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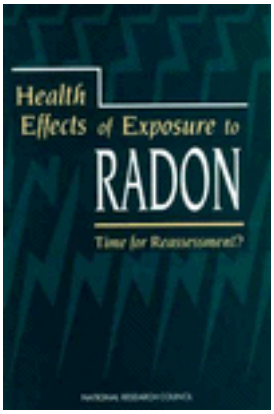

Health Effects of Exposure to Radon: Time for Reassessment?

Committee on Health Effects of Exposure to Radon (BEIR VI), National Research Council

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Time for Reassessment?

Committee on Health Effects of Exposure to Radon (BEIRVI)
Board on Radiation Effects Research
Commission on Life Sciences
National Research Council

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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Preface

The National Research Council Committee on Health Risks of Exposure to Radon (BEIR VI), in the Board on Radiation Effects Research (BRER) of the Commission on Life Sciences (CLS), was formed in August 1992 in response to a request from the Environmental Protection Agency (EPA) that a Research Council committee consider recently published data and soon-to-be-completed studies concerning the risk associated with human exposure to radon. The BEIR series of reports focuses on biological effects of ionizing radiation. The Research Council report *Health Risks of Radon and Other Internally Deposited Alpha-Emitters: BEIR IV* published in 1988, had reviewed the health effects of radon and offered a risk model based on data from four studies of underground miners. Using data from a few studies, it estimated the combined effects of radon and cigarette-smoking on the production of lung cancer. The Research Council report *Comparative Dosimetry of Radon in Mines and Homes,* issued in 1991, provided more complete coverage of radon dosimetry than had been accomplished by the BEIR IV committee. EPA has placed a high priority on a re-evaluation of

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risks to ensure that new data, including data on exposures in homes and schools, can be expeditiously incorporated into risk evaluations. New information on the relationship between radon exposure and cigarette-smoking also needs to be considered, as well as the potential effect of arsenic in mines.

The Research Council established a committee of four members with expertise in radiation biology, radiation physics and dosimetry, epidemiology and biostatistics, and pulmonary medicine. General guidance was provided by BRER. EPA had asked for assistance in two phases. In Phase I, the committee was to collect and evaluate data as studies were completed and to determine whether sufficient data had become available since the publication of BEIR IV and *Comparative Dosimetry of Radon in Mines and Homes* to warrant a full-scale analysis (Phase II). The present report is a summary of the committee's findings in Phase I, including a recommendation regarding the feasibility and likely contributions of a Phase II study.

The committee members were asked specifically to do the following:

- Familiarize themselves with studies completed since the evaluations of data by committees of BRER in 1988 and 1991.
- Inform themselves of the nature and purpose of current studies of underground miners and the general population in the United States and abroad.
- Identify differences and similarities in results among studies analyzed previously and those recently published.
- Identify issues in need of analysis in a full-scale study.
- Establish liaison with international groups that coordinate various radon studies.
- Assess the evaluations of data performed by the international coordinating groups to determine whether these are sufficiently

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definitive to obviate further evaluation by a Research Council group.

- Advise EPA on whether the accumulation of data from current investigations from throughout the world makes it feasible and advisable to perform detailed re-analyses of two critical issues during a second phase of study. The two issues are models of carcinogenesis associated with combined exposure to radon and cigarette-smoking and comparisons of exposure to radon in mines and in homes.
- If Phase II is feasible and advisable, plan the organization and approach for the full-scale committee and study.
- Prepare a report summarizing the committee's findings during the first phase and recording its recommendations for work, if any is feasible and desirable, in the second phase.

The committee completed all the above tasks. It held five meetings-two in Washington, D.C., one in Albuquerque, and two in Denver-and engaged in conference calls. Two of the meetings were workshops during which outside experts were invited to comment on current scientific knowledge and to present the results of their research. The first workshop focused on radon dosimetry and included sessions devoted to respiratory tract models, aerosols, deposition and clearance, dosimetry, cell proliferation, and cells at risk. The second focused on molecular and cellular radiobiology and included sessions devoted to radiation dose and dose rate, interactions between chemicals and radiation, molecular and cellular signatures of exposure, and biologic models. The committee also received status reports from the principal investigators zof current case-control epidemiologic studies addressing the effects of radon in homes.

This report is organized according to the major elements of the

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committee's analysis. After an executive summary containing recommendations, an introduction (Chapter 1) provides the background of the committee's activities and an overview of the radon problem. The three major elements follow as chapters titled "Radiation Biology and Carcinogenesis," "Exposure-Dose Relations," and "Epidemiologic Investigations." Each of those chapters summarizes the information that has emerged since BEIR IV and its companion report on comparative dosimetry, reviews current studies, projects what information is likely to become available during the next 2 years for a Phase II committee working on a BEIR VI report, and concludes with recommendations as to what a Phase II committee should be able to do with this information; they substantiate the committee's recommendation regarding the feasibility of a Phase II study and a BEIR VI report.

The committee acknowledges with thanks the scientific input provided by invited participants who gave freely of their data and findings and were of great help in clarifying some of the scientific issues under study. The committee is especially grateful to Marshall Anderson, William Bair, William Bennett, Bruce Boecker, John Boice, David Brenner, Antone Brooks, Yung Sun Cheng, Fred Cross, Greg Finch, William Griffith, Frank Guilliland, Raymond Guilmette, Thomas Hei, Philip Hopke, Anthony James, David James, Neil Johnson, John Lechner, Jay Lubin, Suresh Moolgavkar, David Swift, Margaret Terzaghi-Howe, and Hsu-Chi Yeh. Michael Alavanja, Sarah Darby, L. Kreienbrock, J. Lyon, Richard McGregor, William Nicholson, Goran Pershagen, Dale Sandler, Janet Schoenberg, Heather Stockwell, Jan Stolwijk, Margot Tirmarche, and H.-Erich Wichmann are thanked for contributing information on their case-control studies in progress.

We also thank Susan Conrath, Neal Nelson, Jerome Puskin, and Anita Schmidt of EPA and Marvin Frazier, Curtis Olsen, and Susan

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Rose of the Department of Energy for information on their radon programs.

Finally, the committee thanks Doris E. Taylor, Maurita DowMassey, and Edward Patte for their assistance with administrative details and in preparing drafts of this report.

Jonathan M. Samet, Chairman

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Executive Summary

The Environmental Protection Agency (EPA) Office of Radiation Programs (now the Office of Radiation and Indoor Air) asked the National Research Council to consider recently published data on the risks associated with human exposure to radon. EPA has given high priority to re-evaluation of risks to ensure that new data, including data on exposure in homes and schools, can be expeditiously incorporated into risk evaluation. This report was prepared by the Committee on Health Risks of Exposure to Radon: BEIR VI in the Board on Radiation Effects Research (BRER) of the Research Council's Commission on Life Sciences, which was charged, in Phase I, with gathering evidence that had accumulated on radon and lung cancer since two prior reviews by BRER committees and determining whether the new information justified a comprehensive study which would constitute Phase II.

In the committee's judgment, information that has become available since publication of the 1988 *Health Risks of Radon and Other Internally Deposited Alpha-Emitters: BEIR IV* and the

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1991 *Comparative Dosimetry of Radon in Mines and Homes* makes it desirable and feasible to proceed with Phase II-a comprehensive reanalysis of health risks associated with radon. *The committee based this judgment on*

- The completion of a joint analysis by Jay Lubin and his colleagues at the National Cancer Institute of data from 11 cohorts of underground miners (including 68,000 miners who experienced over 2,780 lung cancer cases in comparison with the 22,190 miners who experienced 360 lung cancer deaths in the four cohort studies of BEIR IV) that offers a new risk model and strengthens the basis for quantifying indoor (residential) radon as a public-health problem.
- New experimental and epidemiologic evidence of an effect of exposure rate on α -particle carcinogenesis, such as from the laboratories of Richard Miller, David Brenner, Eric Hall, Helen Evans, and Mortimer Elkind.
- Reports of several completed studies, including the recent report of a large study in Sweden by Goran Pershagen and colleagues and the projected completion and publication of additional case-control studies of residential exposure and lung cancer in Europe and the United States during the next 2 years.
- New evidence from the study of miners that the interaction of smoking and radon might be less than multiplicative.
- Further information relevant to the dosimetry of radon in mines and homes. This information emerges from new instrumentation for field measurements of the concentration and activity-size distributions of radon progeny developed in the laboratory of Philip Hopke and the application of noninvasive methods for monitoring ventilation in the field by Jonathan Samet and others.
- New evidence of the potential importance of other factors in

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mine atmospheres, such as the presence of arsenic in Chinese tin mines and silica in underground uranium mines.

The committee concluded that new evidence could lead to the development of a risk model for radon and lung cancer that would be substantially different from that developed by the BEIR IV committee. An opportunity now exists for the development of multidisciplinary models of radon carcinogenesis that incorporate new concepts from cellular and molecular studies. Evaluation of new information concerning the molecular changes occurring in radon-induced cancer and the correlation of these changes to the nature of radon-induced chromosomal aberrations, mutations, and DNA lesions should be informative as to the mechanisms involved in the induction of lung cancer and should be useful in the development of a risk model. Further key uncertainties in the previous estimates and models might be reduced and should be considered formally in a Phase II study. The finding of an inverse dose-rate effect in the miner data establishes a need for extrapolating this effect to lower dose rates. The committee recognizes that much epidemiologic and experimental work is going on and that not all of it is likely to be completed during the time frame for Phase II. Nevertheless, the findings since the earlier BRER-committee reports and those to come soon are sufficient to warrant evaluation and synthesis.

With respect to radiation biology and carcinogenesis, the committee recommends that a Phase II study

- Evaluate experimental evidence on inverse dose-rate relations and the implications of this evidence for domestic radon risks.
- Attempt to correlate risks of radon-induced lung tumors with

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those of tumors induced by external exposures to low-LET radiations.
- Examine in more detail the induction and repair of molecular changes after exposure to α particles.

With respect to exposure-dose relations, a Phase II study could

- Gain access to additional information that is relevant to radon dosimetry from the use of noninvasive methods for monitoring ventilation and from an improved model.
- Use activity-weighted size-distribution data that have become available on residences.
- Use the recent data on growth of particles from various sources typically found in homes.
- Use biologic dosimetry to reduce the uncertainties associated with the exposure-dose relationship and apply the reduced uncertainties in various aspects of lung dosimetry to risk calculations.

With respect to studies of miners, a Phase II study could

- Critique the recently completed pooled analyses of 11 cohorts and whatever new risk models emerge from them and use the database to suggest additional analyses.
- Model the pooled data with emphasis placed on biologically driven modeling.
- Formally evaluate sources of exposure error in the miner cohorts and the consequences of these errors for risk estimation and risk assessment.

With respect to studies of lung cancer in the general population, a Phase II study could

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- Evaluate and interpret the results of completed case-control and ecologic studies, including evaluation of their limitations and uncertainties.
- Determine the appropriate role of case-control studies in developing a risk model of residential exposure to radon.
- Make general recommendations regarding the potential role of case-control studies that are not yet complete.
- Estimate the statistical power for various end points of the completed studies as a group and identify the expected upper and lower confidence limits according to the assumptions of both the recommended model and alternative models.
- Estimate the potential of the completed studies for providing information on the modifying effects of smoking and other factors, taking into account uncertainties in exposure estimates.
- Make recommendations on the desirability of initiating new case-control or ecologic studies of residential radon exposure.

The previously cited Phase II committee tasks include assignments that were included in the original project, as well as new tasks identified by the committee. *The committee also modified some of the original projected charges and now recommends that, with respect to data from studies of miners, a Phase II study*

- Assess the validity and scientific reliability of analytic approaches used by various investigators.
- Examine in detail the interaction between radon exposure and cigarette-smoking on the basis of data on U.S. and other miners.
- Re-examine the effect of the rate of exposure to radon on the incidence of lung cancer.
- Critically examine exposure estimates for miner cohorts and reassess the consequences of the exposure rates.

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- Propose, in light of the Phase I findings, a mathematical model of risk based on more complete and up-to-date U.S. and international miner data.
- Assess the role of arsenic, silica, and other contaminants in mines on the consequences of exposure.
- Examine the uncertainties associated with the miner studies.

With respect to the analysis of data from studies of residential exposure, the committee modified certain proposed tasks so that a Phase II study could also

- Critically review studies and comment on their strengths and weaknesses and their current and future roles in risk assessment.
- If EPA and BRER have agreed that it is feasible, update the assumptions and estimates in the Research Council report that compared miner and home dosimetry, focusing on recent data on such physical and biological factors as aerosol size distribution, ultrafine fraction, equilibrium fraction, and hygroscopicity and deposition of radon daughters in the respiratory tract.
- If EPA and BRER have agreed that it is feasible, examine models of carcinogenesis resulting from the combined effects of radon exposure and cigarette-smoking.
- Test and possibly revise models in light of available residential data.
- Consider the contribution of radon-220 to risk in mines and homes.
- Examine the effects of age, sex, and smoking on radon-associated risk.
- Incorporate concepts from cellular and molecular biology into models for risk assessment.

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The committee is concerned that the original time of 24 months for a Phase II study is too short to complete all tasks suggested here. It recommends that the Phase II study be extended by 10 months for a total of 34 months to end December 31, 1996. This recommendation is not driven by the expectation that additional epidemiologic studies in homes will be completed, but rather by the belief that it would take more time to identify and obtain data and complete the analysis required.

Finally, the present committee recommends that a Phase II committee include at least 12 members. The expertise that should be represented includes radiation biology, biophysics, aerosol science, cellular and molecular biology, epidemiology, biostatistics, carcinogenesis, lung pathology, risk assessment (including uncertainty analysis), and animal studies.

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1 Introduction

Radon (specifically radon-222), a well-documented cause of lung cancer in underground miners, is a contaminant of indoor environments, including homes and schools. This odorless and invisible gas is a naturally occurring decay product of radium-226, the fifth decay product of uranium-238. Uranium-238 and radium-226 are constituents of most soils and rocks, so radon is found in the gas present in soils. It is also released from water in which it has dissolved and from building materials. Radon decays with a half-life of 3.82 days into a series of solid, short-lived radioisotopes that are collectively referred to as radon progeny (formerly radon daughters) or radon decay products. Two of the progeny, polonium-218 and polonium-214, emit particles during decay. When these emissions take place in the lung as inhaled and deposited progeny undergo decay, the cells lining the airways can be damaged in such a way that lung cancer can eventually occur.

Radon has long been known to cause lung cancer (for a review, see National Research Council, 1988). More than 100 years ago, miners of metal ores in Schneeberg, Germany, were found to

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develop intrathoracic malignancy, which was shown to be primary cancer of the lung. Early in the twentieth century, high concentrations of radon were measured in the Schneeberg mines and in the nearby mines of Joachimsthal, where underground miners also developed lung cancer. Radon was considered to be a possible cause of the lung cancer, and this was confirmed through epidemiologic studies of miners of uranium and other ores (for a review, see National Research Council, 1988; Samet, 1989).

Many populations of underground miners exposed to radon and its progeny have been shown to be at increased risk of lung cancer. Except at the highest levels of exposure, the lung-cancer risk in these miners is related roughly linearly to exposure. The information available from miners on the combined effect of cigarette smoking and exposure to radon progeny is consistent with synergism between the two carcinogens. Exposure of animals to radon has provided confirming evidence of carcinogenicity, and laboratory systems have been used to understand mechanisms of genetic injury by α particles. The newer techniques of molecular and cellular biology are now being applied to α -particle carcinogenesis; the initial findings indicate the potential for these techniques to improve understanding.

Research over the last 20 years has shown that radon is a ubiquitous indoor air pollutant, reaching concentrations in some residences as high as were found in mines where excess lung cancers occurred in underground workers. The predominant source of radon in indoor air in homes is the soil beneath the structures, but building materials, water used in the homes, and utility natural gas can also contribute. Radon concentrations are readily measured with passive devices, and early data showed that the distribution of concentrations was approximately lognormal with a mean of about 1.5 picocuries per liter (pCi/L) (Nero et al., 1986). Data gathered from over 4,000 U.S. homes in 1989-1990 showed that the average

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concentration is 1.3 pCi/L (U.S. Environmental Protection Agency, 1992). However, the distribution is skewed with a tail extending well beyond the average; some homes have concentrations of hundreds or even thousands of picocuries per liter. Although detailed data are available on samples of homes, far fewer measurements have been made in other locations where people spend time.

Since the recognition that a carcinogen contaminates indoor air particularly in homes where most time is spent-risk assessment has been used to estimate the extent of the hazard as a basis for risk management. Given a lack of direct evidence from epidemiologic studies on indoor radon and lung cancer, risk models for exposures received by the general population (U.S. Environmental Protection Agency, 1992) have been based on extrapolation from higher exposures in studies of underground miners. Extending the findings in the underground miners to the general population entailed various assumptions each with its own uncertainties. Some of these assumptions are:

- The risks observed at occupational exposure levels and dose rates can be extended to typically lower indoor exposure levels and dose rates.
- The modifying effects of smoking on the risk associated with exposure to radon progeny are similar in miners and the general public.
- The risk of lung cancer in radon-exposed miners is not substantially modified by effects of other agents, e.g., dust.
- The risks observed in adult male miners can be extended to females and to children.
- Either exposure-dose relationships are comparable in miners and the general population or, if there are differences, the differences can be estimated.

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In spite of the uncertainties inherent in risk assessments based on the miner data, indoor radon has been identified as an important public-health problem, estimated by EPA to cause between 7,000 and 30,000 lung-cancer deaths a year (U.S. Environmental Protection Agency, 1992). The lung-cancer risk associated with indoor radon can be estimated from epidemiologic studies that directly assess the risk in exposed populations. When the possible risks of exposure to indoor radon were first recognized, several descriptive or "ecologic" studies (the use of groups-most often defined geographically-rather than individuals as the unit of analysis) were performed; lung-cancer incidence or mortality rates in geographic areas were compared with indexes of radon exposure for inhabitants of these units. However, the evidence from those studies has been inconsistent, and methodologic limitations seriously limit the value of the ecologic design for characterizing the lung-cancer risk associated with indoor radon (Stidley and Samet, 1993).

The case-control design is a more appropriate epidemiologic approach for addressing indoor radon. Most of the many reported case-control studies have had small numbers of subjects or low exposure estimates. Several larger studies are now in progress in the United States and other countries (Samet et al., 1991b). In these studies, past exposures to radon are estimated from present concentrations in current and previous residences of lung-cancer patients and appropriate controls; with information collected on cigarette-smoking and other risk factors, the risk of indoor radon can be assessed and the effects of smoking and other factors can be controlled for. The findings of these studies are limited by uncertainties in the estimation of past exposures and by other methodologic problems (Lubin et al., 1990).

Regardless of the limitations of the data available, risk assessments based on the studies of miners suggest a need for concern

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regarding a positive association between the level of indoor radon and the occurrence of lung cancer; therefore, indoor radon should be considered a potential public-health problem. The scope of the exposed population and the large number of lung-cancer cases attributed to radon have provided a strong impetus for population and laboratory-based research designed to provide a more complete understanding of radon carcinogenesis and more accurate risk assessments.

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2 Radiation Biology and Carcinogenesis

INTRODUCTION

The biologic effects of α particles are at the core of our understanding of radon-induced lung cancer and risk models should appropriately reflect this understanding. Risk estimates for lung cancer related to radon in homes can be derived by at least two quite different approaches. In the so-called *epidemiologic* approach, lung-cancer data on underground miners are extrapolated from the high radon concentrations characteristic of mines to the much lower concentrations in homes. Differences in doses and dose rates can be addressed in laboratory experiments in radiobiology. Still, the data available for this purpose are limited and risk estimates are subject to major uncertainties.

In the *dosimetric* approach, doses to the bronchial epithelium are estimated, and the long-term risks of lung cancer in Japanese atomic-bomb survivors are used to estimate lung-cancer risks from radon exposure. Two scaling factors are required:

- A dose-rate correction, because the Japanese received a single

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acute exposure, whereas radon exposure in homes occurs at low dose rates.

- A factor that represents the change in the nature of the radiation, because the Japanese were exposed largely to sparsely ionizing gamma (γ) rays, whereas radon progeny emit densely ionizing α particles.

The dosimetric approach also is subject to major uncertainties, and neither approach is a priori better.

This section on the radiation biology of α particles summarizes basic concepts in the field, focusing on how radiation biology can contribute to the assessment of radon risks, namely by using doserate corrections and the radiation quality factor for radon-progeny α particles. It also presents selected examples where recent information on mechanisms, oncogenes and tumor-suppressor genes, and possible biologic markers of α-particle exposures will be reviewed in depth in a Phase II study.

RANGE AND TRACK STRUCTURE OF PARTICLES EMITTED BY RADON PROGENY

The decay series for radon involves the emission of two principal α particles with energies of 6 and 7.7 MeV. The passage of α particles through tissue produces essentially linear tracks that are dense columns of ionizations, which give rise to the locally high radiation dose deposited. The ranges of the two principal α particles in tissue are 48 and 71 μm. There is some debate over which respiratory epithelial cells are affected in the radiation induction of lung cancer by radon, but it is generally agreed that the target cells (whether basal or serous) are within the range of α particles depos

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ited on the surface of the bronchial epithelium, as illustrated in Figure 1. These target cells are likely to be close to the end of the α-particle tracks where the density of ionization from the radiation along the tracks is high but changing rapidly (i.e., the radiation has a rapidly changing linear energy transfer, or LET). Figure 2 shows how dose decreases as lineal energy (y_D), a quantity similar to LET, increases along the track of an a particle until near the end of its range, when y_D declines sharply.

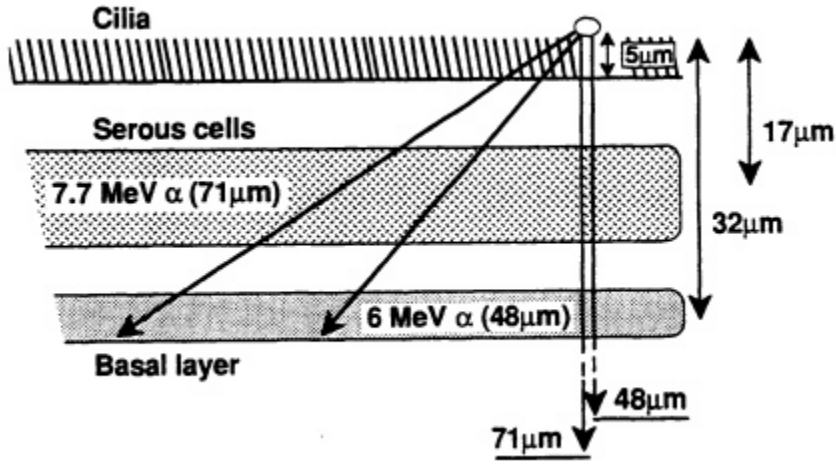

FIGURE 1. Ranges of two α particles emitted by radon progeny deposited on lung surface and average depths of serous and basal cells in human lung, according to study of several hundred "normal" lung sections from Pathology Department at Columbia Presbyterian Medical Center. (Based on data collected by Charles Geard and David Brenner; reproduced from Hall, 1992, with permission of the publisher.)

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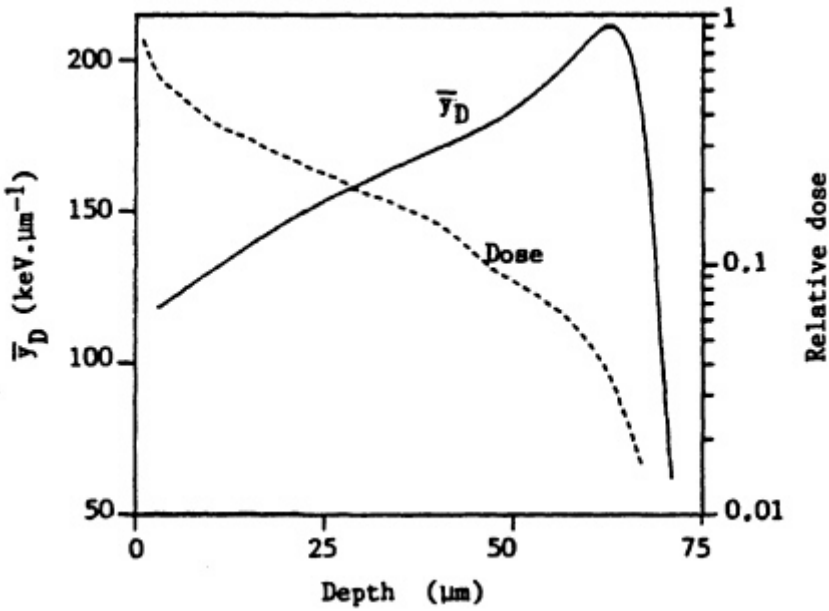

FIGURE 2. Change in dose and dose-averaged lineal energy y_D (1-μm site size) with depth for α particles simulating those emitted by radon progeny. (Reproduced from Brenner, 1990, with permission of the publisher.)

RADIATION BIOLOGY OF -PARTICLE IRRADIATION

When tissues are exposed to α particles, cells can be killed or sterilized, suffer mutations, or be transformed to a malignant state. Cellular models using these end points can address subjects-such as the slope of the dose-response relationship, the effects of dose

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rate, and the effects of radiation quality-that would be more difficult to address through animal experiments and impractical through human epidemiologic studies.

Cell Lethaity

A wide variety of rodent and human cell types have been irradiated with α particles, and cell-survival curves have been generated (Barendsen et al., 1960; Thacker et al., 1982; Robertson et al., 1983; Hei et al., 1988b, 1993; Tsuboi et al., 1992). In all cases, as the dose increases, the fraction of cells surviving decreases approximately as an exponential function of dose. Figure 3 shows survival of mouse C3H10T1/2 cells irradiated in vitro. The shape of the survival curves implies single-hit kinetics-i.e., the cell is killed by a single α particle- but at the mean lethal dose, the mean number of particles traversing the nucleus is often more than 1 and is reportedly as high as 13 (Lloyd et al., 1979). It is generally agreed that the high relative biologic effectiveness (RBE) of α particles, compared with x rays or gamma rays, in killing cells is due to the α particles' ability to induce irreparable DNA damage, inasmuch as these densely ionizing particles deposit a large amount of energy and efficiently induce localized multiple lesions (Ward, 1985; Goodhead, 1989).

Mutations in Cultured Cells

The mutagenic potential of α particles with energies similar to those characteristic of radon progeny has been measured at several

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geneti loci in a variety of human and rodent cell systems (Cox et al., 1977; Cox and Masson, 1979; Thacker, 1986; Hei et al.,1988c, 1994; Evans, 1991; Tsuboi et al., 1992; Jostes et al., 1994). In general, the mutagenicity of α particles depends on both dose and LET. Figure 4 shows mutation induction at the HGPRT locus. As

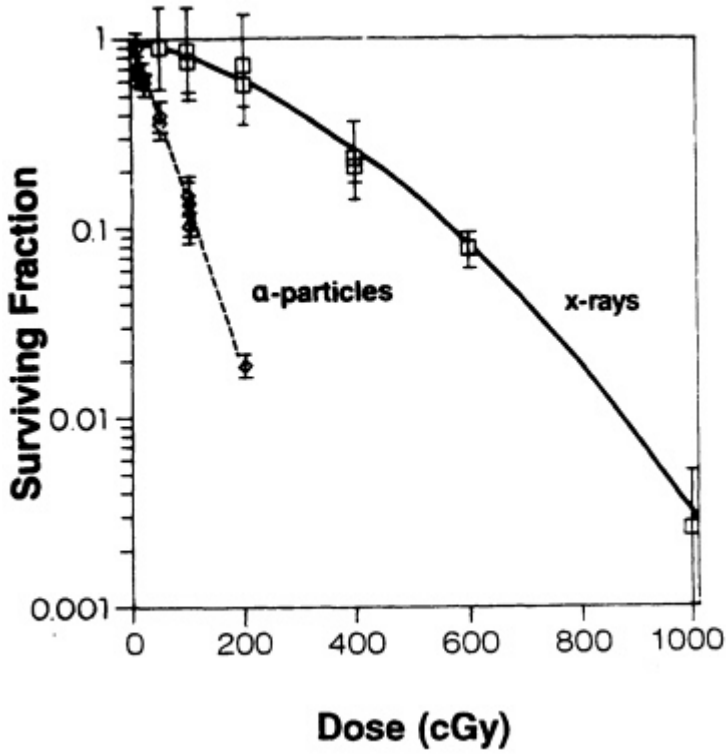

FIGURE 3. Survival of C3H10T1/2 cells irradiated with either x rays or α particles. (Reproduced from Hall and Hei, 1985, with permission of the publisher.)

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shown in Figure 5, the RBE for mutation reaches a peak at an LET of about 100-200 keV/μm, similar to that for cell lethality, and the RBE at a given LET appears to be larger for mutational end points than for cell killing (Cox and Masson, 1979).

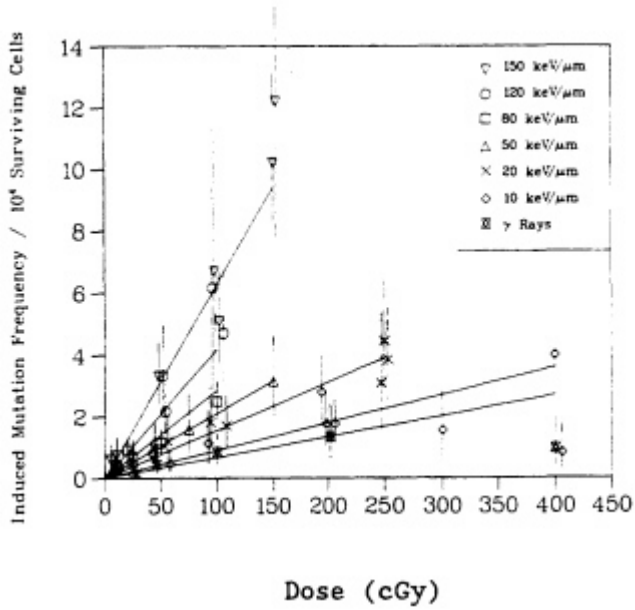

FIGURE 4. Mutation induction at HGPRT locus in primary human fibroblasts irradiated with gamma rays and charged particles of various LET. Mutations were expressed as number of mutants per 10,000 survivors. Data were analyzed according to linear quadratic response, and curves represent best fit to data by method of maximum likelihood. Bars represent 95 % confidence intervals. (Reproduced from Hei et al., 1988a, with permission of the publisher.)

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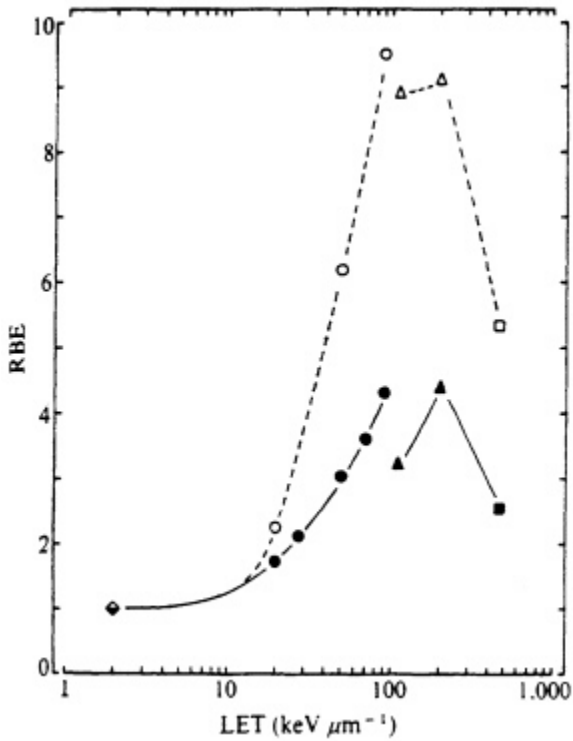

FIGURE 5. RBE-LET relationships for Chinese hamster V79 cells. Standard radiation was cobalt-60 γ rays, which was compared with helium, boron, and nitrogen ions (represented by circles, triangles, and squares respectively). Closed symbols represent cell lethality; open symbols, mutation at HGPRT locus. (Reproduced from Cox and Masson, 1979, with permission of the publishers.)

Oncogenic Transformation In Vitro

Radiation has been used as both an initiator and a complete

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carcinogen in rodent-cell models. In particular, a single exposure to either high- or low-LET radiation has been used successfully to transform a variety of rodent cells in culture (Borek and Hall, 1973; Miller and Hall, 1978; Elkind and Han, 1979; Lloyd et al., 1979; Balcer-Kubiczek and Harrison, 1983; Robertson et al., 1983; Watanabe et al., 1984: Hall and Hei, 1985, 1990; Yang et al., 1985; Hei et al., 1988a). Transformation induction by α particles depends on both dose and LET (Yang et al., 1985, 1989; Hei et al., 1988a; Miller et al., 1993). A very large set of data has been generated by Miller and colleagues (Miller, personal communication) and is illustrated in Figure 6. The transformation incidence induced by α particles can be modulated by various chemical and environmental agents, such as cigarette smoke, asbestos fibers, and 12-o-tetradecanoylphorbol-13-acetate (TPA) (Kennedy and Little, 1980; Han and Elkind, 1982; Hall et al., 1989; Piao and Hei, 1993). For example, Figure 7 shows that TPA substantially enhances the incidence of transformation resulting from low- or high-LET radiation. The α-particle-induced damage that results in oncogenic transformation is apparently not subject to repair during post exposure incubation of cells (Robertson et al., 1983).

In contrast with rodent cells, which are readily transformable by α particles, human cells in culture are refractory to malignant transformation by either radiation or chemicals. Also, unlike rodent cells, normal human cells in culture rarely undergo spontaneous transformation (Harris, 1987; Rhim, 1992). Most transformation studies with cells of human origin have involved either a retrovirus or a chemical carcinogen as the transforming agent (for review, see Rhim and Dritschilo, 1991). Of the few transformation studies involving ionizing radiation, essentially all used multiple high doses either to immortalize the cells (Namba et al., 1986) or to transform

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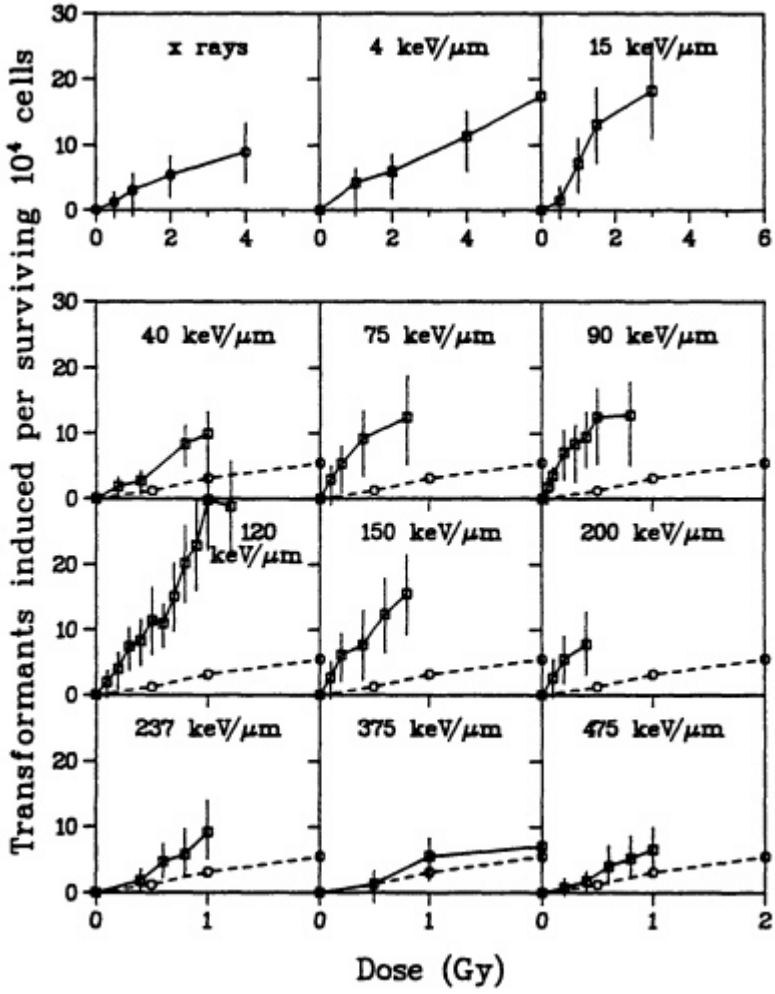

FIGURE 6. Transformation data for C3H10T1/2 cells as a function of dose for x rays (open circles) and charged particles of various LET (open squares). (Unpublished data from R.C. Miller printed with permission.)

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the already immortalized cells after SV40 treatment (Thraves et al., 1990; Yang et al., 1991). Hei and colleagues (Hei et al., 1994) recently used human papillomavirus-immortalized human bronchial

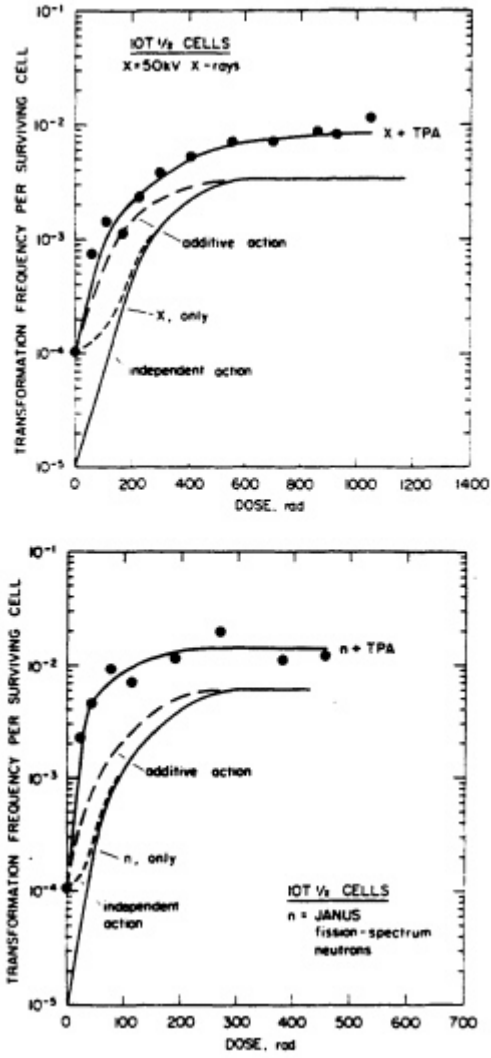

FIGURE 7. Transformation in C3H10T1/2 cells as a function of dose (neutrons and x rays) and TPA. (Reproduced from Han and Elkind, 1982, with permission of the publisher.)

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epithelial cells and showed for the first time that a single 30-cGy dose of α particles can transform these cells.

Preliminary transformation data have also been reported on SV40-immortalized human keratinocytes irradiated with 10 cGy of α particles (Martin et al., 1994) or fission neutrons (Thraves et al., 1993). No dose-response data on the transformation of cells of human origin are available.

Comparison of Effects In Vivo and In Vitro

An important step in the dosimetric approach to risk assessment is to convert exposure to radon progeny in working-level months (WLM) to absorbed dose in the bronchial epithelium. Production of micronuclei in "in vivo" and "in vitro" exposure studies has been used as an index of the relationship between exposure and dose.

In a recent study reported by Khan et al. (in press), male rats were exposed to various numbers of WLM from radon progeny by inhalation. After sacrifice, the cells (deep-lung fibroblasts) were grown in culture and the incidence of micronuclei was determined.

* One working level (WL) is defined as any combination of short-lived radon progeny in 1 L of air with the potential to emit 1.3×10^5 MeV of α particle energy during decay to lead-210. At a condition of equilibrium (secular equilibrium), 1 WL corresponds to exposure to radon-222 at 100 pCi/L. Breathing an atmosphere that contains 1WL for 1 working month (usually rounded off to 170 hr) constitutes 1 working level month (WLM) of exposure.

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In parallel experiments, lung fibroblasts in vitro were exposed to known radiation doses from radon progeny and the incidence of micronuclei was determined. Comparing α-particle dose-response relationships in nonproliferating cells in vitro with the exposure response relationships in cells exposed by inhalation led to the estimate that a 1-WLM exposure in vivo caused the same amount of cytogenetic damage as 0.78 milligray (mGy) in vitro. Although these experiments used rat fibroblasts, not human epithelial cells, the results are of considerable interest. This direct comparison of α-particle exposure in vivo and in vitro must be viewed in the light of a comparison of uranium miners with atomic bomb survivors, though as noted, the latter had only minimal exposure to α particles.

Carcinogenesis in Laboratory Animals

The BEIR IV report summarized studies of experimental animals exposed to radon, including studies of the inverse dose-rate effect (National Research Council, 1988). Since the BEIR IV committee completed its work, additional analyses of data from experiments performed at Battelle, Pacific Northwest Laboratories, have taken account of competing risks and confirmed that, after exposures above 600 WLM, lung cancer in rats shows a significant inverse dose-rate effect. A dose-rate effect is termed inverse if higher dose rates produce less effect per unit dose than lower dose rates. In this case, exposures to the same total dose but spread over a longer period result in higher lung-cancer rates than acute exposures. Furthermore, the analyses suggest that the magnitude of the inverse dose-rate effect varies directly with total exposure and there is no

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evidence of an effect at 320 WLM, the lowest exposure evaluated in these analyses (Gilbert, 1989; Gilbert and Cross, 1989).

However, a recent experiment conducted in France (Morlier et al., 1992) provides contrary evidence: that reduction in dose rate can reduce, rather than increase, the effect. The lung-cancer incidence in a group of rats that received a cumulative exposure of 25 WLM, over a period of 18 months, was similar to the incidence in control rats that were not exposed to radon progeny but significantly lower than the incidence observed in rats that received the same cumulative exposure over a period of 4-6 months. Thus, the influence of dose rate as assessed in experimental studies needs further investigation. However, the biophysical model described later (and illustrated in Figure 9 on page 36) appears to reconcile the apparent discrepancies.

Data from additional experiments conducted at Battelle, Pacific Northwest Laboratories, might also be available for consideration by a Phase II committee. These include results of experiments with lower total exposures and lower exposure rates than those used previously and results of initiation-promotion-initiation (IPI) experiments that address the combined effects of exposure to cigarette smoke and radon in various sequences. The IPI experiments show that cigarette-smoking promotes the radon-induced preneoplastic lesion adenomatosis. The duration of the smoke exposures, however, was insufficient to promote the induction of tumors, as occurred in earlier experiments conducted in France (F.T. Cross, 1992, personal communication).

RBE VERSUS LET

It was pointed out earlier that one of the most important ways in

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which radiobiologic studies can affect radon risk estimates is to help to determine the quality factor (Q) for the densely ionizing α particles emitted by radon progeny.

Numerous past studies, with a variety of biologic systems from cell lethality to mutation to oncogenic transformation, have confirmed the general shape of the RBE-LET curve, namely, an increase of RBE with increasing LET up to a maximum at an LET of about 100-200 keV/μm, followed by a sharp decline at higher LET (as shown in Figure 5). Inasmuch as survival after α-particle irradiation generally varies exponentially with dose (whereas the curves for survival after exposure to x rays or γ rays have a shape at low doses that is not exponential), RBE must vary inversely with dose; i.e., it is higher at lower doses and has its highest equivalent value (RBE) at the lowest doses, where the response to exposure to either kind of radiation is linear.

Another important subject is the dependence of RBE (at a given dose) on the type of end point. This is relevant to risk assessment using the dosimetric approach. In particular, in comparisons of high- and low-LET radiation, it appears to be a general finding that the RBEs are larger (at a given dose) for oncogenic transformation and for mutagenesis than for cell lethality (Borek, et al., 1978; Han and Elkind, 1979; Miller et al., 1989). Transformation incidence per surviving cell rises rapidly as a function of dose, but reaches a plateau at about 400 cGy of x rays or 100 cGy of α particles. If, however, cell killing (which plays a larger part at higher doses) is factored in, the number of transformations per initial cell at risk rises with dose at first, reaches a peak, and then falls rapidly, paralleling the cell-survival curve (Han et al., 1980). The number of transformations per initial cell is probably a more relevant quantity for extrapolation to risk of carcinogenesis in a whole

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organism. The peak transformation frequency moves to lower doses as the LET of the radiation increases and the peak occurs at about 300 cGy of x rays and 30 cGy of α particles. The peak also reaches higher values for high-LET radiation: e.g., 30 cGy of α particles results in a higher rate of transformations per initial cell at risk than is induced by any dose of x rays.

Brenner (1990) has used the transformation incidence in C3H10T1/2 cells irradiated with α particles of various LET in the track-segment mode to estimate the RBE as a function of range of α particles simulating those emitted by radon progeny (see Figure 8). The results should be compared with the quality factors derived from data on chromosomal aberrations in peripheral lymphocytes by the International Commission on Radiation Units and Measurements (ICRU). The "effective Q" depends heavily on the saturation characteristics at high LET of the biologic system used. The transformation data imply a much-reduced effectiveness of α particles near the end of their range and a lower overall effective Q over the range of the α particles compared with those reported previously (International Commission on Radiation Units and Measurements, 1986).

DOSE-RATE EFFECTS AND IMPLICATIONS FOR RISK ESTIMATES

For low-LET radiation, a unit of dose is usually more biologically effective at a high dose rate than at a low dose rate. This is sometimes expressed as a dose and dose-rate effectiveness factor (DDREF) with which high-dose-rate data are extrapolated to low dose rates. However, a considerable body of data shows that with

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oncogenic transformation in C3H10T1/2 cells as an end point, an inverse dose-rate effect is apparent for high-LET radiation such as fission-spectrum neutrons. The effect appears to be confined to particular radiobiologic end points; e.g., for clonogenic survival, the biologic effectiveness at medium or high LET is virtually independent of dose rate. It should be pointed out that published

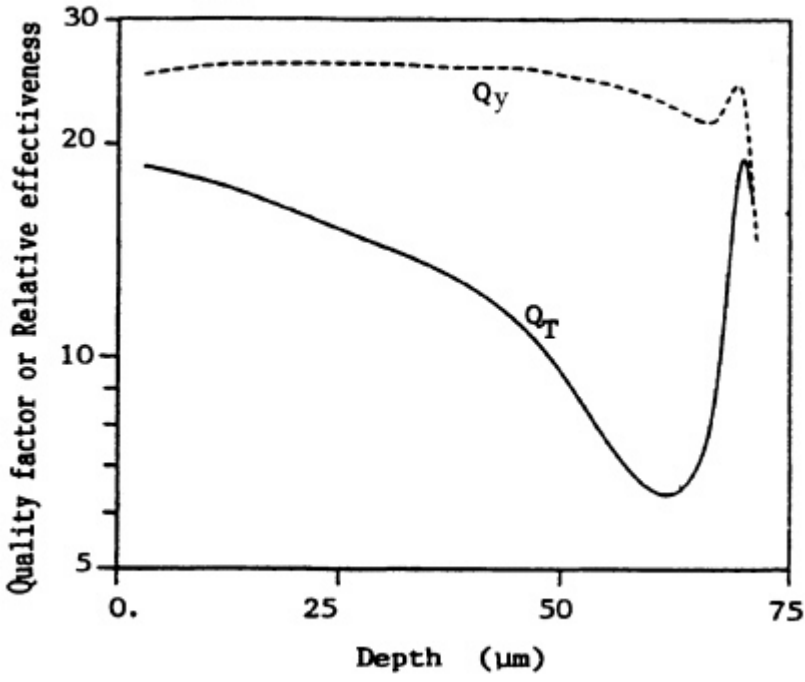

FIGURE 8. Variation in effectiveness (relative to 250-kVp x rays) as a function of depth, derived from the transformation data on C3H10T1/2 cells (Q_T) and from ICRU 40 (ICRU, 1986) function (Q_y). Averaged over whole epithelium (10-72 µm deep), dose mean effectiveness is $\langle Q_T \rangle$ = 15 and $\langle Q_y \rangle$ = 26. (Reproduced from Brenner, 1990, with permission of the publisher.)

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data are equivocal; some investigators have found an inverse doserate effect, and some have not (Hill et al., 1984; Miller et al., 1988; Hieber et al., 1989; Bettega et al., 1992; Miller et al., 1993).

A mechanistic model has been proposed to reconcile the data that support the inverse dose-rate effect. It is based on the presence of a "window" of sensitivity to transformation at some point in the cell cycle (Rossi and Kellerer, 1986; Brenner and Hall, 1990; Elkind, 1991). Together, the model and the relevant data suggest that the magnitude of the inverse dose-rate effect varies in a complex fashion with dose, dose rate, and radiation quality. It can be argued on biophysical grounds that when the exposure rate and total exposure are so low that multiple traversals of target cells are rare, then the inverse dose-rate effect must disappear. That argument is relevant to the relationship of radon progeny exposure and lung cancer; epidemiologic studies have shown that lung-cancer risk from radon-progeny exposure depends on the exposure rate and increases as the exposure rate decreases. Figure 9 shows the result of calculations from the biophysical model referred to above-a surface that describes the enhancement in risk (relative to an acute exposure) due to dose protraction. As expected, the protraction effect increases as the exposure rate decreases, but decreases as the exposure itself decreases. The model implies that for domestic radon exposures, where an average of less than one particle traverses a given cell in the bronchial epithelium, protraction should have little or no effect on risk. However, in the miner studies, the higher exposure rates are more than compensated for by the higher exposures, the result being a significant protraction-related enhancement or a reduction due to shortening of exposure time.

The Phase II committee will need to select a model that controls for time since exposure and dose rate in an effort to determine that the dose-rate effect is really a cause-effect relationship. It should

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be recognized that the risk of a point exposure is zero for a time after exposure, then moves gradually to a higher level, and remains elevated for as long as the subjects are followed. Thus 100 WLM 30 years ago has a bigger effect today than the same dose 10 years ago. More rapid accumulation of a fixed total dose may be correlated with a shorter time since initiation of exposure, so that an observed smaller effect is a result of shorter time since exposure rather than higher dose rate. Questions might arise how secular trends in exposure interact with secular trends in lung cancer. It is at least plausible that higher doses (and shorter times to a fixed total dose) tend to occur in early years, so that a larger part of the follow-up time was in years when rates were lower.

MECHANISMS OF CARCINOGENESIS

Recent years have seen an explosion in new information on the molecular genetics of cancer. In the context of radon risk estimates, it is a tantalizing possibility that the densely ionizing particles released by radon progeny produce characteristic genetic changes that can be recognized at the molecular level and would therefore constitute a "signature" or "footprint" of radon exposure. The possibility is being explored through the study of oncogenes and tumor-suppressor genes in tumors from uranium miners and in particle-induced tumors in experimental animals.

The identification and understanding of human oncogenes make it possible to understand why agents as diverse as retroviruses, ionizing radiation, and chemicals can result in tumors that are indistinguishable one from another (Bishop, 1983; Bishop and Varmus, 1984). Retroviruses insert a gene into the cell, and radiation and chemicals produce a mutation in a gene that is already in the cell. Today, about 100 oncogenes have been identified as

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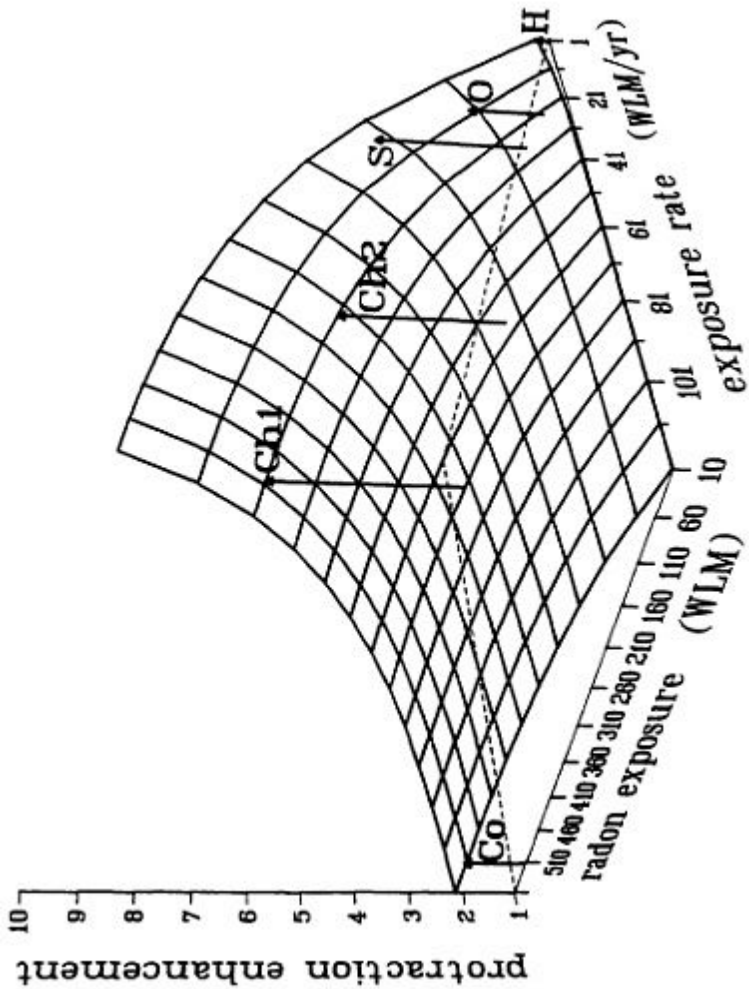

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FIGURE 9. Calculated enhancement in risk (relative to an acute exposure) due to protraction, illustrating the interplay between radon exposure and exposure rate. This surface does not represent a dose-risk relation, but only the enhancement in risk over what would be expected from an acute exposure. Arrows indicate the positions in mean exposure/exposure rate space of various miner studies; calculated relative enhancements for the various miner cohorts, as shown by the heights of the arrows, do reflect the ordering of the relative risk estimated in these studies. Surface and points are from a preliminary calculation provided by D. Brenner, with a "sensitive window" of 20% of the total cell cycle, and with exposure-to-bronchial-dose conversion factors from NRC (1991). No fitting to experimental data was attempted in this exploratory calculation.

Co: Colorado miners (mean WLM; WLM/yr; calculated enhancement = 520; 120; 2.1, respectively).
Ch1: Chinese tin miners (Lubin et al. 1990: mean WLM; WLM/yr; calculated enhancement = 507; 21; 5.3, respectively).
Ch2: Chinese tin miners (Xuan et al. 1993: mean WLM; WLM/yr; calculated enhancement = 275; 21; 4.4, respectively).
S: Swedish iron workers (mean WLM; WLM/yr; calculated enhancement = 120; 5; 3.9, respectively).
O: Ontario miners (mean WLM; WLM/yr; calculated enhancement = 10; 65; 2.4, respectively).
H: Typical domestic exposures.

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associated with human cancer, of which more than 80% belong to the *ras* family. However, activated oncogenes are associated with only a small proportion (10-15 %) of human cancers and tend to be found more commonly in leukemias and lymphomas than in solid tumors. Oncogenes have been shown to be activated by point mutations, such as *in ras* (Bos, 1988); by deletions, such as *infos;* by reciprocal translocations, such as in myc (Dalla-Favera et al., 1983); and by gene amplification, such as in *myc* (Brodeur et al., 1984).

It was discovered in the 1970s that the tumorigenicity of tumor cells could be suppressed by hybridization with normal cells (Harris, 1971; Stanbridge, 1976). For example, the fusion of a normal human fibroblast with a HeLa cell suppressed the expression of the malignant phenotype of the HeLa cell. Those findings, which preceded the notion of oncogenes by several years, led to the hypothesis that normal cells contain a gene or genes that can suppress the neoplastic potential of tumor cells. The putative tumor suppressor genes have been mapped to specific chromosomes, such as chromosome 11 in the example quoted, by analyzing which chromosomes were lost from the hybrids that re-express tumorigenicity (Stanbridge, 1976). The importance of tumor-suppressor genes became evident in the work of Knudson (1971) with retinoblastoma, which occurs in both familial and sporadic forms. Knudson elaborated this two-hit hypothesis in the early 1970s, and by the mid-1970s, the location of the gene was identified on chromosome 13 (Cavenee et al., 1985). In the 1980s the *Rb* gene was cloned and sequenced (Lee et al., 1987). The *Rb* gene is associated in 100% of cases with retinoblastoma, and survivors of childhood retinoblastoma are also predisposed to bone cancers. Mutations of the *Rb* gene are also sometimes associated with various other tumors, such as small-cell lung cancer, bladder cancer, and mam

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mary cancer. An obvious mechanism for knocking out a suppressor gene is radiation-induced deletion. A tumor suppressor gene acts in a recessive way, so the deletion would have to occur in both chromosomes of a pair, an event of very low frequency. In practice, it is often found that the loss of a pair of suppressor genes occurs by the process of somatic homozygosity (Cavanee, 1989): one chromosome of a pair is lost, a deletion occurs in the other, and then the chromosome with the deletion is replicated. The cells in the tumor then have two chromosomes that originated from the same parent. That mechanism has been shown in retinoblastoma, small-cell lung cancer, and glioblastoma. Another possible mechanism is illustrated by familial heterozygosity in which subjects are at increased risk because they harbor one active and one inactive gene. In this case, the loss or mutation of the normal allele on chromosome 13 by nondisjunction, deletion, genetic recombination, or local mutation leads to production of cancer (Knudson, 1985). At least six tumor-suppressor genes and their locations and functions have been identified. The two most common and most intensively studied are the *Rb* gene and the *p53* gene; both are involved in the arrest of cells in the G1 phase of the cell cycle and in tumor differentiation (DeCaprio et al., 1992).

MARKERS OF EXPOSURE

One of the workshops organized by the committee included a summary of studies of molecular markers of radon exposure. Mutations in the *p53* tumor suppressor gene are common in many human cancers, including cancers of the colon, skin, breast, and lung. These mutations are not random, but clustered in the central portion of the gene, exons 5-9. Furthermore, the mutations caused

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by exposure to tobacco smoke are characterized by G:C to T:A transversions in the coding strand, and lung cancers have "hot spots" (regions of DNA with high mutation frequency) for these mutations. The mutation spectra *of p53 and K-ras* in lung cancers of uranium miners exposed to radon at high levels have been studied. The results in 19 miners, 18 of whom also smoked, showed no codon 12-13 mutations in *K-ras (K-ras* mutations are very common in lung cancers of cigarette smokers), but nine mutations in *p53* were detected in seven of these patients. Twenty-two percent of the mutations were deletions. None of the mutations was a G:C to A:T transversion in the coding strand. Five missense mutations and one nonsense mutation were detected. A silent mutation was also detected. In addition to point mutations, two of the patients also had a small deletion in p53, but *p53* deletions are not common in lung cancer. All these mutations were clustered between codons 146-161 and codons 195-208, which could be interpreted as "hot spots" for radon-induced mutations (Vähäkangas et al., 1992). In another study, 16 of 52 large-cell and squamous-cell cancers from uranium miners contained the same AGG to ATG transversion at codon 249, including cancers from three of five miners who had never smoked (Taylor et al., 1994).

Those data contrast with the findings in Japanese atomic-bomb survivors, who were exposed principally to low-LET radiation (Takeshima et al., 1993). Of 17 Japanese with adenocarcinomas, nine had been exposed to radiation, and eight were controls. There were four point mutations in *p53* in the exposed and four in the nonexposed; i.e., the mutation was not characteristic of irradiation. A final conclusion must depend on a larger database, but preliminary data suggest that a signature of densely ionizing particles in *p53* might exist, whereas it might not for low-LET radiation. However, in a recent study comparing the pathology of lung cancers

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in the uranium miners and the atomic-bomb survivors, it was found that both had increased numbers of small cell carcinomas in proportion to the dose and few adenocarcinomas (Land et al., 1993).

SUMMARY AND RECOMMENDATIONS

Laboratory data provide a solid base of information that indicates that α particles from radon progeny cause mutations in cultured cells, oncogenic transformation in cells in vitro, and tumors in experimental animals. The dose-response relationship appears to be linear down to the lowest doses at which an effect can be observed. The response is also very sensitive to the LET of the α particles and peaks at about 100-200 keV/μm. The range of end points and biologic systems studied has been considerably expanded since the BEIR IV report was published in 1988. Experiments with oncogenic transformation induced in cultured cells by high-LET radiation led to a biophysical model for the inverse dose-rate effect, whereby the biologic effectiveness of a given dose is increased if the dose is protracted. The biophysical model appears to be consistent with the dose-rate effect observed in studies of experimental animals and underground uranium miners and has implications for the extrapolation of data from radon exposures in mines to exposures in residences. That is an important development since the publication of BEIR IV and needs to be considered and evaluated by a Phase II (BEIR VI) committee.

The last few years have seen a dramatic increase in our understanding of the molecular genetics of cancer. Preliminary evidence indicates that it might be possible to identify molecular changes that are characteristic of cancers induced by α particles.

As a result of recent radiation-biology studies in molecular

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biology, transformation, and carcinogenesis, as well as some useful data from studies of neutron-radiation biology, the committee recommends that a Phase II Research Council committee

- Evaluate biophysical models of the inverse dose-rate effect and their implications for risks associated with indoor radon exposure.
- Compare risks and pathology of lung tumors induced by exposure to radon with risks and pathology of those induced by external exposures to low-LET radiation.
- Examine in more detail the induction and repair of molecular changes resulting from α-particle exposure.

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3 Exposure-Dose Relations

STATUS OF STUDIES

Extrapolation of the lung-cancer risks observed in underground miners to the risks for the general population, who are exposed to radon indoors, is subject to uncertainties related to the differences in physical environments between homes and mines, the circumstances and temporal patterns of exposure in the two environments, and the potential biologic differences between miners and the general population. For example, of the physical factors at issue, aerosols are present at greater concentrations in mines, and their size distributions differ between mines and homes. The unattached fraction of radon progeny—i.e., atoms of the radon progeny not attached to dust particles—is typically higher in homes. Ventilation is probably greater for working miners than for persons indoors in homes, although patterns of oral and nasal breathing have not been well characterized for those groups. As to important biologic factors, the miners have been exposed previously during adulthood but the entire population, including children, is exposed in homes; miners are exposed for variable periods during adulthood, but

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exposure in homes is lifelong for the population; and most of the miners studied have been smokers, but only a minority of U.S. adults in the general population are currently smokers. Those factors are potential determinants of the relationship between exposure to radon progeny (in working-level months) and equivalent dose of α-energy (in sieverts) delivered to target cells in the respiratory tract. With models of the respiratory tract, the dose to target cells in the respiratory epithelium can be estimated for the circumstances of exposure of a miner in an underground mine and of a man, woman, or child in a home. Uncertainties arising from dosimetric differences between exposures in the two settings can be characterized by comparing the relationships between exposure and dose.

Before the BEIR IV report (National Research Council, 1988) was issued, comparative analyses of dosimetry had been made for the mining and indoor environments. The BEIR IV report included a qualitative assessment of uncertainty associated with differences in lung dosimetry in the two environments. The report's analysis of dosimetry was based on the value of "K," the ratio of dose to exposure in homes divided by the ratio of dose to exposure in mines. Values above unity indicate greater dose and hence greater risk for those exposed in homes than for those exposed in mines; values less than unity indicate lesser risk in homes. The BEIR IV report considered the determinants of K in a qualitative fashion and found the value of K to be 1. The report did not include a detailed assessment of the evidence on the determinants of K, nor did the committee develop its own model.

In followup to the BEIR IV report, EPA asked the National Research Council to study the dosimetry and related matters, considerations that affect the applications of lung-cancer risk estimates based on studies of miners to the general population. The resulting

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report of the Panel on Dosimetric Assumptions Affecting the Application of Radon Risk Estimates was published in 1991 (National Research Council, 1991). The report used a dosimetric model to estimate the relationship between exposure and dose of people working in mines and living in homes (see Figure 10). The committee determined that the value of K was 1 or less for exposures of infants, children, and adults in the general population (Table 1). The panel's literature review identified gaps and limitations in the evidence available through 1990 on the parameters of the lung-dosimetry model. Furthermore, although the panel followed the conventional approach of lung dosimetric modeling to estimate K, the predictions of the models could not be validated in biologic systems. The panel recommended more research on activity-weighted size distributions of radon progeny in various settings, including mines and buildings; on breathing by humans under diverse circumstances; on deposition patterns of submicrometer particles in the upper airways and lung; on hygroscopic growth of particles in the respiratory tract; on the physical behavior of progeny deposited in mucus; and on the cells at risk for transformation to lung cancer.

Since the panel's report was published, new information has become available on several of those subjects. An automated instrument has been developed for field measurements of the concentration and activity-size distributions of radon progeny (Li and Hopke, 1991). This instrument has been used in the home environment to assess activity-weighted size distributions under typical conditions of home occupancy (Wasiolek, et al., 1992). Tu and colleagues (Tu et al., 1991) used other devices for the same objective. The data have shown that combustion sources affect the activity-weighted size distribution: particles from gas stoves and kerosene heaters measure less than 0.1 μm, and cigarette-smoking

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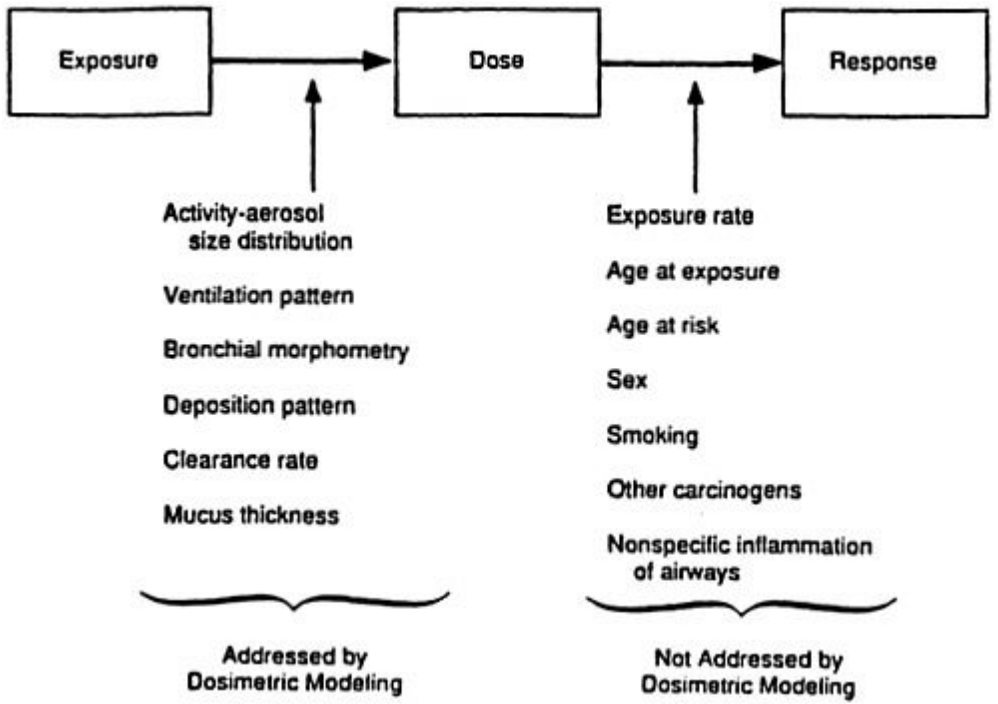

FIGURE 10. Factors influencing the relationship between radon exposures and the risk of lung cancer. (From National Research Council, 1991.)

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tends to produce larger particles. Using the data from three homes, Wasiolek and colleagues (Wasiolek et al., 1992) found similar coefficients for the exposure-dose conversion that used the more refined data from the activity-weighted size distributions and the approach of truncating the distribution into "attached' and "unattached" fractions used in the panel report.

TABLE 1 Summary of K Factors for Bronchial Dose Calculated for Healthy People in the General Environment Relative to Health Underground Miners (From National Research Council, 1991)

	Target-Cell K Factors	
Subjects	Secretory Cells	Basal Cells
Infants, age 1 mo	0.74	0.64
Children, age 1 yr	1.00	0.87
Children, age 5-10 yr	0.83	0.72
Adult Females	0.72	0.62
Adult Males	0.76	0.69

Little progress has been made in determining which respiratory epithelial cells give rise to lung cancer, in spite of additional experimental studies of greater sophistication. The proliferative potential of epithelial cell populations has been examined to gain insight into the target cells for malignant transformation. An assumption underlying interpretation of those experiments is that cells that show proliferative capacity are also the target cells for carcinogenesis-which is not necessarily the case. The radon panel had considered both basal and secretory cells to be at risk, largely on the basis of the work of McDowell and Trump (1983), which showed that secretory cells have proliferative potential. Using a rat tracheal system, Johnson and co-workers (Johnson and Hubbs, 1990; Johnson et al., 1990) confirmed the proliferative capacity of secretory cells. In one set of experiments,

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populations of basal and secretory cells from rat trachea were prepared with flow cytometry and inoculated into denuded tracheal grafts (Johnson and Hubbs, 1990), where the basal cell preparation produced an epithelium of basal and ciliated cells and the secretory cells yielded secretory cells as well as basal and ciliated cells. Similarly, using flow cytometry to obtain the two cell populations and growth in cell culture to assess proliferative potential, Johnson and colleagues (Johnson et al., 1990) found that secretory cells had substantially higher proliferative potential and greater metabolic capacity than basal cells.

However, Ford and Terzaghi-Howe (1992), also working with cells from rat tracheal epithelium, found that basal cells, and not secretory cells, had proliferative potential. Like Johnson and coworkers, they used flow cytometry to sort cell populations, although they used different markers. Ford and Terzaghi-Howe examined the kinetics of cell death and proliferation in a suspension prepared from rat tracheal epithelium. Only cells with basal cell markers survived in the suspension and showed proliferative capacity in cell culture after cell sorting.

The divergent findings of the two investigative groups, addressed at the workshop on dosimetry sponsored by the present committee, cannot be readily reconciled. Although both groups used rat tracheal epithelium, their experimental designs and their markers were distinct. Relatively sophisticated methods were used in these experiments, but the relevance of proliferative capacity in these systems to human lung cancer remains uncertain.

Some additional information relevant to radon dosimetry has been reported. Noninvasive methods for monitoring ventilation in the field have been developed and applied to the general population (McCool and Paek, 1993; Samet et al., 1993) and to small numbers of underground miners (David James, personal communication). Li

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and Hopke (1993) assessed growth of particles from cigarettes, incense, a natural gas flame, a propane flame, and a candle flame. With humidification, particles from those sources showed growth of 10-120%.

Substantial research is in progress on various aspects of lung dosimetry, and key uncertainties might be reduced over the next few years. The report of the radon panel, as well as previous analyses, indicated that differing exposure-dose relationships for exposures to radon progeny in mines and in homes are not associated with a high degree of uncertainty, given the inherent limitations of lung-dosimetry models. Current uncertainties related to the dosimetry of radon progeny in the lung would be best addressed by validation of the predictions of the models, by a more complete understanding of the cells at risk for oncogenesis, and by population-based data on the model parameters, including activity-size aerosol distributions and breathing and deposition patterns. However, only historical information is available on the activity-size distributions of aerosols in mines (Knutson and George, 1992). With the cessation of conventional underground uranium mining in the United States, it is no longer possible to make relevant activity-size distribution measurements in this country. Data could be gathered in Canada and other countries where underground uranium mining continues, but the relevance of such contemporary information to the historical cohorts would be uncertain.

SUMMARY AND RECOMMENDATIONS

The results of workshops conducted by the committee revealed that the proliferative capacity of basal or secretory cells is of uncertain relevance to human lung cancer, in light of conflicting

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evidence from experiments that used rat tracheal epithelium. Measurements of activity-weighted particle-size distributions relevant to the conditions experienced by historical cohorts of miners are unlikely to become available, because those conditions no longer occur. However, the committee recommends that a Phase II Research Council committee

- Use noninvasive methods for monitoring ventilation to obtain additional information that is relevant to radon dosimetry and an improved model.
- Continue to evaluate information on the cells at risk for radon-induced lung cancer.
- Use activity-weighted size-distribution data that have become available on residences.
- Use the recent data regarding growth of particles from various sources typically found in the home.
- Apply the reduced uncertainties in various aspects of lung dosimetry and use revised factors to reassess the uncertainties associated with the lung dosimetry in risk calculations.

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4 Epidemiologic Investigations

STUDIES OF MINERS

Overview

Underground miners, especially those working in uranium or tin mines, are exposed to a wide range of, and in some cases to high levels of, radon and its progeny. This exposure of underground miners to radon progeny has been causally linked to lung cancer (National Research Council, 1988). It is therefore not surprising that those populations of miners have served as a valuable resource for epidemiology studies, and the resulting database has been used to establish risk estimates for lung cancer that have then been extrapolated to the lower exposure levels found in homes. However, a majority of uranium miners are cigarette-smokers, and the miners are also exposed to silica, arsenic, blasting fumes, and, in some mines, diesel exhaust. The contributions of the other agents to the excess risk of lung cancer in miners have not been adequately characterized (National Research Council, 1991), and nonmalignant respiratory disorders might also be a risk factor for lung cancer (Tockman, 1994).

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Cohorts of Miners

The BEIR IV report, published in 1988, reviewed epidemiologic studies of underground-miner cohorts that had been published through 1987:

- Uranium miners in the Colorado Plateau; Ontario, Port Radium, and Beaverlodge, Canada; Czechoslovakia; and France.
- Tin miners in Cornwall, U.K.
- Fluorspar miners in Canada.
- Iron miners in Sweden.
- Other miners in Sweden.
- Niobium miners in Norway.

The BEIR IV committee analyzed data on four of the cohorts Malmberget (Sweden) iron miners, Colorado Plateau uranium miners, Beaverlodge uranium miners, and Ontario uranium miners-to develop a risk model. Those four yielded the only data on radon-progeny exposures of individual participants to which the committee could gain access; at that time, data from the Czechoslovakian miners could not be obtained, and several other investigations were still in progress.

Since publication of the BEIR IV report, the findings on additional cohorts have been reported; all confirm the excess lung cancer incidence found in previous studies, and all demonstrate increasing risk with increasing exposure to radon progeny. The more recent cohorts include Chinese tin miners (Xuan et al., 1993), notable for the large population of exposed miners, the large number first exposed as children, and the complications caused by arsenic exposure; New Mexico uranium miners in the

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Grants area (Samet et al., 1991a); Australian uranium miners in the Radium Hill mine (Woodward et al., 1991); and French uranium miners (Tirmarche et al., 1993).

Although carcinogenicity of radon progeny had been well established in humans by 1988, the year of publication of the BEIR IV report, the new studies have contributed new estimates of the relationship between radon-progeny exposure and lung-cancer risk and new evidence on the validity of assumptions used for risk modeling. The Chinese tin miners included a unique group that had started working underground as children; age at first exposure did not modify the eventual risk of lung cancer (Xuan et al., 1993). In a pilot case-control study conducted within the cohort, skeletal lead-210 concentrations were estimated by counting cranial lead-210 activity (Laurer et al., 1993). In this study of 19 lung-cancer cases and 141 age-matched controls, there was a smooth gradient of lung-cancer risk with category of lead 210 concentration; this finding indicates the potential for using skeletal lead-210 to improve the retrospective exposure estimates constructed for the epidemiologic studies.

The study of New Mexico uranium miners included information on smoking for most miners (Samet et al., 1991a). The data indicated a multiplicative interaction between smoking and radon progeny exposure, although the combined effect of the two agents could not be described with precision, because of the small number (68) of lung-cancer deaths. A case-control study conducted within the New Mexico cohort found that the presence of chest-radiograph abnormalities indicative of silicosis was not associated with lung-cancer risk (Samet et al., 1994). The studies of Port Radium, Radium Hill, and French uranium miners provided new data on exposures lower than in some of the earlier cohorts.

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The published reports on uranium miners in Czechoslovakia were reviewed in the BEIR IV report. Followup of these miners has been extended, and patterns found for lung cancer (Tomásek et al., 1994) and cancers other than lung cancer (Tomásek et al., 1993) have been reported. Lung-cancer risk varied with exposure rate, stratified by the authors at intervals of 10 WL. Among men whose exposure rates never exceeded 10 WL, the risk increased linearly with time-weighted cumulative exposure, was higher in younger men, and declined with lengthening interval since exposure. These patterns are similar to those found in the BEIR IV analysis. Higher risks in men who had worked in one particular mine suggested an effect of arsenic in the dust on lung-cancer risk. When the analysis included all miners, the patterns of risk were more complex.

Lung Cancer in Pooled Analysis of 11 Cohorts

The pooled analysis of four cohorts performed by the BEIR IV committee demonstrated the informativeness of combining data sets to derive risk models. The sets used by that committee included data on 360 lung-cancer deaths among 22,190 miners. With the publication of additional studies and the new opportunity to work with the team investigating the Czechoslovakian uranium miners, the U.S. National Cancer Institute (NCI) took the lead in a pooled analysis of data from 11 studies of underground miners, each of which was large (at least 40 lung-cancer deaths) and included estimates of individual exposures to radon progeny. The pooled dataset included over 2,700 lung-cancer deaths among 68,000 miners followed for nearly 1.2 million person-years. A

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full description of the analysis has recently been published as an NCI monograph (Lubin et al., 1994a). We summarize here the findings most relevant to radon risk assessment.

The cohorts in the joint analysis are listed in Table 2; the NCI monograph provides detailed descriptions of the cohorts and the methods for exposure assessment. The cohorts included uranium, tin, iron, and fluorspar miners. Various methods were used to estimate exposure to radon progeny. Six studies had some data on cigarette-smoking, and a few had information on exposures in addition to radon progeny, including arsenic and silica. The birth years and followup intervals varied widely among the cohorts; the Malmberget miners were born in 1880-1919, whereas the other cohorts were much younger.

TABLE 2 Study Populations Included in Joint Analysis of Miners (Lubin et al., 1994a).

Area	Type of Mine	Reference
Yunnan Province, China	Tin	Xuan et al., 1993
Western Bohemia, Czech Republic	Uranium	Sevc et al., 1988
Colorado Plateau	Uranium	Hornung and Meinhardt, 1987
Ontario, Canada	Uranium, gold	Kusiak et al., 1991
Newfoundland, Canada	Fluorspar	Morrison et al., 1988
Malmberget area in northern Sweden	Iron	Radford and Renard, 1984
Grants, New Mexico	Uranium	Samet et al., 1991a
Beaverlodge, Saskatchewan	Uranium	Howe et al., 1987
Port Radium, Northwest Territories, Canada	Uranium	Howe et al., 1987
Radium Hill, Southern Australia	Uranium	Woodward et al., 1991
France	Uranium	Tirmarche et al., 1993

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The data were analyzed with Poisson regression methods similar to those used by the BEIR IV committee, whose approach was generally followed. The effect of cumulative exposure to radon progeny was estimated, and the relation between risk and various potential modifiers was considered: attained age, duration of exposure, rate of exposure, age at first exposure, time since last exposure, and time since exposure during specified temporally defined exposure windows. Most analyses were based on a linear excess-relative risk (ERR) model:

$$RR = 1 + \beta w$$

where RR is relative risk, w is cumulative exposure to radon progeny in WLM, and β is a parameter representing the unit increase in ERR per unit increase in w. As in the BEIR IV analysis, cumulative exposure was divided into the exposures received during windows defined by time since exposure. Effect modification was examined with categorical approaches and parametric functions. Curvilinearity in exposure-response trends was assessed, and attributable-risk models were fitted to the data.

As anticipated, ERR was linearly related to cumulative exposure to radon progeny. The ERR/WLM ratio decreased significantly with attained age, time since exposure, and time after cessation of exposure, but it was not affected significantly by age at first exposure. Over a wide range of total cumulative exposures, lung-cancer risk increased as exposure rate declined; that effect was not included in the BEIR IV committee's model. Although an effect of exposure rate was found in the BEIR IV analysis of data on the Colorado cohort, such an effect was not evident in the three other cohorts, and exposure rate was not considered further by the BEIR IV committee. On the basis of comparison of the risk of lung

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cancer in Beaverlodge and Port Radium uranium miners, two groups considered to have substantially different exposure rates, Darby and Doll (1990) had also hypothesized that lung-cancer risk would increase with declining exposure rate.

The finding in the pooled analysis of an exposure-rate effect confirms the pattern reported from the Colorado Plateau study and supports the previously mentioned hypothesis. The inverse exposure rate has potentially important implications for the use of the miner studies to estimate risk associated with typical indoor exposure levels. However, the pooled analysis does not directly address the exposure-rate range typical of indoor environments, which lies within the lowest categories used in the models discussed below.

Information on tobacco use was available for six cohorts, and the combined effect of smoking and radon progeny was estimated with a mixed model. The combined data were consistent with a relationship between additive and multiplicative. Over 50,000 person-years and 64 lung-cancer deaths were accrued by miners who were identified as having never smoked. In this group, there was a linear exposure-response trend that was about 3 times greater than that observed in smokers. That difference might lead to modification of the multiplicative relationship of smoking and radon used in the BEIR IV model.

Other occupational agents that might confound or modify the relationship between radon progeny exposure and lung-cancer risk were also considered. Such information was available on five of the 11 cohorts. Information was available on previous hard-rock mining experience of the Colorado, New Mexico, and French cohorts of uranium miners. The effect of radon-progeny exposure did not vary significantly across strata of prior hard-rock mining. Similarly, in the Ontario uranium miners, prior gold-mining had no significant impact on risk associated with exposure to radon

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progeny. Information on arsenic exposure, a causal risk factor for lung cancer, was available for the Chinese tin miners and the Ontario uranium miners. In the Chinese cohort, adjustment for arsenic exposure substantially reduced the risk associated with exposure to radon progeny, but was not statistically significant.

The NCI monograph (Lubin et al., 1994a) offers preferred models in categorical or contiguous forms. The models incorporate radon-progeny exposure during time-since-exposure windows and variables for modification of the effect of radon-progeny exposure by attained age and exposure rate or by attained age and duration of exposure. These models are similar in form to the BEIR IV model but have terms for either rate of exposure or duration of exposure (which is also an indicator of exposure rate). In addition, the larger data set available for the pooled analysis made it possible to estimate the effects of age and exposure in four windows of time since radon-progeny exposure, rather than three as in the BEIR IV model. As in the BEIR IV model, the effect of exposure declined with increasing time since exposure and attained age. A major departure from the BEIR IV model was the inclusion of terms expressing an inverse dose-rate effect. However, the range of exposure rates encompassed by the miner studies does not include the usual indoor exposure rates.

Assessment of Uncertainty in Lifetime Risk Estimates

To make the best decision regarding the handling of risks, the uncertainties in risk estimates must be understood. Uncertainties arise from sampling variation in estimated parameters, potential biases in data (such as exposure-measurement error), and, especially, lack of knowledge regarding the correct model. The latter

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is particularly important when it is necessary to extrapolate to age sex groups, time-since-exposure periods, and doses and dose rates that are outside the range of the data analyzed.

The report of the BEIR IV committee discussed in detail these and other uncertainty sources, but its quantitative assessment of uncertainty included only the sampling variation. Standard statistical theory can be used to assess uncertainty from this source, possibly including computer simulations as well as analytic solutions. Methods are also available to assess uncertainty resulting from exposure-measurement errors and other errors in the data, but these are generally difficult to apply and require a thorough understanding of the magnitude and nature of the errors. Less rigorous methods are available to evaluate the third source of uncertainties, and they generally require subjective judgments about the nature and magnitude of the uncertainties from various sources. Examples of such subjective assessments are found in the BEIR V report (National Research Council, 1990) and in the National Institutes of Health radioepidemiologic tables (National Institutes of Health, 1985). Such problems can be studied in part by "sensitivity analysis" in which parts of the model are varied to assess effects on conclusions.

An overall assessment of uncertainty that combines uncertainties from all or most relevant sources has not been attempted in past radiation risk assessments. Such an assessment would be difficult and would require many assumptions, but it is a highly desirable objective for a Phase II (BEIR VI) committee.

Nonrespiratory Cancers

After the publication of the BEIR IV report, ecologic analyses

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showed associations between exposure indexes for radon and the incidence of several cancers, including myeloid leukemias and lymphomas (Henshaw et al., 1990; Eatough and Henshaw, 1991). The BEIR IV report summarized mortality data from several sources for cancer sites other than the lung. Because most of the individual cohort studies have inadequate statistical power for addressing malignancies other than lung cancer, an additional pooled analysis of the 11 cohorts directed at cancers other than lung cancer has been organized by Sarah Darby at the Imperial Cancer Research Fund Cancer Epidemiology Unit, University of Oxford. Publication of the findings of this study is expected by the end of 1994.

A recent report addressed cancers other than lung cancer among 4,320 male uranium miners in West Bohemia (Tomásek et al., 1993). These men had been followed for an average of 25 years. There was a small but not statistically significant excess mortality from cancers other than lung cancer compared with that expected from national rates: the observed/expected mortality (O/E) was 1.11, and the 95% percent confidence interval was 0.98-1.24. The investigators examined 28 sites and types of cancer and found significantly increased risks of cancers of the liver (O/E= 1.67) and of the gallbladder and extrahepatic bile ducts (O/E=2.26). For liver cancer, mortality did not increase significantly with exposure to radon progeny; the trend for cancers of the gallbladder and extrahepatic bile ducts was statistically significant. Those findings need to be evaluated in the light of findings from other cohorts; the analyses being conducted by Dr. Darby should be very useful in this regard.

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Nonmalignant Respiratory Diseases

An appendix to the BEIR IV report addressed nonmalignant respiratory diseases in miners exposed to radon. The report noted that silicosis had been documented among underground uranium miners in the United States and that adverse effects of underground uranium mining on lung function had been shown in miners in the Colorado Plateau and New Mexico. The report concluded that the investigations had not separated the effects of radon-progeny exposure from those of exposure to other potentially harmful contaminants of the air in mines, including silica, diesel-engine exhaust, and blasting fumes. Since the release of the BEIR IV report, detailed literature reviews have reached similar conclusions (Samet and Morgan, 1991; Samet and Simpson, 1991). Further evaluation of all these studies is needed.

STUDIES OF LUNG CANCER IN THE GENERAL ENVIRONMENT

Overview

Risk assessments of lung cancer associated with residential radon exposure have been based on extrapolation of estimates obtained from studies of underground miners. Concentrations in the mines were generally much higher than typical concentrations in residences, and factors influencing exposure-dose relations, such as breathing and activity patterns, are also expected to be different between the residential and mining environments. In addition, the exposed underground miners were predominantly male smokers of

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a narrow age range. Those differences necessarily lead to uncertainties in applying miner-based estimates of risk to the general population, which includes males and females of all ages, both smokers and nonsmokers, who are exposed to the lower levels found in homes.

To reduce the uncertainties, epidemiologic investigations designed to estimate the risk associated with indoor radon directly have been undertaken. Since the publication of the BEIR IV report, numerous case-control and ecologic studies on indoor radon and lung cancer have been initiated. The findings of some of the studies have already been reported and the results of the principal case-control studies now in progress should become available over the next few years. Both case-control and ecologic studies are discussed below. For each type of study, the current status of the research is reviewed first, and then the problems and limitations of the studies are discussed.

Case-Control Studies

In case-control studies of the effects of residential radon, persons with lung cancer (cases) and persons without lung cancer (controls) are characterized and compared with regard to radon exposure and other factors. In most recent studies, cases and controls have been matched on age, sex, and possibly other factors; and interviews have been conducted to obtain information on residential histories, time spent in the home, occupation, smoking, and other potential risk factors. Most recent studies have also included long-term (several months) residential radon measurements, and some have been limited to females or to nonsmoking females. Because these studies include information on individuals,

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they are regarded as much less subject to bias than ecologic studies. The case-control design was endorsed by the 1989 International Workshop on Residential Radon Epidemiology as the method of choice for the direct assessment of risks associated with residential radon exposure (Samet et al., 1991b).

Status

When the BEIR IV report was prepared, only a few small studies in Sweden, including about 100 lung-cancer cases, had been completed. The findings of these studies suggested an association of lung cancer with residential radon exposure, but radon had been measured in only one study. Since the BEIR IV committee completed its review, results of additional studies have been reported, and many new studies have been initiated. Neuberger (1992), in a recent review article on studies in progress, listed 20 studies that included a total of more than 12,000 lung-cancer cases and more than 19,000 controls. Most of these studies incorporate long-term radon measurements in the homes of cases and controls and the collection of data on smoking and other risk factors.

Results of three such studies that included measurements in homes of individual subjects had been published at the time of this review. These studies--conducted in New Jersey (Schoenberg et al., 1990), Sweden (Pershagen et al., 1992), and China (Blot et al., 1990)-include 480 cases and 442 controls, 210 cases and 400 controls, and 308 cases and 356 controls, respectively, and were considered in a pooled analysis recently by Lubin et al. (1994b). The analyses indicate that the findings from the studies are not inconsistent with one another and that pooling of all three studies

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makes the estimate of risk sufficiently imprecise to be consistent both with no effect and with predictions of the BEIR IV model. This initial pooled analysis provides warning of the difficulty of precisely estimating the risk associated with indoor radon directly from case-control data.

Results of a second study in Sweden (with 1,360 cases and 2,847 controls) (Pershagen, personal communication) and of a study in Winnipeg, Manitoba, Canada (with 738 cases and 738 controls) (Létourneau, personal communication) are in press and would be available for evaluation by a Phase II (BEIR VI) committee. For studies presented at the Second International Workshop on Residential Radon, held in July 1991, but not yet reported in print, investigators were queried; Table 3 shows when investigators expect results to be available. The study in Florida has been completed, and results of the Missouri study are expected to be published within a year. Results of a few additional studies might be available in time to be included in a BEIR VI report, but results of other studies, such as the large study in Germany, are unlikely to be available.

The participants in the second international workshop strongly recommended that pooled analyses of data from case-control studies be conducted (U.S. Department of Energy, 1991). Such analyses are needed to obtain the most precise direct quantitative assessment of risk, to evaluate the consistency of findings from different studies, and to achieve sufficient power to address questions related to effect modification by smoking, sex, age at exposure, and other factors. As indicated above, a pooled analysis has already been conducted, and pooled analyses involving additional studies might be available for evaluation by a BEIR VI committee. Planning for pooling of the data from European studies has also been initiated. However, it is clear that a pooled analysis includ

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TABLE 3 Summary of Some Case-Control Studies in Progress

Investigator	Study Location	Approx. Cases	Sample Size Controls	Start Date	Actual or Planned End of Data Collection
M.C.R. Alavanja	Missouri	600	1,400	1/88	8/92
S.C. Darby	Devon and Cornwall, U.K.	900	1,800	1/88	1/95
C.F. Lynch	Iowa	600	600	1/93	12/96
J.L. Lyon	Utah and Idaho	529	885	10/89	1/95
W.L. Nicholson	New Jersey	500	600	9/89	1/94
A. Poffijn	Ardennes, France	1,200	3,600	9/90	1/94
H.G. Stockwell	Florida	145	215	1/88	1/92
J.A.J. Stolwijk	Connecticut	964	954	6/90	1/94
M. Tirmarche	Bretagne, France	600	1,200	1/91	1/95
H.E. Wichmann	Germany	3,000	3,000	9/90	3/97

Modified from U.S. Department of Energy (1991).

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ing all the major studies now in progress will not be complete in time for BEIR VI evaluation.

Problems and Limitations

The direct study of the effects of residential radon exposure is subject to several methodologic limitations. The most obvious is that large samples are needed if predicted risks based on the studies of underground miners are correct. Lubin and colleagues (Lubin et al., 1990) evaluated the sample sizes required in a case control study to detect an association between lung cancer and residential radon exposure under the assumption predictions based on underground miners are correct, to detect that the quantitative effect is half that predicted from underground miners, and to detect a departure from an additive interaction between smoking and radon exposure if the true interaction is multiplicative rather than additive. Their sample-size estimates for a case-control study assume that the distribution of exposure in the population being studied is similar to that described by Nero and colleagues (Nero et al., 1986) for the U.S. population, that cases and controls are 60-65 years old, and that the study includes twice as many controls as cases. Under the assumptions that subjects lived in a single residence for 60 years and that the underground-miner risk is that from the BEIR IV analysis, the numbers of cases required to achieve 90% power for testing the three hypotheses were 251, 1,610, and 764, respectively. However, both lowering the underground miner-risk and increasing the number of assumed residences increased the sample sizes substantially. For example, the assumption of three residences for each case and control and lowering the assumed underground-miner risk from 1.5 %/WLM to

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1.0%/WLM increased the sample size requirements for testing the three hypotheses to 952, 5,163, and 3,344, respectively.

A second limitation of residential radon studies is that exposure estimates are subject to many sources of error. Even in the most straightforward scenario in which subjects have lived their whole life in a single residence for which long-term exposure measurements are available, there are uncertainties in exposure estimates. For example, the measurements might not adequately reflect conditions in the home over the full period of residence, the amount of time the subject spent in different rooms in the home cannot be determined precisely, and exposures received in places other than the home cannot be estimated. When persons have resided in more than one residence, additional error can be introduced, particularly if measurements cannot be made in all residences.

It is well known that even unbiased measurement error can lead to underestimation of the risk coefficient and can reduce the power to detect effects. The sample-size determinations described above were based on the assumption that exposures of all study subjects are measured perfectly. Modification of this assumption to include the possibility of 50% misspecification of exposure (that is, the error is assumed to constitute 50% of the true exposure) increased required sample sizes for testing the hypothesis of no effect (hypothesis 1) by a factor ranging from 1.5 to 2.8, depending on assumptions made about the number of residences occupied by each subject. Statistical analyses of case-control studies conducted thus far have not accounted for exposure measurement error; thus, both risks and uncertainties were probably underestimated.

A third limitation is posed by the observational nature of epidemiologic studies and the resulting potential for confounding bias; confounding is of particular concern when small changes in risk

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are studied (Monson, 1980; Boice and Land, 1982; Rothman, 1986), as expected in most studies of residential radon exposure. In the studies of residential radon, information on key variables of interest is obtained through interviews, and cases and controls might differ in the adequacy and validity of their responses, especially when interviews must be conducted with persons other than the subject. Information bias is probably not of great concern in residential histories, but it could be important with regard to other factors, such as smoking. Even if the information on potential confounding factors is equally valid for cases and controls, data on smoking and other risk factors are not likely to be sufficiently detailed and accurate to permit complete adjustment in analyses. Like exposure measurement error, potential confounding introduces additional uncertainty that is not reflected in usual statistical confidence limits. Because of the enormous confounding effect of cigarette use, some studies limited to life-long nonsmokers may be needed despite the costs and sample sizes.

In summary, because of the limitations described here, case-control studies of exposure to indoor radon probably cannot provide quantitative risk estimates that are sufficiently precise to allow these studies to supplant extrapolation from underground miners for risk-assessment purposes, particularly if the consequences of measurement error and confounding factors are fully acknowledged. Reported results indicate that individual studies are likely to yield a range of results, extending from no apparent effect to effects greater than anticipated from the studies of miners. A definitive assessment of risk should not be anticipated from any individual study, and combined analyses are clearly needed. In interpreting the findings of the case-control studies, it will also be important to consider uncertainties from sources other than statistical variation. An important task for a BEIR VI committee will be

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to evaluate the appropriate role of case-control studies in radon risk assessment.

Ecologic Studies

In ecologic studies, groups, rather than individuals, are used as the unit of analysis. Because the groups are usually defined in terms of geographic areas in which mortality or incidence data are available, ecologic studies can often make use of existing data and so can be conducted quickly and inexpensively. However, methodologic problems greatly limit the usefulness of ecologic studies, and they are generally considered to be useful primarily for developing new hypotheses regarding exposure-disease relationships.

Status

Stidley and Samet (1993) provide a detailed review of the results and methods of 15 ecologic studies of lung cancer and indoor radon exposure. In eight of the studies, lung-cancer rates were compared for two or more groups defined by exposure status, and seven were regression studies in which rates were modeled as a function (usually linear) of exposure. Exposure estimates used in these studies included both surrogate measures, such as the geologic characteristics of an area, and estimates based on current measurements of indoor radon from samples of homes in an area. Most of the studies were published recently, and only three were evaluated by the BEIR IV committee. Seven of the 15 studies reported positive associations, six no

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association, and two negative associations. Of the seven positive studies, only one included adjustment for smoking, and six of these were based on surrogate measures of indoor radon exposure. Of the six studies showing no association, three included adjustment for smoking, and three of these were based on surrogate measures of exposure. All were judged by Stidley and Samet to have low power for detecting effects under reasonable alternative hypotheses. The two studies showing negative associations were both regression studies that included adjustment for smoking and were based on samples of exposure measurements (Haynes, 1988; Cohen, 1990; Cohen and Colditz, 1992); an additional comparison study recently reported a negative association but did not include adjustment for smoking (Neuberger et al., 1992). Several methodologic shortcomings could have biased all studies.

Problems and Limitations

Limitations of the ecologic-study design and the special biases to which ecologic studies are subject have been discussed extensively (Piantadosi et al., 1988; Greenland and Morgenstern 1989; Greenland, 1992; Stidley and Samet, 1994). There are often problems with the exposure measurements used in these studies. The need to use groups on which vital statistics are available can obscure much of the variability in indoor radon exposure and lead to low statistical power for detecting effects, even if the average exposures are assessed correctly. Estimation of exposure from surrogate measures or from sampled homes is likely to reduce power still further and might also introduce bias.

An additional difficulty is that grouped data can be especially subject to confounding if the geographic regions chosen reflect

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differences in other risk factors. It is often not possible to control for potential confounders adequately because suitable data are not available or because, with grouped data, adjustment for confounders cannot be correctly carried out unless the risk is a linear function of both indoor radon concentration and other variables for which adjustment is needed. In evaluating lung-cancer risks, smoking is the factor of greatest concern, and data on smoking are generally not available for finely defined geographic regions. Stidley and Samet (1994) show that even a small negative correlation of radon exposure and smoking could induce a negative correlation of radon exposure and lung-cancer risk. As noted before, ecologic studies are regarded as useful primarily for the generation of hypotheses that must be further examined by means of with other study designs. There is already strong evidence from studies of underground miners that exposure to indoor radon can cause lung cancer. The major uncertainty is the magnitude of risk at residential concentrations.

Radon-Induced Cancers Other than Lung Cancer

Ecologic studies by Henshaw and colleagues (1990) examined average radon exposures and disease rates for leukemia and other cancers in 14 countries and in regions of the United Kingdom and Canada. They identified significant positive correlations for childhood and adult leukemia, kidney cancer, melanoma, and prostatic cancer. Henshaw and colleagues (1992) presented calculations for radon-derived a-radiation dose to bone marrow and skin and proposed that these calculations supported a causal explanation for the identified correlations.

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Butland and co-workers (1990) noted the poor quality of radon exposure data from some countries, indicating that these data did not always cover the same areas as the cancer data. They also noted that countries with the highest-quality cancer data (e.g., Scandinavian countries) tended to be those with the highest radon exposures, and they pointed to problems in the statistical methods used by Henshaw and colleagues. Muirhead and co-workers (1991) conducted an ecologic analysis based on small areas of the United Kingdom and found no significant associations with radon exposure, even though analyses by aggregated areas (counties) did show a correlation.

SUMMARY AND RECOMMENDATIONS

Results of several epidemiology studies have been published since the BEIR IV report. The results from miner studies have increased our knowledge of the association between radon-progeny exposure and lung-cancer risk, including an increase in the population database, the introduction of new information in humans first exposed as children, and information regarding the potential role of other agents and nonmalignant respiratory disease in causing lung cancer. Results of one of these studies (Laurer et al., 1993) suggest that skeletal lead-210 measurements might be useful for dose reconstructions to improve the epidemiologic studies. Data have also been used to investigate the interaction between smoking and radon-progeny exposure. A pooled analysis of data from 11 studies of underground miners has recently been published (Lubin et al., 1994), and it contains several observations relevant to risk reassessment, including information regarding the confounding

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effects of smoking. Ecologic analyses have shown associations between exposure indexes for radon and the incidence of nonrespiratory cancers.

Numerous case-control and ecologic studies on indoor radon and lung cancer have been initiated. Results of some studies have been published, and results of the case-control studies now in progress should become available in the next few years. The most recent case-control studies include long-term residential radon measurements and matching on age, sex, and other factors. At least 20 studies in progress include more than 12,000 lung-cancer cases and more than 19,000 controls (Neuberger, 1992). Results of some of these studies might be available in time to be included in a BEIR VI reassessment, but the committee recognizes that the results of several studies will not be completed in time to be available to the Phase II committee. Ecologic studies of other cancers and indoor radon exposure have been also published (Stidley and Samet, 1993), but limitations in these studies have made it difficult to ascertain whether there is a correlation between radon exposures and cancers other than lung cancer.

Studies of Miners

- Because the pooled analyses of 11 cohorts are likely to serve as the basis for developing a new risk model for radon and lung cancer, a Phase II committee will have to critique this work, identify additional analyses needed, and possibly gain access to the data on the 11 cohorts.
- The Phase II committee should consider biologically driven modeling of the pooled data.

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- The Phase II committee should formally evaluate sources of exposure error in the miner cohorts and the consequence of these errors for risk estimation and risk assessment.
- The Phase II committee should consider new evidence on arsenic, silica, and other factors that can modify or confound the risks estimated from miner studies.
- Formal analysis of uncertainties in extending risk models from miners to the general population should be undertaken.
- The Phase II committee should evaluate possible risks of cancer at sites other than lung, particularly with the data from the pooled analysis of the miner studies in progress.

Studies of Lung Cancer in the General Environment

- The Phase II committee must evaluate and interpret the results of case-control and ecologic studies that have been reported and of the forthcoming studies, including evaluation of the limitations and uncertainties in these studies.
- Results of case-control studies reported thus far have generally been consistent with estimates based on extrapolation from data on underground miners but have not provided enough precision to rule out the possibility of no risk or of risks that are substantially larger than those obtained through extrapolation. The Phase II committee should determine the potential role of current and future case-control studies for validating risk models based on miners and more generally for developing risk models of residential exposure to radon.
- The Phase II committee should make recommendations regarding whether it is desirable to initiate new case-control or ecologic studies of residential radon.

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Health Effects of Exposure to Radon: Time for Reassessment?
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Information on Committee Members

JONATHAN M. SAMET (Chairman) is professor of medicine at the University of New Mexico, an internist with a subspecialty in pulmonary diseases, and an epidemiologist with the New Mexico Tumor Registry. He has published on human respiratory disorders associated with uranium mining and other environmental exposures. Dr. Samet led the Subcommittee on Radon of the National Research Council's BEIR IV committee, whose report was published in 1988, and chaired the Research Council's Panel on Dosimetric Assumptions Affecting the Application of Radon Risk Estimates, whose final report was published in 1991.

ETHEL S. GILBERT is a senior staff scientist and statistician at Battelle, Pacific Northwest Laboratories in Richland, Washington. Her research has focused on epidemiologic studies of nuclear workers and have included combined analyses of national and international data and the development of statistical methods for examining the relationship of health effects and low-level chronic exposures. Dr. Gilbert has also analyzed data on experimental animals exposed to radon and inhaled plutonium and was a member of the working group responsible for revising the health-effects

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model for somatic effects in the Nuclear Regulatory Commission's reactor-safety study.

ERIC J. HALL is Higgins Professor of Radiation Biophysics and professor of radiology and radiation oncology at Columbia University. Dr. Hall's research has included study of the effects of ionizing radiation on cells in culture and mechanisms of carcinogenesis. He was a member of the BEIR V committee. He has received awards from several radiology societies, including the gold medal of the Radiological Society of North America, the gold medal of the American Society of Therapeutic Radiology and Oncology, the Failla Award of the Radiation Research Society, and the Silvanus Thompson Award of the British Institute of Radiology.

WARREN K. SINCLAIR is president emeritus of the National Council on Radiation Protection and Measurements and emeritus professor of radiobiology at the University of Chicago. Dr. Sinclair's research has focused on radiologic physics, radiation biology, and radiation protection and included cell-cycle studies in mammalian cells and radiation risk estimates in humans. He has served as president of the Radiation Research Society and the American Association of Physicists in Medicine and was secretary general of the Fifth International Congress of Radiation Research. He has been Curie Lecturer, Failla Lecturer, Parker Lecturer, and Taylor Lecturer and has received the Coolidge Award. He served on the International Commission on Radiological Protection, the U.S. delegation to UNSCEAR, and the International Commission on Radiation Units and Measurements.

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