues as a result of ingestion in foods, inhalation of tobacco smoke, and decay of lead-210 deposited in bone. Polonium-214 and polonium-218 are short-lived daughters of radon-222 and contribute a large fraction of the radiation dose from inhaled radon. Extensive work with animals, primarily with polonium-210, has indicated that it does not localize appreciably in bone, in contrast with many other alpha-emitters; it concentrates instead in the reticuloendothelial system, in kidney, and in blood cells. Its effects at higher doses resemble those of generalized whole-body radiation and involve all major organ systems. At lower doses, soft-tissue tumors, nephrosclerosis, hypertension, cataracts, generalized atrophy of the lymphoid system, and nonspecific lifespan shortening occur.

In laboratory animal experiments, the relative toxicity of polonium-210 is a function of duration of exposure and dose. At high doses, it is much more toxic than uranium, plutonium, radium, or the transplutonic elements. Because of its shorter half-life and its toxicity at longer times and lower doses, it is comparable with plutonium-239, i.e., about 5 times as effective as radium-226; at very

low doses and very long times, its effectiveness approaches that of radium-226.

Experimental studies in humans and accidental exposures have indicated that metabolism in the human body is similar to that in laboratory animals. Only a few cases of effects in humans due directly to exposure to polonium-210 have been documented, so carcinogenic risk associated with exposure to polonium cannot be estimated directly. Risks can be estimated indirectly from the experience with other internally deposited alpha-particle emitters.

RADIUM

The main sources of information on the health effects of radium deposited in human tissues are the U.S. cases of occupational exposure (mostly in dial painters and radium chemists) and medical exposure to radium-226 and radium-228 and the German cases of repeated injection of radium-224 into patients for treatment of ankylosing spondylitis in adult life or tuberculosis in childhood. Malignant effects are almost exclusively the induction of skeletal tumors and of carcinomas in the paranasal sinuses and mastoid air cells. The evidence of induction of leukemia is weak, except at doses far greater than those in occupational, environmental, or therapeutic exposures currently encountered.

The dose-response data on bone sarcomas are characterized by low-dose regions of zero observed risk. Depending on which isotope of radium is being considered, a variety of dose-response relationships are consistent with the human data—linear, dose squared, linear with correction for dose protraction, dose-squared exponential, linear-quadratic exponential, 1 minus an exponential, and threshold.[6] In the dose range in which bone tumors have occurred, the lifetime risk associated with radium-224 is estimated to be about 2×10^{-2} excess bone sarcomas per person Gy (200 per million person-rad) when a linear function is assumed and an apparent increase in risk with dose protraction is taken into account. However, analyses that take into account competing risks lead to the rejection of a linear dose response on statistical grounds, and the best fit to the data on children and adults is found to be linear-quadratic exponential. The lifetime probability of excess bone cancer induction per person Gy to bone is then estimated to be approximately $(0.0085D + 0.0017D^2)$ $\exp - 0.025D$ after an average skeletal dose of less than 1 Gy and a 25-yr expression period. Tumors are distributed over time, with their

frequency diminishing with a half-life of about 4 yr after a minimum latent period of 5 yr. In the low-dose range in which no tumors have been observed, the uncertainty in the risk estimates for radium-224 increases monotonically with decreasing dose.

For radium-226 and radium-228 bone sarcoma induction, a number of dose-response functions provide statistically acceptable fits to the data within the range of doses where tumors have been observed. All of these functions predict approximately the same risk for a given exposure, but not at lower doses where no tumors have been observed. Below the dose range in which tumors have been observed, the uncertainty in the estimate of risk based on extrapolation of the dose-response function increases monotonically with decreasing exposure. Bone sarcomas induced by radium-226 and radium-228 have appeared 7 yr after first exposure and continued to appear throughout life. The time to tumor appearance apparently increases with decreasing dose and dose rate. Below an average skeletal dose of about 0.8 Gy, the chance of developing bone cancer from radium-226 and radium-228 during a normal lifetime is extremely small—possibly zero.

Carcinomas in the paranasal sinuses and mastoid air cells are observed after exposure to radium-226 or to radium-226 in combination with radium-228, but have not yet been observed among persons exposed to radium-224. The working hypothesis in most analyses of the data is that radionuclides other than radium-226 are ineffective for the induction of these carcinomas (although such carcinomas have occurred at a statistically significant frequency in dogs exposed to other radium isotopes and to the actinides). The tumors occurred as early as 10 yr after exposure and continued to occur throughout life. A linear dose-response relationship describes the data either as a function of average skeletal dose or of radium-226 intake. In terms of systemic intake, the risk coefficient for these carcinomas is estimated as 16 excess cancers per million person-yr at risk per μCi of intake. Causation is thought to be associated partly with the generation of radon-222 by radium-226 decay and later irradiation of the sinus and mastoid epithelial tissues by radon-222 and its progeny.

The cells at risk of bone cancer induction appear to be proliferating osteogenic cells or their precursors at bone surfaces. Identification of cell type and location is complicated by the diversity of cells that lie within the range of alpha particles emitted from bone surfaces. In the mastoids, the cells at risk for carcinoma appear to be the epithelial cells in the squamous or cuboidal epithelium of the lining

mucosa. In the paranasal sinuses, where the epithelial structure is more complex, the location and identity of the cell at risk are less certain.

THORIUM

Thorium-232 is a primordial, long-lived, alpha-emitting radionuclide; its decay series can be considered as consisting of two steps: the formation of radium-224 by successive decays from thorium-232 and then the decay of radium-224 and its daughters to stable lead. The alpha-emitters from radium-224 are biologically the most important in the dosimetry concerned with the radioactive properties of the thorium series. Colloidal [^{232}Th]thorium dioxide (Thorotrast) was used widely as a contrast medium in diagnostic radiology from 1928 to 1955. Intravascularly injected Thorotrast aggregates tend to be incorporated into the tissues of the reticuloendothelial system, mainly the liver, the bone marrow, and the lymph nodes. The radioactive daughter products can escape into the bloodstream and thus reach the bone and bone marrow; the important bone-seeking daughter products are radium-224, radium-228, and thorium-228. Aggregates in the liver, bone, and bone marrow are often taken up by macrophages that are mobile, thereby distributing the radiation in relation to the reticuloendothelial, hematopoietic, and endosteal cells. The radiation dosimetry is therefore complex and can be further complicated by the colloidal and elemental chemical and physical characteristics.

Epidemiological surveys of Thorotrast patients are in progress in Germany, Denmark, and Portugal; additional studies are being carried out in Japan and the United States. Approximately 4,000 patients are being followed. A typical injection of 25 ml of Thorotrast would result in an average liver dose rate of 25 rads/yr (0.25 Gy/yr) and an average endosteal bone dose rate of about 16 rads/yr (0.16 Gy/yr). The late effects of Thorotrast incorporated in the body are primarily the induction of liver cancers, bone sarcomas, and myeloproliferative disorders, including leukemias. Liver cancers appear in excess in all epidemiological studies. Hemangioendotheliomas in the liver occur uniquely after Thorotrast is intravascularly administered; it has been described as a Thorotrast-specific liver cancer.

Risk estimates for thorium-232-induced liver cancer, bone cancer, and leukemia have been calculated on the basis of Thorotrast patients who received injections of colloidal [^{232}Th]thorium dioxide

and its progeny. For liver cancer, a lifetime risk is estimated to be about 3×10^{-2} per person-Gy (300 excess liver cancers per million person-rad), where the alpha radiation dose is to the liver. For bone sarcomas, the lifetime risk is estimated to be about $(0.55–1.2) \times 10^{-2}$ excess bone sarcomas per person-Gy (55–120 per million person-rad), where the dose is to the skeleton without bone marrow. For leukemia, a lifetime risk of about $(0.5–0.6) \times 10^{-2}$ per person-Gy (50–60 excess leukemia cases per million person-rad) is estimated. Those estimates are uncertain because of the nonuniform deposition of thorium in the tissues (which results in high local tissue doses), the chemical nature of thorium, the wasted radiation dose in necrotic and fibrotic tissues (particularly in the liver), and the incomplete follow-up in the epidemiological studies.

URANIUM

Natural uranium is of low specific activity and consists mainly of uranium-238 (over 99% by weight) with smaller amounts of uranium-235 and -234. The latter radionuclides have shorter half-lives than uranium-238 and account for about 50% of the radioactivity in natural uranium. Uranium is ubiquitous in rocks and soil and is a trace element in foods, particularly crops or cereals, and in drinking water. Wide geographical differences have been noted. Gastrointestinal absorption from food or water is the principal source of internally deposited uranium in the general population. It is stored mainly in bone, where it has a uniform distribution. Inhalation of aerosols containing uranium is a hazard of industrial exposure, and this uranium might consist of depleted or enriched uranium. The distribution and retention of uranium in the body after inhalation of an aerosol depends critically on the aerodynamic size of the particles and on their solubility in biological fluids. Inhalation of insoluble compounds is associated with uranium retention in lung tissue and hilar lymph glands.

Uranium compounds may induce detrimental health effects due to both chemical toxicity and alpha-radiation damage. Animal experiments have demonstrated a specific toxic effect of uranium on the kidney, but with little evidence of toxic effects on other organs. There are considerable interspecies differences in sensitivity, possibly owing to differences in the acidity of urine. The dog is thought to be the animal model with greatest similarity to humans. Uranium of

high specific activity (uranium-232 and -233) can cause bone sarcomas in mice, and massive doses of uranium oxide have produced lung fibrosis and lung cancer in the primates, dogs, and rodents. This is interpreted as resulting from alpha-particle irradiation of the lung.

Epidemiological surveys of uranium millers and miners occupationally exposed to dusts containing natural uranium at relatively high concentrations have not yielded convincing evidence of serious renal damage nor of increased rates of malignant tumors. Those studies had limited power to detect increased rates of disease, and confounding factors obscured the interpretations. Emphasis has therefore been on animal data concerning renal damage after exposure to uranium and on data on animals and humans exposed to other alpha-emitting elements, such as radium-226.

Observations on animals exposed to high-specific-activity uranium suggest that a small excess of bone sarcomas in human populations could result from naturally occurring uranium, but that the magnitude of the excess depends on which mathematical model is chosen. If the dose-response relationship is quadratic, virtually no effect is expected at environmental natural uranium concentrations. If a linear dose-response relationship is chosen, it has been estimated that ingestion in water or food at an environmental rate of 5 pCi/day could be associated with a lifetime risk of 1.5 bone sarcomas per million persons. That may be contrasted with about 750 naturally occurring bone sarcomas per million persons in the United States. It is concluded, on the basis of present evidence, that the general population risk associated with natural uranium is very low and might be negligible. Higher risks could be associated with higher uranium concentrations in local water supplies.

TRANSURANIC ELEMENTS

Transuranic elements are members of the actinide series beyond uranium; all are artificially produced in nuclear reactors, accelerators, and explosions of nuclear weapons and several include alpha-emitting radioisotopes with very long half-lives. Neptunium, plutonium, americium, and curium are the most abundant and the most extensively used. The transuranic elements are not readily absorbed through the skin or from the gastrointestinal tract. Because of the short range of alpha radiation in tissues, these elements are not of potential health concern unless they enter the body and deposit in tissues through wounds or the respiratory tract. Inhalation

of airborne particles into the respiratory tract and subsequent deposition probably represents the most common pathway by which transuranic elements might enter the body to cause alpha irradiation of human tissues and eventual health effects. Following deposition in the lungs, inhaled aerosol particles are quickly phagocytized by alveolar macrophages, and may be transported from the lungs, depending on solubility; the target tissues include primarily the lungs, liver, bone, bone marrow, and lymph nodes.

Insoluble transuranic compounds, primarily plutonium oxide, are retained in the lungs and thoracic lymph nodes. Other plutonium compounds are more mobile when taken into the body through the respiratory tract or through wounds and deposited primarily in the liver, and bone. Distribution within tissues tends to be diffuse initially, but the compounds often accumulate or form aggregates within cells. Only under conditions of very high deposition would there be more than a few percent of the total cells exposed to alpha radiation. Nevertheless, an association exists between cancers of the lung, bone, and liver and deposition of transuranic elements in these tissues in several animal species under experimental conditions. Inhalation of large amounts of transuranic compounds, e.g., plutonium oxide particles, in experimental rodents and dogs results in radiation pneumonitis, pulmonary fibrosis, and lung cancer. Inhaled plutonium compounds can also cause an increase in the incidence of bone tumors but this has not been observed in experimental animals that inhaled highly insoluble $^{239}PuO_2$ particles. Alpha particles from plutonium are considerably more mutagenic and carcinogenic than are x rays; the experimental animal data in rats and dogs are extensive. In the absence of sufficient human surveys to calculate risk estimates for cancer induction, the animal data, together with data on radium-224 and radium-226 in humans, provide a basis for cancer risk estimation.

Human exposures occur primarily among occupationally exposed workers in nuclear facilities. The United States Transuranium Registry and other studies involving several thousand workers who have been accidentally exposed, predominately to low levels of transuranic elements, have shown that plutonium tends to concentrate in the tracheobronchial lymph nodes, with smaller amounts accumulating in the lungs, liver, and bone. The most extensive epidemiologic study of plutonium workers found that mortality experience for the entire cohort was less than that expected based on U.S. mortality rates.

The only significant excess risk was for benign and unspecified neoplasms. The analysis showed no elevated risks for cancer in tissues with the highest concentrations of plutonium, namely, lung, liver, and bone. The human data and the alpha-radiation dosimetry alone are, at present, inadequate to provide direct calculation of cancer-risk coefficients in the radiosensitive organs and tissues.

Although cancer-risk estimates have been derived from the animal studies, extrapolation of these numerical values to humans introduces uncertainties and technical difficulties. The experimental animal data are quite extensive, and the committee has applied Bayesian components of variance models to 15 data sets for bone sarcoma induction in humans and laboratory animals. The analysis yields, for plutonium deposition in human bone, a lifetime risk estimate of 3×10^{-2} per person-Gy (300 excess bone-cancer deaths per million person-rad) to bone. This is consistent with risk estimates based on data from laboratory animals.

Genetic and Fetal Effects

The genetic disorders that can arise in the progeny of persons exposed to alpha radiation are of the same classes as those arising after exposure to low linear energy transfer (LET) radiation: single-gene autosomal dominant and X-linked disorders, irregularly inherited disorders, recessive disorders, and chromosomal aberrations. Estimates of genetic risk have been made by the BEIR III committee[5] based on the current incidence of hereditary disorders and their estimates of the dose of low-LET radiation required to double the mutational frequency. That information was combined with relative biological effectiveness (RBE) values for alpha irradiation derived from plutonium-239 experiments in mice—specifically, RBEs of 2.5 for mutations and 15 for chromosomal aberrations—to estimate the risk due to internally deposited alpha-particle emitters. Numerical estimates of the incidence of genetic effects over a 150-yr span (five generations) were made for continuous average population gonadal doses of 0.01 Gy (1 rad) per 30 yr reproductive generation, 0.33-mGy alpha dose/yr. For a stable population of about 1 million persons, nearly 200 dominant, X-linked, and translocation genetic effects would accumulate over 150 yr.

Although alpha-emitting radionuclides can be transmitted across the placenta and incorporated in the body of the developing fetus, only the alpha decays that occur during intrauterine life can cause

teratogenesis. The teratogenic effects are closely related to the stage of embryonic development at which the radiation dose is received; preimplantation is the stage of specific teratogenic effects that can occur only during specific, relatively brief periods during intrauterine development. Data on radiation effects on the developing embryo and fetus in humans are sparse, and risk estimates must be based mainly on experimental animal data.

Most of the alpha-emitting radionuclides demonstrate low fetal accretion in laboratory animals, although they vary widely in fetoplacental distribution. Developmental studies on internal alpha-emitters have included radon and its daughters, radium, polonium, uranium, and the transuranic elements. Almost all the teratogenic effects are considered to be due to cell killing. RBE values for cell killing by alpha particles exceed 10, but could be higher for very low dose rates. However, because alpha irradiation is delivered chronically, most of the total dose accumulated during gestation is not effective—only that received during the sensitive interval is effective.

RECOMMENDATIONS FOR FURTHER RESEARCH

RADON

- The committee's model for estimating the lung-cancer risks due to radon exposures is based on the application of multivariate statistical procedures to the data from four major epidemiological surveys of underground miners. Several current underground-miner surveys could provide a more extensive data base with increased person-years of follow-up and help to refine lung-cancer risk coefficients; provide more information on the interaction between smoking and radon exposure; and, with improved dosimetry, narrow the uncertainties in the application of lung-cancer risk data derived from miners to the estimation of risk in the general population. Collecting and reporting smoking data on these miners should be an essential part of the study design.
- The committee recommends continued epidemiological study, with parallel multivariate analysis, of the temporal expression of lung cancer in underground miners exposed to radon progeny.
- The present need to apply lung-cancer risk projections from surveys of underground miners to estimate risk to the general population associated with indoor radon introduces uncertainties and technical difficulties. The domestic environment has not been characterized adequately in terms of the variables affecting the dose and risk related to radon progeny. Variations in indoor radon concentrations, alterations of aerosol characteristics, and impacts of smoking-related risk factors suggest that health consequences of indoor radon exposure require more epidemiological study and basic research. Further studies of dosimetric modeling in the indoor environment and in mines are necessary to determine the comparability of risk per WLM in domestic environments and underground mines.
- The committee recommends continuation of epidemiological studies of lung cancer and other health outcomes resulting from indoor radon exposure; such studies must have sufficient statistical power to quantify any significant differences between the risks in environmental and occupational settings.

POLONIUM

- The committee recommends that studies continue to evaluate the role of polonium from tobacco smoke in the production of lung cancer, including bronchial and lung dosimetry, identification and characterization of target cells, and the role of cofactors and mechanisms of the carcinogenic response.
- The induction of nonstochastic health effects, both acute and long term, particularly in the renal, cardiovascular, and reproductive systems, requires further study.
- The committee recommends that the effects of small exposures to polonium on the pathophysiological response in some organs and tissues deserve continued study in laboratory animals.

RADIUM

- The bone-cancer risk appears to have been completely expressed in the populations exposed to radium-224 in the 1940s and to have been nearly completely expressed in the populations exposed to radium-226 and radium-228 before 1930. Further analysis of these data should involve reevaluation of the dosimetry. More quantitative information is required for the evaluation of the magnitude of the dosimetric uncertainties and their impact on uncertainties of quantitative risk estimation.
- The committee recommends that the bone-cancer risk data from the two studies be integrated and analyzed with newer statistical methods.

- The committee recommends that the follow-up studies of the lower-dose radium-224 patients exposed since the 1940s now in progress in Germany and of similar groups of radium-226 and radium-228 patients continue.
- The discovery of bone cancer or sinus/mastoid cancer after exposure at the lower doses and the additional person-years of follow-up should substantially reduce the uncertainties of risk estimation related to the low doses.
- The committee recommends that research should continue on the identification of the cells at risk of bone-cancer induction; on cell behavior over time, including where the cells are in the radiation field at various stages of their life cycles; on modifying factors, such as the formation of fibrotic layers that might reduce the radiation that the cells receive; and on the time course and distribution of radioactivity in bone.
- The sinus and mastoid carcinomas in persons exposed to radium-226 and radium-228 are produced largely by the action of radon-222 and its daughters; continued study might offer insights into the effects of occupational and environmental radon. The dosimetry of the mastoid air cell system is much simpler than that of the bronchial tree; the mastoid mucosa might be the only respiratory tissues whose epithelial structure is simple enough to permit accurate dose estimation.
- The committee recommends that the dosimetry of the mastoids should be examined as completely as possible, so that the risk per unit of epithelial tissue dose and per unit of cell dose can be determined accurately; this might improve the understanding and estimation of the carcinogenic risk in the epithelium of the lower respiratory tract.

THORIUM

- The carcinogenic risk estimates related to thorium-232 depend primarily on studies of patients who received Thorotrast. These studies are incomplete, and except for those of the German patients, they have little statistical power to establish with precision the types of diseases produced, their influence on carcinogenic risks at low doses, the effects of dose and dose rate, and the chemical effects of the colloidal heavy metal, particularly in the liver.
- The committee recommends that the data be obtained from all five principal epidemiological studies of Thorotrast-exposed patients, to develop risk models for liver and other cancers from original multivariate analyses.

- The dosimetry of Thorotrast and thorium radionuclides in target organs is poorly understood. The radiation effects depend on the physical properties of the emitted radiation and on the physical and chemical characteristics of the radionuclide and its aggregation, movement, and deposition.
- The committee recommends further study of the dosimetry of thorium radioisotopes at the cellular level in the target organs or tissues; these processes are central to an understanding of the biological effects, notably in liver and bone.

URANIUM

- The committee recommends that experimental studies of the nephrotoxic effects of uranium should be continued to determine the threshold concentration of uranium that is associated with substantial renal tubular damage and the animal and metabolic models most appropriate for predicting human effects.
- The committee recommends that cross-sectional and longitudinal epidemiological investigations of occupational exposure to natural uranium be vigorously pursued.
- Assessment of renal function and other health outcomes should be examined and correlated with environmental measurements designed specifically to estimate individual exposures. Studies of mortality and morbidity might be warranted if stable populations of sufficient size can be identified in areas with high concentrations of uranium in drinking water or food.
- The committee recommends that the mechanism of uranium deposition and redistribution in bone should be further investigated, so that the potential carcinogenic effect of natural uranium can be more reliably predicted from the results obtained with enriched uranium or with other alpha-emitters, such as radium-226 and radium-228 decay chains.

TRANSURANIC ELEMENTS

- While no health effects have been associated with such human exposures, the results of experimental animal studies suggest that effects may eventually be observed in the highest-exposed worker populations. Such studies should emphasize the importance of thorough

postmortem examinations of deceased persons whose deaths may be related to transuranic element exposures to confirm the cause of death and the possible presence of other lesions and to obtain tissue samples for radiochemical analysis and cellular-molecular biological studies.

- The committee recommends the continuation of current epidemiological studies of worker populations exposed to transuranic elements.
- Analysis of data from life span experimental animal studies using an epidemiological approach will ensure maximum use of this invaluable large data base for extrapolating the results of animal studies to humans. This should have a high priority because it is unlikely that these expensive life-span studies, particularly the dog experiments, will be repeated.
- The committee recommends that current life-span studies with dogs be completed and reported in a manner that will ensure that the maximum information is obtained.
- It is important to expand the effort to correlate the available human and experimental animal data on the deposition, translocation, metabolism, clearance, and excretion of transuranic elements. Considerably more work is required with respect to biokinetics and to the development of models that can be applied to the practice of radiation protection, including bioassay procedures and assessment of exposures. Additional research is needed to correlate the gross and microscopic distribution of transuranic elements within tissues and the site of tumor formation to ensure relevant dosimetry.
- The application of the powerful new tools of modern biology to multilevel studies (molecular, cellular, tissue, organ, animal, and human) will lead to improved understanding of the interactions of alpha radiation with biological targets from transuranic elements deposited in various tissues. Such studies have the potential for detecting potential harmful biological effects at low radiation doses, identifying persons of special risk to radiation injury, determining whether certain diseases are attributable to transuranic exposures, and directing therapeutic measures to sites of injury.
- The committee recommends that the Bayesian methods for interspecies extrapolation be developed further and applied to the determination of other risk factors in humans.

GENETIC EFFECTS

- The committee recommends that investigations continue on the retention and cellular distribution of the alpha-emitting radionuclides in appropriate chemical forms in the ovaries and testes of selected primates suitable as surrogates for humans.

REFERENCES

1. International Commission on Radiological Protection (ICRP). 1979. Limits of Intake of Radionuclides by Workers. ICRP Publication 30. Oxford: Pergamon.
2. Mays, C. W., G. N. Taylor, and R. D. Lloyd. 1986. Toxicity ratios: Their use and abuse in predicting the risk from induced cancer. Pp. 299–310 in Life Span Radiation Studies in Animals: What Can They Tell Us?, R. C. Thompson and J. A. Mahaffey, eds. CONF-830951. Springfield, Va.: National Technical Information Service.
3. National Council on Radiation Protection and Measurements (NCRP). 1984. Evaluation of Occupational and Environmental Exposures to Radon and Radon Daughters in the United States. NCRP Report 78. Bethesda, Md.: National Council on Radiation Protection and Measurements.
4. National Council on Radiation Protection and Measurements (NCRP). Exposures of the Population in the United States to Ionizing Radiation. NCRP draft report. Bethesda, Md.: National Council on Radiation Protection and Measurements.
5. National Research Council, Committee on the Biological Effects of Ionizing Radiation (BEIR). 1980. The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. Washington D.C.: National Academy Press. 524 pp.
6. Rowland, R. E., A. F. Stehney, and H. F. Lucas. 1983. Dose-response relationships for radium-induced bone sarcomas. Health Phys. 44(Suppl. 1):15–31.
7. United Nations Scientific committee on the Effects of Atomic Radiation (UNSCEAR). 1977. Sources and Effects of Ionizing Radiation. Report E.77.IX.1. New York: United Nations. 725 pp.
8. U.S. Environmental Protection Agency. 1986. Radon Reduction Methods: A Homeowner's Guide. OPA-86-005. Washington D.C.: U.S. Environmental Protection Agency.
9. U.S. Environmental Protection Agency and U.S. Department of Health and Human Services. 1986. A Citizens Guide to Radon. OPA-86-004. Washington, D.C: .U.S. Government Printing Office.
10. van Kaick, G., H. Muth, A. Kaul, H. Wesch, H. Immich, D. Liebermann, D. Lorenz, W. J. Lorenz, H. Luhrs, K. E. Scheer, G. Wagner, and K. Wegener. 1986. Report on the German Thorotrast study. Strahlentherapie (80 Suppl.):114–118.
11. Wick, R. R., D. Chmelevsky, and W. Gössner. 1986. ^{224}Ra: Risk to bone and haematopoietic tissue in ankylosing spondylitis patients. Strahlentherapie (80 Suppl.):38–44.